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Activation of N,N-*bis*(alkoxycarbonyl) Amino Acids. Synthesis of N-Alkoxycarbonyl Amino Acid N-Carboxyanhydrides and N,N-Dialkoxycarbonyl Amino Acid Fluorides, and the behavior of these Amino Acid Derivatives.

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Abstract: Series of Boc- and Cbz-NCAs (**2**), and of N,N-*bis*(alkoxycarbonyl) amino acid fluorides U_2AAFs (**3**) have been prepared by activation of N,N-*bis*-Boc- and N-Cbz,N-Boc-α-amino acids (**1**) with the Vilsmeier reagent or cyanuric fluoride. The absence of epimerization of **2** and **3** during both their formation and their coupling under standard conditions of peptide synthesis had been demonstrated by optical purity Young's tests. In other activated derivatives of *bis*-urethane protected activated amino acids, the exchangeability of the α-H is shown by the considerable racemization of Boc_2Phe-OSu (**8**) in the presence of base, and by the formation of a Dakin-West type product **11** from the dipeptide Boc_2Phe-Leu-OBn.

INTRODUCTION

Since the introduction by Fuller *et al.*[1] of urethane-protected amino acid N-carboxyanhydrides (UNCAs), these activated amino acids have been shown to be peptide bond forming reagents of choice in either the solid phase[2] or the classical liquid phase[3] peptide synthesis procedures. The main advantage of the UNCAs is their efficiency in the coupling step during which they generate only carbon dioxide as byproduct.

In this paper we report in full an efficient alternative preparation[4] (Figure 1) of Boc- and Cbz-NCAs (**2**) from N,N-bis(alkoxycarbonyl) amino acids (**1**) (U_2AAOH), and the synthesis of N,N-bis(alkoxycarbonyl) amino acid fluorides (**3**) (U_2AAF) which are useful acylating reagents of neutral and anionic nucleophiles. We present also the improved preparation of some new starting U_2AAOHs from the corresponding allyl esters and some unusual observations on the t-butyloxycarbonylation of the peptide bond with the $(Boc)_2O$/DMAP reagent.

For structural reasons,[5] neither UNCAs nor activated derivatives of U_2AAOH can racemize during a coupling reaction through the usual oxazolone mechanism. We were therefore surprised to find that N,N-bis-Boc-L-Phenylalanine 1-succinimidyl ester (Boc_2-L-Phe-OSu) (**8**) racemized to the extent of 37% when coupled, although under severe conditions, to proline. For this reason we present here direct evidence

(Young's test[6a,b]) that under standard peptide synthesis conditions UNCAs and U_2AAFs of usual amino acids do not racemise to any significant extent.

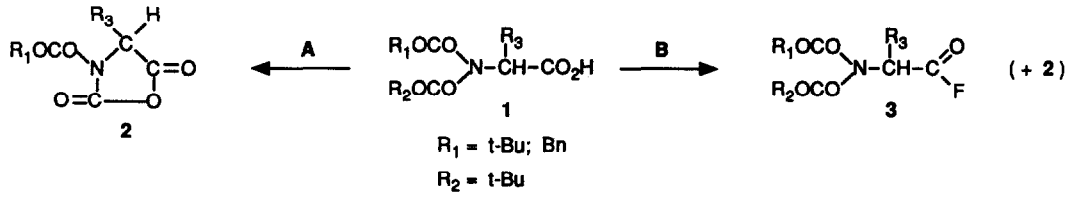


Figure 1: Formation of Boc- and Cbz-NCAs (2), and of U_2AAFs (3) from U_2AAOHs (1). Path A: DMF/$SOCl_2$/pyridine/CH_3CN. Path B: cyanuric fluoride/pyridine/CH_2Cl_2.

