Facile Approach to Enantiomerically Pure α-Amino Ketones by Friedel−Crafts Aminoacylation and Their Conversion into Peptidyl Ketones

Maria Luisa Di Gioia, Antonella Leggio, Angelo Liguori,* Anna Napoli, Carlo Siciliano, and Giovanni Sindona

Dipartimento di Chimica, Università degli Studi della Calabria, Via Ponte P. Bucci, Cubo 15/C, I-87030 Arcavacata di Rende (CS), Italy

a.liguori@unical.it

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In this article we describe a versatile and straightforward preparative approach to chiral aryl α-amino ketones via a Friedel−Crafts-type reaction of stable and enantiomerically pure *N*-Fmoc protected L-amino acid chlorides with toluene in the presence of aluminum trichloride. The developed methodology provided aryl α-amino-*p*-methylphenyl ketones, which can be obtained and isolated as free bases or recovered as their *N*-acetyl derivatives, after treatment with acetic anhydride in chloroform at room temperature, subsequent to the Lewis acid induced removal of the 9-fluorenylmethoxycarbonyl protecting group. The Friedel−Crafts-like process and the cleavage of the amino function masking group can selectively be performed since, as verified in all cases, the α-aminoacylation step occurred with kinetics that were faster than those required to remove the *N*-protection. The presented approach was also explored as a facile and useful synthetic tool for the preparation of optically pure ketone di- and tripeptides. These compounds can be obtained in exceptionally overall yields without need of chromatographic purification. Moreover, either aryl α-amino ketones or modified di- and tripeptides, in all cases, can be isolated in very high chemical and optical purity without recourse to resolution of diastereomeric mixtures, since the chiralities of the asymmetric amino acid educts were completely conserved throughout the entire process.

Introduction

Substituted α-amino ketones containing the trifluoromethyl group or different aryl moieties represent a very important class of compounds characterized by biological activity.[1] In particular, trifluoromethyl α-amino ketones have been proven to be effective as good renin inhibitors[2] and as analgesics.[3] Moreover, aryl α-amino ketones belong to an interesting family of drugs employed in the clinical treatment of nicotine dependence.[4] For example, bupropion, a potent large spectrum therapeutic agent, is actually considered as one of the most advanced pharmacological aids to smoking cessation treatment.[5] Many other compounds chemically related to the class of aryl α-amino ketones are also widely used as late life antidepressants,[6] since they show appreciable inhibitory activity of the neuronal uptake of norepinephrine, serotonine, and dopamine.[7]

In the last years, many synthetic routes to the preparation of trifluoromethyl and aryl substituted α-amino ketones have been exploited. The most favorable strategies are all based on the application of derivatives of natural or modified α-amino acids. These compounds can be chosen as appropriate acylating reactants in processes carried out under Friedel−Crafts classical conditions, in the presence of selected aromatic substrates. Previously reported methods,[8−11a] however, suffer from some limitations mainly as a result of the selection of an appropriate protecting group for the masking of the α-amino function. In fact, the choice of suitable protecting group able to minimize the percentage of racemization of the chiral precursors is a crucial factor in the Friedel−Crafts acylation process. Since one of the most important features of biologically active α-amino ketones is associated with the presence of an asymmetric carbon atom in their structures, total control of the chirality represents the main goal when new synthetic approaches have to be planned.

Results and Discussion

N-Trifluoracetyl protected α-amino acid chlorides have been indicated as advantageous reactants in the Friedel−Crafts acylation.[8] These compounds have also proven useful to limit the level of racemization of the chiral acylating substrates. Additionally all of the established

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synthetic protocols describe the use of *N*-trifluoroacetylated chlorides that are obtained in situ without isolation.

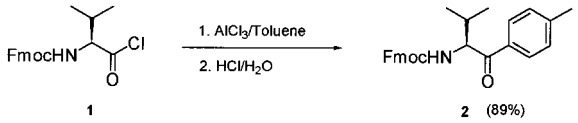
In our preliminary Friedel−Crafts reactions using *N*-trifluoroacetyl derivatives the corresponding racemic oxazolinones[9] were isolated. In the previously studied Friedel−Crafts-type processes, the acylating agent was presumably the *N*-protected oxazolinone rather than the corresponding α-amino acid chloride. The widely used benzyloxycarbonyl group (Z) has not been shown to be a suitable masking moiety for Friedel−Crafts α-aminoacylations.[10] In this case, the Lewis acid promoted unblocking of the amino function present in the α-amino acid chlorides resulted preferentially in the acylation process. Diketopiperazines, arising from the reaction of the amino acid derivatives containing both a free amino function and an activated carboxyl moiety, were recovered as the main products from the respective reaction mixtures. Methyloxy- and ethyloxycarbonyl blocking groups allowed Friedel−Crafts acylations in good extents.[11] However, despite their compatibility with Friedel−Crafts acylation conditions, their incorporation is hampered by the difficulties found during the protecting group removal step. The same troublesome problems have been observed with *N*-tosyl protected α-amino acid chlorides[11a] because the tosyl amide linkage is too difficult to cleave under mild reaction conditions.

Consequently the use of a urethane-type blocking group may allow the development of *N*-protected α-amino acid halides[12] as useful reagents for simultaneous Friedel−Crafts acylation and unblocking of the obtained optically pure aryl α-amino ketones under mild conditions. The possibility to have a routine method[11b] to prepare stable and easy to handle enantiomerically pure *N*-9-fluorenylmethoxycarbonyl protected α-amino acid chlorides that are storable at room temperature opened new and interesting perspectives in the study of amino acid coupling methods, as well as its application in the field of the biologically occurring peptides. Introduction of the Fmoc protecting group[13] may allow α-amino acid chlorides to be incorporated in this strategy since problems related to the stability and to the storage of the analogous methyloxy-, ethyloxy-, *tert*-butyloxy-, and benzyloxycarbonyl derivatives may be avoided.