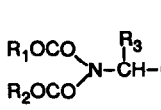
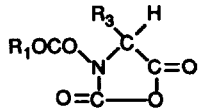
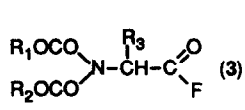
RESULTS

Preparation of the starting N,N-*bis*(alkoxycarbonyl) amino acids: The final step in the preparation of Boc_2AAOHs by catalytic hydrogenolysis over Pd/C of the corresponding benzyl (Bn) esters[5] is straightforward. These compounds are highly crystalline and a possible N-mono-Boc contamination is easily removed through crystallization. However, in the case of N-Cbz,N-Boc amino acids or in the case of a Bn based side chain protection in polyfunctional amino acids, it is necessary to remove the allyl (All) ester protecting the α carboxylic acid function in the presence of Wilkinson's catalyst.[7] We found, as Ragnarsson did[5] in the case of $Boc_2Tyr(Bn)$-OH, that highly lipophilic derivatives such as $Boc_2Ser(OBn)$-OH or **1a-d** (Table 1), were not extracted from AcOEt in saturated aqueous $NaHCO_3$ but that these compounds were to be found in the subsequent water washes. We have thus developped a routine procedure giving good yields of any U_2AAOHs (see experimental).

Synthesis of Boc- and Cbz-amino acid N-Carboxyanhydrides: The action of the Vilsmeier reagent $SOCl_2$/DMF[8] (Figure 1, path A) on the pyridinium salts of Boc_2AAOHs gave persistently almost quantitative yields of the corresponding Boc-NCAs. After extraction and drying, evaporation gave either a solid or an oil which spontaneously crystallized. The crude product is obtained in over 95% yields with physical constants comparable to those of the analytically pure material (Table 1).

In the case of mixed Cbz,BocAAOHs, the action of the reagent gave exclusively the corresponding Cbz-NCA. It appears that in **4b** (R_1 = Bn, R_2 = *t*-Bu) the participation of a *tert*-butyl carbamate is preferred to that of a benzyl carbamate, probably because of the higher stability of a tertiary carbonium ion. To obtain good yields of Cbz-NCAs it is preferable to conduct the reaction at 0°C and for longer periods than for the preparation of Boc-NCAs. No formation of Cbz-Glu(OBu^t)-NCA from (**1b**) could be observed. Most probably the intermediary acid chloride (**4b**) preferentially cyclized with the side chain γ t-butylester to give the cyclic anhydride.[9]

Synthesis and aminolysis of N,N-*bis*(alkoxycarbonyl) amino acid fluorides: Applying the conditions used by Carpino[10] for the preparation of N-Boc amino acid fluorides, we previously found[4] that

Table 1. Properties[a] of  (1),  (2) and  (3)

Compound	R_1	R_2	R_3	Yield %[b]	Recryst. solvent[c]	mp °C	$[\alpha]_D$[d]
1a	t-Bu	t-Bu	CH_2CO_2Bn	77	A	128-130	-55.2° c 1, DMF
1b	Bn	t-Bu	$CH_2CH_2CO_2$-t-Bu	76[e]	A[e]	138-140[e]	-20.7° c 1, DMF[e]
1c	Bn	t-Bu	CH_2Ph	66	B	68-70	-119.3° c 1, DMF
1d	t-Bu	t-Bu	$(CH_2)_4N(Cbz,Boc)$	71[f]		oil	-19.6° c 2.3, DMF[g]
2a	t-Bu		CH_2CO_2Bn	82	A	106-108	+35.1° c 1.8, THF
2b[h]	t-Bu		CH_2OBn	89	A	99-100	+52.3° c 1.0, THF
2c	t-Bu		$(CH_2)_4N(Cbz,Boc)$	61[i]	A	122-124	+33.0° c 1.0, THF
2d	Bn		H	87	C	130-132	
3a	t-Bu	t-Bu	CH_2CO_2Bn	62		oil	-48.5° c 1, AcOEt
3b	t-Bu	t-Bu	$(CH_2)_4N(Cbz,Boc)$	85[f]		oil	-19.3° c 1.4, AcOEt
3c	Bn	t-Bu	H	76	D	36-38	
3d	Bn	t-Bu	$CH_2CH_2CO_2$-t-Bu	89		oil	-40.1° c 1.2, AcOEt
1e	N-Benzoyl-,N-Boc-Leu-OH			72	E	124-126	-40.1° c 1, DMF
2e	N-Benzoyl-Leu-NCA			85	A	134-136	+272.3° c 0.5 THF
3e	N-Benzoyl,N-Boc-Leu-F			91	D	38-40	-59.2 c 1.8, AcOEt

[a]The properties of other 2s and 3s have been reported in reference 4. [b]Yields of analytically pure compounds except for **1d**. Elemental analyses and NMR parameters are reported in the experimental part. [c]A: AcOEt/n-hexane; B: MeOH/H_2O; C: CH_2Cl_2; D: n-hexane; E: AcOH/H_2O. [d]$[\alpha]_D^{25}$ for compounds **1** and **2**, and $[\alpha]_D^{22}$ for compounds **3**. [e]Dicyclohexylammonium salt of **1b**. [f]Crude product. [g]$[\alpha]_D$ of a pure sample isolated by preparative silica gel TLC in CH_2Cl_2-MeOH-AcOH 40:1:0.5. [h]Compound **2b** has been reported to be prepared in 52% yield (reference 1b) with mp 99-99.5°C and $[\alpha]_D$= + 47.2° (reference 1a). [i]Yield of analytically pure compound obtained from crude **1d**.

the action of cyanuric fluoride on U_2AAOH (Figure 1, path B) led to the formation of U_2AAFs (**3**). Depending on the reaction temperature, parallel side reactions to those observed[10] in the case of N-monoprotected amino acids occurred in our case. Thus at 20°C up to 35% of UNCAs (**2**) were formed as contaminants. At low reaction temperatures (-50 to -30°C) this side reaction is minimized and the crude product is usually made up of 90% U_2AAF, 5% UNCA and 5% of starting material U_2AAOH. Reaction in the presence of larger amounts of cyanuric fluoride did not eliminate the free acid. Thus the presence of this last contaminant is probably due to the hydrolysis of the fluoride during work-up. On the other hand, once formed, the U_2AAFs do not cyclize to the UNCAs, neither under heating, nor in the presence of tertiary base. Thus the presence of UNCAs as contaminants of the reaction is probably due to the cyclization of the

intermediary activated ester (**4c**).

In contrast to the action of the $SOCl_2$/DMF reagent, cyanuric fluoride reacts with Cbz,Boc-Glu(OBu^t)-OH (**1b**) following the normal pathway[9] to yield the expected fluoride (**3d**). Owing to the poor crystallization properties of the U_2AAFs, it is best to use the crude products, obtained in over 90% yields, for synthetic purposes. However, in a number of cases, analytically pure crystalline compounds could be obtained (Table 1). As an example of the aminolysis of N,N-*bis*(alkoxycarbonyl) amino acid fluorides we reported the preparation in 80% yield of Boc_2Phe-Leu-OBn by coupling Boc_2Phe-F with H-Leu-OBn.[4] Very recently, the group of Carpino,[11] extended the preparation and the aminolysis of a few Boc_2AAFs. The authors have shown that these derivatives withstand a chromatographic purification on silica gel and that they can be used in peptide synthesis. Because of the small size of the fluorine atom, U_2AAFs couple with little steric hindrance to amino acid esters[4,11] in contrast to other carboxyl activated U_2AAOHs.[5]

Acylation of pyrrole derivatives with N,N-*bis*(alkoxycarbonyl) amino acid fluorides: Acetylation or t-butoxycarbonylation of pyrrole is easily accomplished by acetic anhydride or $(Boc)_2O$ in the presence of DMAP,[12,13] but a parallel acylation of pyrrole derivatives in the presence of DMAP using symmetrical Boc-Phenylalanine anhydride failed. Standard coupling procedures (mixed anhydrides, DCC, UNCAs, etc...) also fail to form an amide bond between an N-protected amino acid and the nitrogen of a neutral pyrrole derivative. On the other hand N-acylation of pyrrole anions by acyl chlorides is well documented.[14] N-Phthaloyl-Phenylalanine chloride was used successfully to acylate Pyrrole-2-carboxaldehyde.[15] The drawback in this last example is the probable difficulty of removal of the N-protecting phthaloyl group by hydrazinolysis, without rupturing the formed, easily aminolysable,[16] amino acid-pyrrole amide bond.