To evaluate the competition between the kinetics associated with the Friedel−Crafts-type acylation compared to the removal of the 9-fluorenylmethoxycarbonyl protecting group, we studied the reactivity of an easily accessible model substrate, *N*-Fmoc-valine chloride, in the presence of the combined reagent system aluminum trichloride/toluene.[11b]

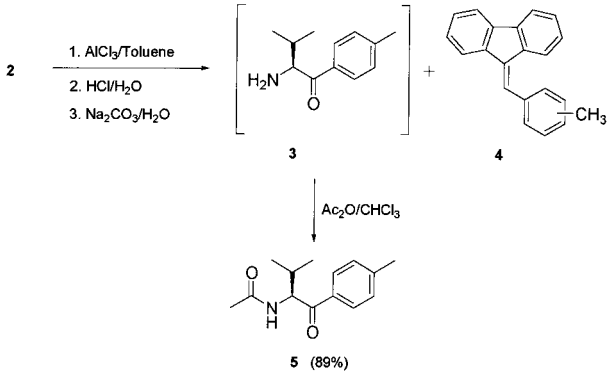
The first goal was the selection of the best experimental conditions required to perform the entire acylation/unblocking process. In a preliminary experiment, a solution of *N*-Fmoc-valine chloride (**1**) in toluene was allowed to react with 2 equiv of aluminum trichloride at room temperature (Scheme 1).

Scheme 1



1 **2** (89%)

Scheme 2



3 **4** **5** (89%)

After complete conversion of the starting amino acid chloride, the reaction mixture was subjected to work up to furnish the chiral 2-(*N*-Fmoc-amino)-3-methyl-1-(*p*-methylphenyl)-1-butanone **2**. It is worth noting that compound **2** was recovered in good overall yield (89%) and isolated in an extremely high purity grade (>95%), without need of chromatographic purification. Moreover, acylation was totally regioselective. In fact, compound **2** was the only product obtained from the Friedel−Crafts reaction. No traces of the possible *ortho* isomer were detected. A second experiment was performed by treating the protected aryl α-amino ketone **2**, recovered from the above reaction, with a 2-fold molar excess of the Lewis acid in toluene, under the same conditions adopted for the preparation of **2**. Treatment yielded the aryl α-amino ketone **3**, obtained as a free base, and a mixture of the dibenzofulvene-toluene adducts **4**. After hydrolysis of the reaction mixture under acidic conditions and pH-controlled solvent extraction, the mixture of regioisomers **4** was separated. Basification of the mother liquors and extraction afforded the crude ketone **3**, which was in turn subjected to acylation with a stoichiometric excess of acetic anhydride in chloroform. This last step allowed the isolation of the previously formed vicinal amino ketone and its characterization as the respective *N*-acetyl derivative **5** (Scheme 2).

As a result of these initial results, the preparation of aryl α-amino ketones starting from the corresponding optically pure *N*-Fmoc protected α-amino acid chlorides appeared to be feasible. These readily available and very stable derivatives of naturally occurring amino acids were then investigated as potential acylating agents in one-pot processes performed by controlling both stoichiometry and reaction times. The suggestive hypothesis of a one-pot approach to the synthesis of chiral vicinal amino ketones, in which a Friedel−Crafts-like acylation occurs prior to the removal of the protecting group, was more profoundly verified by treating a solution of *N*-Fmoc-valine chloride (**1**) in toluene with a 3-fold excess of aluminum trichloride, at room temperature. After 2 h, TLC analysis of the reaction mixture showed complete conversion of the starting amino acid derivative, with

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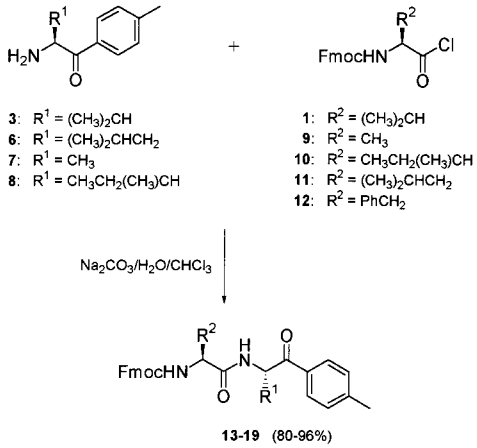
Scheme 3



concomitant formation of the desired free base aryl α-amino ketone **3**. The latter compound was separated from the reaction mixture by simple hydrolytic workup under basic conditions, followed by solvent extraction. Treatment of the organic layers with acetic anhydride at room temperature afforded the *N*-acetylated ketone **5** in excellent total yield (89%).

To examine all aspects and the potential of the presented one-pot methodology, we further investigated the preparation of modified dipeptides in which the carboxylic function of the *C*-terminal α-amino acid residue is replaced by an aryl keto group having fixed stereochemistry. These unusual compounds may constitute valuable molecular models for new synthetic approaches to some chiral targets such as tripeptide analogues and related species possessing biological importance, which include potential inhibitors of the elastases responsible for pathological states associated with grave human respiratory system diseases.[14] Therefore, we planned a convenient preparative strategy based on the coupling reaction between *N*-Fmoc α-amino acid chlorides and aryl α-amino ketones in which the latter is generated in situ by means of the previously discussed one-pot Friedel−Crafts acylation/unblocking process performed on the corresponding *N*-protected α-amino acid chloride.

The free base chiral aryl α-amino ketones **3** and **6**−**8**, obtained as described but not isolated from the respective reaction environment, smoothly underwent couplings with the appropriate *N*-Fmoc protected chlorides **1** and **9**−**12** in chloroform at room temperature (Scheme 3). All processes showed total consumption of the starting substrates after 1 h. Modified dipeptides **13**−**19** were easily recovered by subjecting the respective reaction mixtures to the previously described workup, from which compounds **13**−**19** were isolated in very high to excellent overall yields (Table 1). Furthermore, peptide analogues **13**−**19** were obtained without the need of chromatographic purification. A significant synthetic finding was that in all the examples, the availability of stable and enantiomerically pure *N*-Fmoc α-amino acid chlorides represents the unique requisite reagent either for generating the dissymmetric aryl amino ketone educts or for realizing the coupling steps.