Using U_2AAFs we were able to acylate efficiently, on the nitrogen, sodium salts of pyrrole-2-derivatives. Thus we have prepared the N-(Boc_2-phenylalanyl)-2-pyrrolecarboxylic acid benzyl ester (**5a**) and the N-(Boc,Cbz-phenylalanyl)-2-pyrrolecarboxylic acid t-butyl ester (**5b**), as well as the aldehyde **6** and the "depsipeptide ester" **7**. These pyrrole peptide analogs contain easily removable protecting groups.

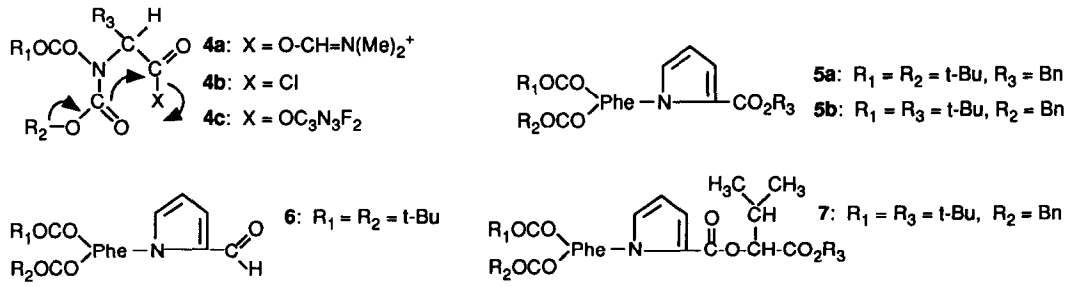


Figure 2. (**4**): Possible reaction intermediates leading to UNCAs. (**5,6,7**): N-acylated pyrrole derivatives.

Young's tests of racemization of N-benzoyl-L-Leu-NCA and of N-benzoyl,N-Boc-L-Leu-F: The considerable racemization observed during the coupling of Boc_2-L-Phe-OSu to proline (see below), prompted

us to perform assays of optical purity for couplings of our fully nitrogen protected NCAs and fluorides. We submitted N-benzoyl-L-Leu-NCA (**2e**), obtained from **1e**, to the Young test.[6a,b] In this very sensitive assay the widely used DCC/HOBt method for segment coupling leads to more than 24% epimerization in DMF.[6b]

Coupling of **2e** to HCl·H-Gly-OEt in DMF in the presence of N-methylmorpholine (NMM) led to an ee of 98.2% of isomer L (Table 2). Thus, not only N-protected NCAs couple without any significant racemization, but the assays prove also that our synthetic method leads to Boc- and Cbz-NCAs of great optical integrity.

Coupling of Benzoyl,Boc-L-Leu-F (**3e**) with HCl·H-Gly-OEt in CH_2Cl_2 or DMF, in the presence of NMM or NEt_3, followed by trifluoroacetolysis of the Boc group, doesn't lead, either, to any significant racemization (Table 2).

Table 2. Young's tests of racemization of N-Benzoyl-L-Leu-NCA (**2e**) and of N-Benzoyl,N-Boc-L-Leu-F (**3e**).

A: **2e** + 1eq. tert. amine + HCl · H-Gly-OEt ⟶ Benzoyl-Leu-Gly-OEt

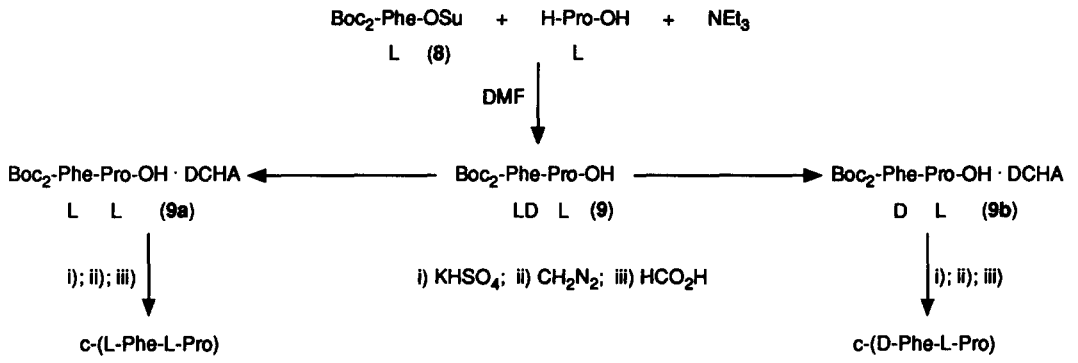
B: **3e** + 2eq. tert. amine + HCl · H-Gly-OEt ⟶ Benzoyl,Boc-Leu-gly-OEt $\xrightarrow{TFA}$ Benzoyl-Leu-Gly-OEt