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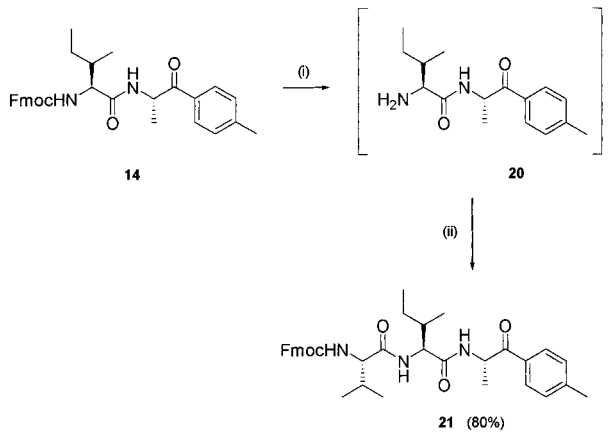
Table 1. Synthesis of Dipeptidyl Ketones; Yields of Isolated Products

compound	R^1	R^2	yield (%)
13	$(CH_3)_2CHCH_2$	CH_3	90
14	CH_3	$CH_3CH_2(CH_3)CH$	96
15	$(CH_3)_2CH$	$(CH_3)_2CHCH_2$	95
16	$(CH_3)_2CH$	CH_3	92
17	$CH_3CH_2(CH_3)CH$	$(CH_3)CH$	86
18	CH_3	CH_3	80
19	CH_3	$PhCH_2$	85

Scheme 4[a]

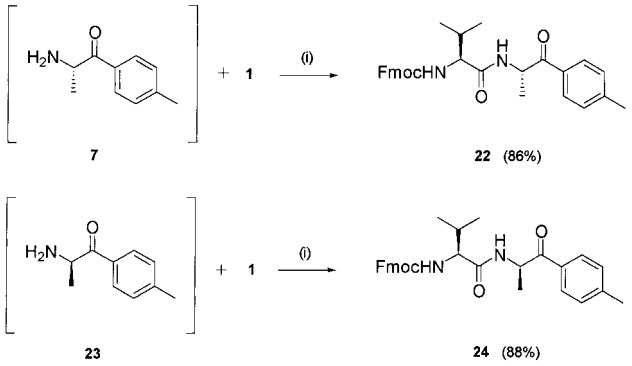


[a] (i) (1) $AlCl_3$/toluene; (2) HCl/H_2O; (3) Na_2CO_3/H_2O; (ii) *N*−Fmoc-lle-Cl/$CHCl_3$.

To thoroughly investigate the full applicability of the proposed methodology to the preparation of short oligopeptide sequences possessing either natural amino acids or their ketone modified congeners, dipeptide analogue **14** was selected as a suitable starting material for the synthesis of tripeptide **21** (Scheme 4). By applying experimental conditions similar to those adopted for the preparation of the precursor **14**, the same chiral compound was initially unblocked by treatment with the combined reagent system aluminum trichloride/toluene. Removal of the Fmoc protecting group from **14** provided the intermediate **20**, which was not isolated and directly coupled with *N*-Fmoc-valine chloride (**1**), according to the synthetic protocol used in the preparation of peptidyl ketones **13**−**19**. After complete conversion of the starting reactants, workup of the homogeneous mixture allowed the recovery of compound **21** in very good overall yield (80%) and with extraordinary high purity grade (>95%), without recourse to chromatographic fractionation of the crude reaction.

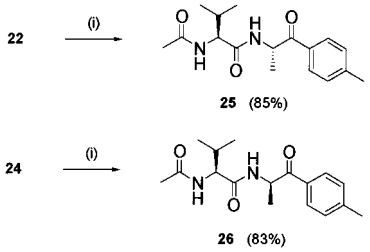
The facile preparation of monomeric vicinal aryl α-amino ketones and their easy utilization in the stereocontrolled approach to structurally variable short oligopeptide chains having *C*-terminal chiral ketone moieties should constitute a valuable improvement in the chemistry field of pharmacologically interesting compounds. Therefore, the usefulness of the proposed synthetic route could dramatically be enhanced if the enantiomeric integrity of the optically active aryl α-amino ketones can be preserved until complete buildup of the modified peptide structures. Thus, to assess the validity of the present reactions, it was indispensable to check the extent of racemization that might be observed for the chiral α carbon atom present in all the products obtained by the studied Friedel−Crafts α-aminoacylation.

Scheme 5[a]



[a] (i) $Na_2CO_3/H_2O/CHCl_3$.

Scheme 6[a]



[a] (i) (1) $AlCl_3$/toluene; (2) HCl/H_2O; (3) Na_2CO_3/H_2O; (4) $Ac_2O/CHCl_3$.

To this end, L-2-amino-1-*p*-methylphenyl-propanone (**7**) and its optical antipode **23**, each synthesized starting from the respective *N*-Fmoc protected L- and D-alanine chlorides by applying the above explained Friedel–Crafts-like acylation and unblocking procedure, were chosen as model compounds for a conclusive and representative test. Both enantiomerically pure aryl α-amino ketones were not isolated and were directly converted into the corresponding diastereomeric modified dipeptides **22** and **24** by coupling with *N*-Fmoc-L-valine chloride (**1**) (Scheme 5). Workup of the reaction mixtures furnished crude materials, which were successively subjected to instrumental characterization.

For all the considered processes, ^{1}H NMR analysis performed on the respective reaction crudes excluded the presence of both possible diastereomeric modified dipeptides obtained from each chiral aryl α-amino ketone educt. The experimental evidence was thus indicative that α-aminoacylations occurred with total retention of either precursor or product chiralities. The collected results were finally confirmed by treating the two crude reaction mixtures dissolved in toluene with aluminum trichloride at room temperature. Under the usual experimental conditions, removal of the amino function masking group took place and the recovered free base dipeptide analogues were successively acetylated in chloroform at room temperature. Ketone modified dipeptides present in each reaction mixture were recovered as their *N*-acetylated derivatives **25** and **26** (Scheme 6), which were obtained in extremely high purity grade, as verified by GC–MS analysis and ^{1}H NMR spectroscopy. It is notable that recorded chromatograms showed the presence of only one diastereomeric peptidyl ketone in each crude mixture arising from the *N*-acetylation processes.

The use of *N*-9-fluorenylmethoxycarbonyl protected α-amino acid chlorides could be hampered by the inability to handle side chains protected with orthogonal acid labile masking groups,[12a] thereby not allowing trifunctional α-amino acids to be used. Further developments of the proposed *N*-Fmoc strategy concerning its applicability to the preparation of chiral trifunctional α-amino acid educts, as well as an examination of the optical integrity and epimerization in the case of *N*-protected α-amino acids, which are more prone to racemization, are currently under investigation.

Conclusion

The illustrated aryl α-amino ketone synthesis methodology clearly represents the basis for a novel, straightforward and inexpensive, large scale preparation of biologically and pharmacologically important short oligopeptide sequences containing naturally occurring amino acids and enantiomerically pure chiral ketone functionalities that replace the carboxyl group of the *C*-terminal amino acidic residue.

Experimental Section

Solvents and reagents were purified and dried by standard procedures and distilled prior to use. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz using $CDCl_3$ as solvent. GC–MS analyses were carried out with a 30 m cross-linked 5% PHMesiloxane capillary column with a 0.25 mm internal diameter and a 0.25 μm film thickness. The mass detector was operated in the electron impact ionization mode (EIMS) with an electron energy of 70 eV. Mass spectra were recorded on a B/E instrument by fast atom bombardment (FAB^+ MS), using 3-nitrobenzyl alcohol as matrix. Optical rotations were measured by using a digital polarimeter with a 10-cm cell. Reaction mixtures were monitored by TLC using Merck silica gel 60-F_{254} precoated glass plates.

Synthesis of 2-(*N*-Fmoc-amino)-3-methyl-1-(*p*-methylphenyl)-1-butanone (2). $AlCl_3$ (0.42 g, 3.18 mmol) was added to a magnetically stirred solution of *N*-Fmoc-L-valine chloride (**1**) (0.57 g, 1.59 mmol) in dry toluene (24 mL). The resulting mixture was maintained at room temperature and under inert atmosphere (N_2) for 30 min with monitoring of the conversion of **1** by TLC (diethyl ether/light petroleum bp 40–60 °C, 50:50 v/v). HCl (1 N) was then added, and the acidified solution (pH 2) was extracted with diethyl ether (4 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to give **2** (0.58 g, 89% yield) as a white solid, mp 118–120 °C. IR (KBr): ν 3288 cm^{-1}, 3064, 2958, 1676, 1606, 1540, 1297, 1032, 739. ^{1}H NMR: δ 0.78 ppm [d, J = 6.8 Hz, 3 H, $(CH_3)_2CH$)], 1.04 [d, J = 6.8 Hz, 3 H, $(CH_3)_2$-CH)], 2.18 (m, 1 H, 3-H), 2.41 (s, 3 H, $CH_3C_6H_4$), 4.23 (m, 1 H, $CHCH_2O$), 4.39 (m, 2 H, $CHCH_2O$), 5.29 (dd, J_1 = 5.4 Hz, J_2 = 8.8 Hz, 1 H, 2-H), 5.77 (d, J = 8.8 Hz, 1 H, NH), 7.24–7.90 (m, 12 H, Ar–H). FAB^+ MS: m/z (%) 414 (17.4) [$(M + H)^+$], 294 (16), 192 (29), 179 (100), 178 (99), 165 (32), 119 (37). $[\alpha]^{28}_D$ −85.9° (c 0.5, $CHCl_3$). Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.39; H, 6.60; N, 3.41.

Synthesis of 2-(*N*-Acetyl-amino)-3-methyl-1-(*p*-methylphenyl)-1-butanone (5). $AlCl_3$ (0.20 g, 1.50 mmol) was added to a solution of 2-(*N*-Fmoc-amino)-3-methyl-1-(*p*-methylphenyl)-1-butanone (**2**) (0.31 g, 0.75 mmol) in dry toluene (12 mL). The resulting mixture was stirred at room temperature and under inert atmosphere (N_2) for 1.5 h until complete conversion of the protected precursor **2**. HCl (1 N) was then added, and the acidified solution (pH 2) was extracted with diethyl ether (3 × 10 mL). The aqueous solution was basified with saturated aqueous Na_2CO_3 (pH 9) and then extracted with chloroform (4 × 10 mL). The combined organic extracts

were dried (Na_2SO_4) and evaporated to dryness to give pure 2-amino-3-methyl-1-(*p*-methylphenyl)-1-butanone (**3**) (0.125 g, 87% yield). GC/MS (EI): *m/z* (%) 148 (3.2), 119 (6.2), 91 (12), 72 (100), 65 (7), 55 (25).