	coupling reagent	solvent	tertiary amine	Benzoyl-Leu-Gly-OEt yield %	Benzoyl-Leu-Gly-OEt e.e. %(L)
A	N-Benzoyl-L-Leu-NCA (**2e**)	CH_2Cl_2	$N(Et)_3$	83	72.9
	- " -	CH_2Cl_2	N-Me Morpholine	85	96.9
	- " -	DMF	N-Me Morpholine	92	98.2
B	N-Benzoyl,N-Boc-L-Leu-F (**3e**)	CH_2Cl_2	N-Me Morpholine	67	91.2
	- " -	CH_2Cl_2	$N(Et)_3$	60	95.3
	- " -	DMF	$N(Et)_3$	59	96.0

Racemization of N,N-bis-Boc-Phenylalanine 1-succinimidyl ester and the formation of a Dakin-West type product during t-butoxycarbonylation of a peptide bond. Because of the very efficient and clean reaction of Boc_2AAOHs with the DMF/$SOCl_2$ reagent to give Boc-NCAs, we investigated the possibility of the dipeptide N-(Boc_2-L-Phenylalanyl)-L-Proline (**9a**), to cyclize under these conditions, to a hypothetical 8-membered cyclic Boc-dipeptide-NCA.

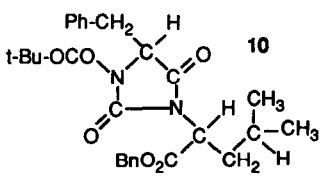
Because of our experience[17] in the preparation of carboxyl free N-protected dipeptides via 1-succinimidyl esters, we reacted Boc_2-L-Phe-OSu (**8**) with free proline in DMF in the presence of NEt_3. The slow reaction gave an almost quantitative yield of the expected, chromatographically homogenous, dipeptide **9** (Scheme 1), but its ^{1}H NMR spectrum showed it to be a mixture of two components in the proportion of 37% and 63%. These two components were efficiently separated via their dicyclohexylammonium (DCHA) salts. The proof of the epimerization of the L-Phenylalanine residue and of the production of a pair of diastereoisomeric dipeptides was obtained (Scheme 1) via the formation of the well-known[18] diketopiperazines c-(L-Phe-L-Pro) and c-(D-Phe-L-Pro). None of the two starting L,L and D,L dipeptides (**9**) cyclized under the action of DMF/$SOCl_2$ and were recovered unchanged.

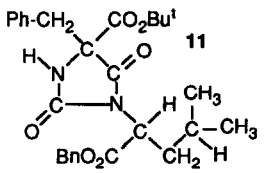
Scheme 1



We also attempted to t-butoxycarbonylate the peptide bond of the dipeptide Boc_2Phe-Leu-OBn intending to submit the *per*-t-butoxycarbonylated dipeptide, after hydrogenolysis of the benzyl ester, to the DMF/$SOCl_2$ reagent. We wondered whether a dipeptide C-terminal NCA could be thus obtained.

While Ragnarsson's group and others have successfully t-butoxycarbonylated a number of urethanes,[5] primary[19a,b] and secondary[20a,b] amides as well as a peptide bond[21] using $(Boc)_2O$ and DMAP as a catalyst, these conditions led in the present case to the formation of two major compounds, **10** and **11**, both of which possessed only one Boc group. Compound **10** was identified as a hydantoin. The formation of hydantoins was already observed[5] during the coupling of Boc_2AAOHs. The structure, obtained by X-ray analysis[22] (Figure 3) of **11** is more surprising. Beside the hydantoin ring, t-butoxycarbonylation occurred at the Cα of the Phenylalanine residue. These types of products do not seem to be reserved to sterically hindered amino acid residues. Thus, N-(Boc_2-Phenylalanyl)-Glycine benzyl ester apparently behaved similarly.