A solution of the latter compound **3** (0.125 g, 0.65 mmol) in ethanol-free chloroform (5 mL) was treated with acetic anhydride (0.12 mL, 1.30 mmol) at room temperature for 30 min. The mixture was basified with saturated aqueous Na_2CO_3 (pH 9) and then extracted with chloroform (3 × 8 mL). The organic phase was washed with distilled water (2 × 6 mL), dried, and evaporated to dryness to afford **5** (0.135 g, 89% yield) as a white solid, mp 120−124 °C. IR (KBr): ν 3287 cm^{-1}, 2965, 1677, 1636, 1542, 1088, 1017, 782. ^1H NMR: δ 0.77 ppm [d, J = 6.8 Hz, 3 H, $(CH_3)_2CH$)], 1.01 [d, J = 6.8 Hz, 3 H, $(CH_3)_2$-CH)], 2.10 (s, 3 H, CH_3CO), 2.18 (m, 1 H, 3-H), 2.43 (s, 3 H, $CH_3C_6H_4$), 5.58 (dd, J_1 = 4.3 Hz, J_2 = 8.8 Hz, 1 H, 2-H), 6.45 (d, J = 8.8 Hz, 1 H, NH), 7.28 (d, J = 8.4 Hz, 2 H, Ar−H) 7.90 (d, J = 8.4 Hz, 2 H, Ar−H). GC−MS: *m/z* (%) 233 (1) [M^+], 148 (5), 119 (28), 114 (69), 91 (16), 72 (100), 43 (11). $[\alpha]^{28}_D$ −145.1° (*c* 4.5, $CHCl_3$). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.09; H, 8.18; N, 6.04.

Synthesis of Dipeptides 13−19. General Procedure. To a magnetically stirred solution of the appropriate *N*-Fmoc-α-amino acid chloride **1**, **9**−**11** (1 mmol) in dry toluene (16 mL) was added $AlCl_3$ (3 mmol). The resulting mixture was maintained at room temperature and under inert atmosphere (N_2) for 1−3 h. HCl (1 N) was then added, and the acidified solution (pH 2) was extracted with diethyl ether (3 × 15 mL). The aqueous phase was basified with saturated aqueous Na_2CO_3 (pH 9). The basic liquors, containing the respective α-aminoalkyl *p*-methylphenyl ketones **3**, **6**−**8**, were then treated with a solution of *N*-Fmoc-α-amino acid chloride **1**, **9**−**12** (1 mmol) in ethanol-free chloroform (10 mL). The reaction 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 over Na_2SO_4 and evaporated under vacuum to afford dipeptides **13**−**19** (80−96% overall yields).

Data for 13: 90% yield, white solid, mp 160−164 °C. IR (KBr): ν 3316 cm^{-1}, 3060, 2954, 1714, 1686, 1656, 1254, 760, 739. ^1H NMR: δ 0.82 ppm [d, J = 6.3 Hz, 3 H, $(CH_3)_2CHCH_2$)], 1.02 [d, J = 6.3 Hz, 3 H, $(CH_3)_2CHCH_2$)], 1.30[m, 1 H, $(CH_3)_2CHCH_2$], 1.39 (d, J = 6.8 Hz, 3 H, $CH_3CHCONH$), 1.47 [m, 1 H, $(CH_3)_2CHCH_2$], 1.61 [m, 1 H, $(CH_3)_2CHCH_2$], 2.40 (s, 3 H, $CH_3C_6H_4$), 4.18−4.26 (m, 2 H, $CHCH_2O$ and $CHCONH$), 4.37 (d, J = 6.8 Hz, 2 H, $CHCH_2O$), 5.62 (m, 1 H, $CHCOC_6H_4$-CH_3), 5.75 (d, J = 7.8 Hz, 1 H, FmocNHCH), 6.93 (d, J = 7.8 Hz, 1H, CONHCHCOC$_6$H$_4$CH$_3$), 7.25−7.75 (m, 12 H, Ar−H). FAB^+ MS: *m/z* (%) 499 (11) [$(M + H)^+$], 379 (2), 303 (2), 277 (7), 206 (16), 179 (100), 178 (55), 165 (19). $[\alpha]^{28}_D$ −106.3° (*c* 10.0, $CHCl_3$). Anal. Calcd for $C_{31}H_{34}N_2O_4$: C, 74.67; H, 6.87; N, 5.62. Found: C, 74.58; H, 6.82; N, 5.63.

Data for 14: 96% yield, white solid, mp 184−187 °C. IR (KBr): ν 3288 cm^{-1}, 3060, 2961, 1718, 1691, 1646, 1540, 1234, 1032, 757, 739. ^1H NMR: δ 0.85−0.98 ppm [m, 6 H, CH_3CH_2-(CH_3)CH], 1.22 [m, 1 H, $CH_3CH_2(CH_3)$CH], 1.41(d, J = 6.9 Hz, 3 H, $CH_3CHCOC_6H_4CH_3$), 1.50 [m, 1 H, $CH_3CH_2(CH_3)$CH], 1.88 [m, 1 H, $CH_3CH_2(CH_3)CH$], 2.40 (s, 3 H, $CH_3C_6H_4$), 4.16−4.24 (m, 2 H, $CHCH_2O$ and $CHCONH$), 4.39 (m, 2 H, $CHCH_2O$), 5.51 (m, 1 H, $CHCOC_6H_4CH_3$), 5.75 (d, J = 8.6 Hz, 1 H, FmocNHCH), 7.11 (d, J = 7.7 Hz, 1H, CONHCHCOC$_6$H$_4$-CH_3), 7.25−7.90 (m, 12 H, Ar−H). FAB^+ MS: *m/z* (%) 499 (10) [$(M + H)^+$], 303 (4), 287 (12), 277 (7), 273 (16), 259 (18), 245 (15), 179 (100), 178 (61), 165 (37). $[\alpha]^{28}_D$ −347.5° (*c* 2.8, $CHCl_3$). Anal. Calcd for $C_{31}H_{34}N_2O_4$: C, 74.67; H, 6.87; N, 5.62. Found: C, 74.61; H, 6.84; N, 5.59.

Data for 15: 95% yield, white solid, mp 130−134 °C. IR (KBr): ν 3304 cm^{-1}, 2959, 2954, 1707, 1684, 1653, 1534, 1261, 758, 738. ^1H NMR: δ 0.74 ppm [d, J = 6.8 Hz, 3 H, $(CH_3)_2$-$CHCH_2$], 0.91−0.98 [m, 9 H, $(CH_3)_2CHCH_2$) and $(CH_3)_2CH$], 1.31 [m, 1 H, $(CH_3)_2CHCH_2$], 1.54−1.74 [m, 2 H, $(CH_3)_2$-$CHCH_2$], 2.19 [m, 1 H, $(CH_3)_2CH$], 2.40 (s, 3 H, $CH_3C_6H_4$), 4.22 (m, 1 H, $CHCH_2O$), 4.33 (m, 1 H, $CHCONH$), 4.40 (m 2 H, $CHCH_2O$), 5.50 (dd, J_1 = 4.4 Hz, J_2 = 8.8 Hz, 1 H, $CHCOC_6H_4$-CH_3), 5.62 (d, J = 8.7 Hz, 1 H, FmocNHCH), 6.93 (d, J = 8.8 Hz, 1H, CONHCHCOC$_6$H$_4$CH$_3$), 7.24−7.89 (m, 12 H, Ar−H). FAB^+ MS: *m/z* (%) 527 (14) [$(M + H)^+$], 407 (2), 331 (17), 305 (13), 192 (64), 165 (100). $[\alpha]^{28}_D$ −110.4° (*c* 11.0, $CHCl_3$). Anal. Calcd for $C_{33}H_{38}N_2O_4$: C, 75.26; H, 7.27; N, 5.32. Found: C, 75.22; H, 7.29; N, 5.29.

Data for 16: 92% yield, white solid, mp 114−118 °C. IR (KBr): ν 3285 cm^{-1}, 2965, 1714, 1686, 1651, 1530, 1250, 1032, 758, 739. ^1H NMR: δ 0.75 ppm [d, J = 6.8 Hz, 3 H, $(CH_3)_2$-CH], 0.99 [d, J = 6.8 Hz, 3 H, $(CH_3)_2CH$], 1.40 [d, J = 6.9 Hz, 3 H, $CH_3CHCONH$], 2.19 [m, 1 H, $(CH_3)_2CH$], 2.39 (s, 3 H, $CH_3C_6H_4$), 4.22 (m, 1 H, $CHCH_2O$), 4.34 (m, 1 H, $CHCONH$), 4.40 (d, J = 6.8 Hz, 2 H, $CHCH_2O$), 5.55 (dd, J_1 = 4.3 Hz, J_2 = 8.8 Hz, 1 H, $CHCOC_6H_4CH_3$), 5.68 (d, J = 7.6 Hz, 1 H, FmocNHCH), 6.99 (d, J = 8.8 Hz, 1H, CONHCHCOC$_6$H$_4$CH$_3$), 7.26−7.90 (m, 12 H, Ar−H). FAB^+ MS: *m/z* (%) 485 (23) [$(M + H)^+$], 365 (5), 263 (18), 192 (34), 179 (100), 178 (99), 165 (40). $[\alpha]^{28}_D$ −308.5° (*c* 2.9, $CHCl_3$). Anal. Calcd for $C_{30}H_{32}N_2$-O_4: C, 74.36; H, 6.65; N, 5.78. Found: C, 74.33; H, 6.68; N, 5.75.

Data for 17: 86% yield, white solid, mp 117−120 °C. IR (KBr): ν 3289 cm^{-1}, 2975, 1691, 1648, 1540, 1230, 760, 725. ^1H NMR: δ 0.74 ppm [t, J = 6.8 Hz, 3 H, $CH_3CH_2(CH_3)CH$], 0.86−1.02 [m, 9 H, $(CH_3)_2CH$ and $CH_3CH_2(CH_3)CH$], 1.24−1.35 [m, 2 H, $CH_3CH_2(CH_3)CH$], 1.93 [m, 1 H, $CH_3CH_2(CH_3)$-CH], 2.07 [m, 1 H, $(CH_3)_2CH$], 2.40 (s, 3 H, $CH_3C_6H_4$), 4.14 (dd, J_1 = 6.8 Hz, J_1 = 8.8 Hz, 1 H, $CHCONH$), 4.23 (m, 1 H, $CHCH_2O$), 4.39 (m 2 H, $CHCH_2O$), 5.56 (dd, J_1 = 4.9 Hz, J_2 = 8.8 Hz, 1 H, $CHCOC_6H_4CH_3$), 5.79 (d, J = 8.8 Hz, 1 H, FmocNHCH), 6.90 (d, J = 8.8 Hz, 1H, CONHCHCOC$_6$H$_4$CH$_3$), 7.23−7.95 (m, 12 H, Ar−H). FAB^+ MS: *m/z* (%) 527 (8) [$(M + H)^+$], 407 (1), 331 (1), 305 (3), 206 (10), 179 (100), 178 (48), 165 (16). $[\alpha]^{28}_D$ −31.4° (*c* 25.8, $CHCl_3$). Anal. Calcd for $C_{33}H_{38}N_2O_4$: C, 75.26; H, 7.27; N, 5.32. Found: C, 75.28; H, 7.24; N, 5.30.

Data for 18: 80% yield, white solid, mp 116−118 °C. IR (KBr): ν 3294 cm^{-1}, 3060, 2982, 1689, 1648, 1541, 1260, 738. ^1H NMR: δ 1.42 ppm [d, J = 7.4 Hz, 6 H, $CH_3CHCONH$ and $CH_3CHCOC_6H_4CH_3$], 2.41 (s, 3 H, $CH_3C_6H_4$), 4.22 (m, 1 H, $CHCH_2O$), 4.37−4.42 (m, 3 H, $CHCH_2O$ and $CHCONH$), 5.51 (m, 1 H, $CHCOC_6H_4CH_3$), 5.63 (d, J = 7.4 Hz, 1 H, FmocN-HCH), 7.15 (d, J = 6.9 Hz, 1H, CONHCHCOC$_6$H$_4$CH$_3$), 7.25−7.98 (m, 12 H, Ar−H). FAB^+ MS: *m/z* (%) 457 (44) [$(M + H)^+$], 337 (3), 294 (2), 279 (3), 261 (7), 235 (15), 178 (100), 165 (25), 164 (29). $[\alpha]^{28}_D$ −117.2° (*c* 22.0, $CHCl_3$). Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.14. Found: C, 73.64; H, 6.20; N, 6.17.