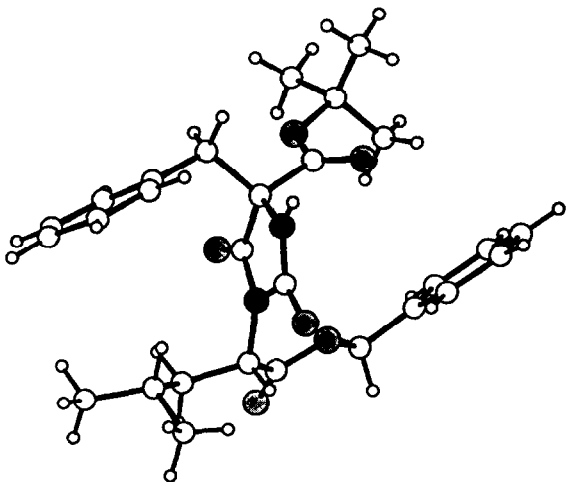


Figure 3. Structures of **10** and **11** with an ORTEP view of **11**.

DISCUSSION

The thermal cyclization of urethane protected amino acid chlorides[23,24] to NCAs has been known for a long time and constitutes one of the methods for the preparation of "Leuchs-anhydrides". We therefore expected that U_2AA-OHs (**1**), under conditions of formation of the corresponding acid chlorides (**4b**), would cyclize to give UNCAs (**2**). When at least one of the alkoxycarbonyl groups in **1** is a Boc group, the cyclization reaction involving the participation of the *tert*-butyl carbamate occurs under very mild conditions (O°C) leading thus to high yields of UNCAs. The method of preparation of UNCAs presented in this paper is particularly suited for the formation of Boc-NCAs. The cyclization avoids the use of phosgene and of unstable reagents such as the *tert*-butyl chloroformate and NCAs required in the previously described[1] procedure. The Boc-NCAs are easily obtained optically pure in excellent yields. The drawback of our method is the rather lengthy[5] preparation of the U_2AA-OHs, obtained notwithstanding in good yields. Also, Fmoc-amino acid NCAs[1] cannot be obtained by our synthetic route.

While the cyclization of **1** to **2**, in the presence of DMF/$SOCl_2$, proceeds probably through the acid chloride **4b**, the possibility of a cyclization of the reaction intermediate **4a** at an earlier stage, cannot be excluded. In the case of the formation of fluorides **3**, the side reaction leading to UNCAs (**2**) seems to be due to the cyclization of the intermediate ester **4c**, as the fluorides U_2AAFs once formed do not show any tendency to cyclize to the UNCAs.

U_2AAFs (**3**) couple apparently without steric hindrance with amino acid- and peptide-esters.[4,11] These coupling agents, devoid of an exchangeable NH hydrogen, seem to be advantageous for the acylation of anionic nucleophiles, as we have demonstrated during the preparation of "pyrrole containing peptides" **5**, **6** and **7**.

We became aware of the possible racemization of U_2AAFs during coupling reactions, when we observed the strong epimerization of Boc_2Phe-OSu (**8**) during a coupling with Proline in the presence of NEt_3. As racemization of **8** cannot proceed through the oxazolone mechanism,[5] epimerization must have occurred through the triethylamine favored α-H exchange in this derivative (**8**) possessing several electron-withdrawing groups. Under normal peptide bond synthesis conditions, especially when the coupling reaction is fast, as seems to be the case in DMF,[2] the risk of racemization of U_2AAFs (**3**) and UNCAs (**2**) is minimal, as shown by Young's tests using Benzoyl,Boc-L-Leu-F **3e** and Benzoyl-L-Leu-NCA **2e** (Table 2). The problem of racemization, with parallel results to ours, has also been addressed, by different means, by Naider[2] for the UNCAs, and by Carpino[11] for the U_2AAFs.