Data for 19: 85% yield, white solid, mp 176−178 °C. IR (KBr): ν 3302 cm^{-1}, 3060, 2926, 1718, 1690, 1654, 1540, 1259, 1033, 739, 700. ^1H NMR: δ 1.37 ppm [d, J = 6.9 Hz, 3 H, CH_3-$CHCOC_6H_4CH_3$], 2.41 (s, 3 H, $CH_3C_6H_4$), 3.04 (dd, J_1 = 6.4 Hz, J_2= 13.3 Hz, 1 H, $PhCH_2CH$), 3.14 (dd,, J_1 = 6.3 Hz, J_2 = 13.3 Hz, 1 H, $PhCH_2CH$), 4.18 (m, 1 H, $CHCH_2O$), 4.37 (m, 2 H, $CHCH_2O$), 4.54 (m, 1 H, $CHCONH$), 5.43 (m, 1 H, $CHCOC_6H_4CH_3$), 5.53 (d, J = 8.3 Hz, 1 H, FmocNHCH), 6.98 (d, J = 6.9 Hz, 1H, CONHCHCOC$_6$H$_4$CH$_3$), 7.15−7.90 (m, 17 H, Ar−H). FAB^+ MS: *m/z* (%) 533 (23) [$(M + H)^+$], 413 (2), 370 (1), 337 (6), 311 (11), 179 (100), 178 (59), 165 (19), 164 (12). $[\alpha]^{28}_D$ −112.1° (*c* 8.6, $CHCl_3$). Anal. Calcd for $C_{34}H_{32}N_2$-O_4: C, 76.67; H, 6.06; N, 5.26. Found: C, 76.65; H, 6.03; N, 5.28.

Synthesis of *N*-Fmoc-L-Val-L-Ile-L-Ala-$C_6H_4CH_3$ (21). $AlCl_3$ (0.27 g, 2 mmol) was added to a solution of the dipeptide **14** (0.25 g, 0.50 mmol) in dry toluene (10 mL). The resulting mixture was stirred at room temperature for 2 h until complete conversion of the protected precursor. The mixture was then acidified with a solution of HCl (1 N), extracted with diethyl ether (3 × 10 mL), and basified with saturated aqueous Na_2-CO_3. The basic liquors containing the unblocked dipeptide **20** were treated with *N*-Fmoc-L-valine chloride **1** (0.18 g, 0.50 mmol) dissolved in ethanol-free chloroform (10 mL). After 50 min at room temperature, the chloroform layer was separated, and the aqueous phase was extracted with three additional portions of chloroform (3 × 10 mL). The combined chloroform extracts were then dried over Na_2SO_4 and evaporated under

vacuum to afford the tripeptide **21** (0.24 g, 80% yield) as a white solid, mp 160−165 °C. IR (KBr): ν 3284 cm^{-1}, 2962, 1693, 1638, 1541, 1294, 1032, 753, 738. ^{1}H NMR: δ 0.84−0.98 ppm [m, 12 H, C*H*$_3$CH$_2$(C*H*$_3$)CH and (C*H*$_3$)$_2$CH], 1.28 [m, 1 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.37 (d, J = 6.8 Hz, 3 H, C*H*$_3$CHCOC$_6$H$_4$-CH$_3$), 1.52 [m, 1 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.84 [m, 1 H, CH$_3$CH$_2$-(CH$_3$)C*H*], 2.08 [m, 1 H, (CH$_3$)$_2$C*H*], 2.38 (s, 3 H, C*H*$_3$C$_6$H$_4$), 4.22 (m, 1 H, FmocNHC*H*CONH), 4.40 (m, 3 H, C*H*CH$_2$O and CHC*H*$_2$O), 5.50−5.70 (m, 2 H, NHC*H*CONH and C*H*COC$_6$H$_4$-CH$_3$), 6.16 (d, J = 8.8 Hz, 1 H, FmocN*H*CH), 7.05 (d, J = 6.8 Hz, 1H, CON*H*CH), 7.21−7.90 (m, 13 H, N*H*CHCOC$_6$H$_4$CH$_3$ and Ar−H). FAB$^+$ MS: *m*/*z* (%) 598 (4) [(M + H)$^+$], 435 (4), 277 (2), 178 (100), 165 (35), 164 (22). [α]$^{28}_D$ −207.3° (*c* 12.6, CHCl$_3$). Anal. Calcd for C$_{36}$H$_{43}$N$_3$O$_5$: C, 72.34; H, 7.25; N, 7.03. Found: C, 72.37; H, 7.22; N, 7.00.

Synthesis of Dipeptidyl Ketones 22 and 24. The title compounds were obtained by adopting a procedure similar to that previously described for the preparation of dipeptides **13**−**19**.

Data for 22: 88% yield, white solid, mp 150−153 °C. IR (KBr): ν 3289 cm^{-1}, 2960, 1690, 1643, 1544, 1250, 739. ^{1}H NMR: δ 0.99 ppm [m, 6 H, (C*H*$_3$)$_2$CH], 1.46 [d, J = 7.2 Hz, 3 H, C*H*$_3$CHCOC$_6$H$_4$CH$_3$], 2.19 [m, 1 H, (CH$_3$)$_2$C*H*], 2.44 (s, 3 H, C*H*$_3$C$_6$H$_4$), 4.18 (dd, J_1 = 6.4 Hz, J_2 = 8.8 Hz, 1 H, C*H*CONH), 4.25 (m, 1 H, C*H*CH$_2$O), 4.43 (m, 2 H, CHC*H*$_2$O), 5.57 (m, 1 H, C*H*COC$_6$H$_4$CH$_3$), 5.75 (d, J = 8.8 Hz, 1 H, FmocN*H*CH), 7.15 (d, J = 8.7 Hz, 1H, CON*H*CHCOC$_6$H$_4$CH$_3$), 7.28−7.95 (m, 12 H, Ar−H). FAB$^+$ MS: *m*/*z* (%) 485 (90) [(M + H)$^+$], 365 (6), 322 (8), 263 (43), 165 (96), 164 (100). [α]$^{28}_D$ −304.3° (*c* 8.1, CHCl$_3$). Anal. Calcd for C$_{30}$H$_{32}$N$_2$O$_4$: C, 74.36; H, 6.65; N, 5.78. Found: C, 74.34; H, 6.63; N. 5.80.

Data for 24: 86% yield, white solid, mp 191−194 °C. IR (KBr): ν 3286 cm^{-1}, 2928, 1688, 1644, 1533, 1247, 1020, 732. ^{1}H NMR: δ 1.05 ppm [m, 6 H, (C*H*$_3$)$_2$CH], 1.46 [d, J = 7.0 Hz, 3 H, C*H*$_3$CHCOC$_6$H$_4$CH$_3$], 2.21 [m, 1 H, (CH$_3$)$_2$C*H*], 2.43 (s, 3 H, C*H*$_3$C$_6$H$_4$), 4.17 (m, 1 H, C*H*CONH), 4.24 (m, 1 H, C*H*CH$_2$O), 4.41 (m, 2 H, CHC*H*$_2$O), 5.56 (m, 1 H, C*H*COC$_6$H$_4$CH$_3$), 5.62 (d, J = 8.6 Hz, 1 H, FmocN*H*CH), 7.15 (d, J = 6.9 Hz, 1 H, CON*H*CHCOC$_6$H$_4$CH$_3$), 7.28−7.93 (m, 12 H, Ar−H). FAB$^+$ MS: *m*/*z* (%) 485 (35) [(M + H)$^+$], 365 (1), 322 (1), 263 (7), 179 (100), 178 (61), 165 (16), 164 (14). [α]$^{28}_D$ −274.3° (*c* 2.4, CHCl$_3$). Anal. Calcd for C$_{30}$H$_{32}$N$_2$O$_4$: C, 74.36; H, 6.65; N, 5.78. Found: C, 74.38; H, 6.68; N. 5.75.

Synthesis of *N*-Acetyl Derivatives 25 and 26. The title compounds were obtained by adopting a procedure similar to that previously described for the preparation of **5**.

Data for 25: 85% yield, white solid, mp 195−197 °C. IR (KBr): ν 3291 cm^{-1}, 2962, 1684, 1634, 1542, 1250,736.^{1}H NMR: δ 0.92 ppm [d, J = 6.7 Hz, 6 H, (C*H*$_3$)$_2$CH], 1.41 [d, J = 7.3 Hz, 3 H, C*H*$_3$CHCOC$_6$H$_4$CH$_3$], 2.04 [s, 3 H, C*H*$_3$CO], 2.09 [m, 1 H, (CH$_3$)$_2$C*H*], 2.42 (s, 3 H, C*H*$_3$C$_6$H$_4$), 4.45 (dd, J_1 = 6.8 Hz, J_2 = 8.7 Hz, 1 H, C*H*CONH), 5.53 (m, 1 H, C*H*COC$_6$H$_4$CH$_3$), 6.75 (d, J = 8.7 Hz, 1 H, CH$_3$CON*H*CH), 7.28 (d, J = 8.5 Hz, 2 H, Ar−H), 7.34 (d, J = 7.0 Hz, 1 H, CON*H*CHCOC$_6$H$_4$CH$_3$), 7.90 (d, J = 8.5 Hz, 2 H, Ar−H). FAB$^+$ MS: *m*/*z* (%) 327 (7) [(M + Na)$^+$], 305 (50) [(M + H)$^+$], 263 (9), 185 (3), 164 (100), 142 (21). GC−MS: 185 (23), 168 (5), 142 (55), 119 (34), 114 (72), 91 (24), 72 (91), 55 (18), 44 (100). Anal. Calcd for C$_{17}$H$_{24}$N$_2$O$_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.05; H, 7.97; N. 9.18.

Data for 26: 83% yield, white solid, mp 187−189 °C. IR (KBr): ν 3282 cm^{-1}, 2966, 1686, 1636, 1542, 1250,740.^{1}H NMR: δ 0.97 ppm [m, 6 H, (C*H*$_3$)$_2$CH], 1.43 [d, J = 6.8 Hz, 3 H, C*H*$_3$CHCOC$_6$H$_4$CH$_3$], 2.02 [s, 3 H, C*H*$_3$CO], 2.12 [m, 1 H, (CH$_3$)$_2$C*H*], 2.42 (s, 3 H, C*H*$_3$C$_6$H$_4$), 4.45 (m, 1 H, C*H*CONH), 5.53 (m, 1 H, C*H*COC$_6$H$_4$CH$_3$), 6.61 (d, J = 6.8 Hz, 1 H, CH$_3$-CON*H*CH), 7.28 (d, J = 8.0 Hz, 2 H, Ar−H), 7.36 (d, J = 7.3 Hz, 1 H, CON*H*CHCOC$_6$H$_4$CH$_3$), 7.88 (d, J = 8.0 Hz, 2 H, Ar−H). FAB$^+$ MS: *m*/*z* (%) 327 (11) [(M + Na)$^+$], 305 (52) [(M + H)$^+$], 263 (2), 185 (9), 164 (100), 142 (22). GC−MS: 185 (23), 168 (5), 142 (53), 119 (32), 114 (69), 91 (23), 72 (86), 55 (18), 44 (100). Anal. Calcd for C$_{17}$H$_{24}$N$_2$O$_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.10; H, 7.94; N. 9.18.

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