The formation of the hydantoin **10** and of a Dakin-West type product **11** during the *t*-butyloxycarbonylation of Boc_2Phe-Leu-OBn by $(Boc)_2O$ in the presence of DMAP demonstrates, in our view, the danger of handling peptides possessing a N-terminal *bis*-urethane protected amino acid residue in the presence of a base (DMAP). Urethane protected peptide esters are known to lead to hydantoins[25] during ammonolysis or saponification. Ragnarsson[5] observed the formation of hydantoins during couplings of activated U_2AA-OHs. The formation of the compound **11** is not clear. However we have demonstrated the ease of abstraction by base of the α-H in Boc_2Phe-OSu **8** leading to racemization. It may well be that in the hydantoin **10** the α-H, surrounded by electron-withdrawing groups, is equally labile and allows the acylation of the Phenylalanine α-C.

EXPERIMENTAL

Materials and Methods. Melting points were determined in capillary tubes on a Tottoli apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. ^{1}H-NMR and ^{19}F-NMR spectra were recorded in $CDCl_3$ on a Bruker WM 200 spectrometer. For ^{1}H, chemical shifts are quoted in parts per million downfield from TMS, and for ^{19}F relative to $CFCl_3$. Coupling constants are given in Hz. Optical rotations were obtained on a Perkin-Elmer 421 polarimeter. TLC was carried out on precoated silica gel (F_{254}) plates in the following systems: toluene-CH_3CN 4:1 (A); toluene-CH_3CN 8:1 (B); CH_2Cl_2-MeOH-AcOH 40:1:0.5 (C); toluene-CH_3CN 16:1 (D). Spots were visualized by inspection under UV, ninhydrin after exposure to HCl vapors, and/or chlorine-tolidine reagents. During work-up the organic solutions were dried over $MgSO_4$. t-Butyl 2-pyrrolecarboxylate was purchased from Bachem. All N,N-*bis*-Boc-, N-Cbz,N-Boc-, and N-Benzoyl,N-Boc-α-amino acids benzyl or allyl esters were prepared according to Ragnarsson's[5] procedure and were used crude without attempts at crystallization.

General procedure for the preparation of U_2AA-OHs (1a-d) from the corresponding allyl esters. The allyl esters of *bis*-urethane protected amino acids (10 mmol) were treated with tris(triphenylphosphine)-rhodium (I) chloride (0.7 to 0.9 mmol) added in small portions over 3 to 4h as described.[5] After filtration of the reaction mixture and evaporation to dryness, the residue was taken up in toluene and extracted with 1M $KHCO_3$ (30 ml) and with three water (30ml) washes. This complete extraction cycle was repeated two more times in difficult cases. The combined $KHCO_3$ and water extracts were acidified to pH 2 with 2M H_2SO_4, extracted with AcOEt, washed with water and dried. After evaporation of the solvent, the residue was crystallized as indicated in Table 1. In the case of $(Boc)_2$Tyr(Bn)-OH, reported[5] to be incompletely extracted (less than 5%) by aq. $NaHCO_3$ from an AcOEt solution, our extraction method (toluene, M $KHCO_3$, water) led to an extraction yield of over 80% of an oil which spontaneously crystallized. Recrystallization in ether/n-hexane gave 65% of pure $(Boc)_2$Tyr(Bn)-OH with mp 93-95°C.

Compound **1a**. ^{1}H NMR: δ= 7.27(s, 5H); 5.47(t, 1H); 3.22(dd, 1H, J= 16.8, 7.2); 2.72(dd, 1H, J= 16.8, 6.3); 1.41(s, 18H). Elemental analysis for $C_{21}H_{29}NO_8$ (423.47): calcd. C 59.56%, H 6.90%, N 3.31%; found C 59.61%, H 6.69%, 3.27%.

Compound **1b**. ^{1}H NMR: δ= 7.25-7.32(m, 5H); 5.17(s, 2H); 5.00(dd, 1H, J= 9.1, 5.1); 2.02-2.48(m, 4H), 1.37(s, 9H); 1.38(s, 9H). Elemental analysis of the dicyclohexylammonium salt of **1b** $C_{34}H_{54}N_2O_8$ (618.82): calcd. C 65.99%, H 8.80%, 4.53%; found C 65.78%, H 8.65%, N 4.47%.

Compound **1c**. ^{1}H NMR: δ= 7.15(m, 10H); 5.21(dd, 1H, J= 10.1, 5.3); 5.04(s, 2H); 3.34(dd, 1H, J= 13.8, 5.3); 3.13(dd, 1H, J= 10.1); 1.28(s, 9H). Elemental analysis for $C_{22}H_{25}NO_6$ (399.45): calcd. C 66.15%, H 6.31%, N 3.51%; found C 65.93%, H 6.46%, N 3.38%.

Compound **1d**. ^{1}H NMR: δ= 7.28(m, 5H); 5.14(s, 2H); 4.81(dd, 1H, J= 9.3, 5.0); 3.55(t, 2H, J= 7.3); 1.2-2.1(m, 6H); 1.41(s, 18H); 1.39(s, 9H). Elemental analysis for $C_{29}H_{44}N_2O_{10}$ (580.69): calcd. C 59.98%, H

7.64%, N 4.83%; found C 60.05%, H 7.54%, N 4.69%.

Compound **1e.** This derivative was obtained by catalytic hydrogenolysis over Pd/C of the corresponding benzyl ester. 1H NMR: δ= 7.3-7.5(m, 5H); 5.12(dd, 1H, J= 9.2, 5.5); 1.9-2.1(m, 2H); 1.60(m, 1H); 1.09(s, 9H); 0.97(t, 6H, J= 7.0). Elemental analysis for $C_{18}H_{25}NO_5$ (335.41): calcd. C 64.46%, H 7.51%, N 4.18%; found C 64.54%, H 7.45%, N 4.14%.

General procedure for the preparation of Boc-NCAs (2a-c). Dry DMF (10 mmol) was cooled to 0°C, $SOCl_2$ (10 mmol) was added under exclusion of moisture and the mixture was left to stand at room temperature for 30min. Boc_2AA-OH (10 mmol), dissolved in dry CH_3CN (10 ml) in the presence of dry pyridine (10 mmol), was cooled to 0°C and added to the DMF/$SOCl_2$ reagent at 0°C. The mixture was left to stir in an ice bath for 30min, then at 20°C for 2h and finally poured into ice cold water. The product was extracted in AcOEt, the organic layer was washed three times with water and dried. After evaporation of the solvent, the product (≥95% yield) is usually obtained as a solid or an oil which spontaneously crystallizes. Recrystallization gave analytically pure Boc-NCAs.

Compound **2a.** ^{1}H NMR: δ= 7.48(m, 5H); 5.30(s, 2H); 4.87(dd, 1H); 3.54(dd, 1H, J=17.8, 4.6); 3.29(dd, 1H, J= 17.8, 3.1); 1.67(s, 9H). Elemental analysis for $C_{17}H_{19}NO_7$ (349.35): calcd. C 58.45%, H 5.48%, N 4.01%; found C 58.61%, H 5.47%, N 3.89%.

Compound **2b.**[1a,b] ^{1}H NMR: δ= 7.22(m, 5H); 4.58(t, 1H); 4.47(dd, 2H); 3.96(dd, 1H, J= 10.0, 2.4); 3.79(dd, 1H, J= 10.0, 2.0); 1.43(s, 9H).

Compound **2c.** ^{1}H NMR: δ= 7.29(m, 5H); 5.13(s, 2H); 4.55(t, 1H, J= 4.9); 3.55(t, 2H, J= 7.1); 1.96(m, 2H); 1.48(s, 9H); 1.38(s, 9H); 1.3(m, 4H). Elemental analysis for $C_{25}H_{34}N_2O_9$ (506.57): calcd. C 59.28%, H 6.76%, N 5.53%; found C 59.12%, H 6.63%, N 5.47%.

General procedure for the preparation of Benzoyl- or Cbz-NCAs (2d,e). Using Benzoyl,Boc-AA-OH or Cbz,Boc-AA-OH, the formation of Benzoyl- or Cbz-NCA proceeds as described above for the preparation of Boc-NCAs, except that the reaction mixture is first left overnight at 0°C and 2h at room temperature.

Compound **2d.** ^{1}H NMR: δ= 7.33(s, 5H); 5.28(s, 2H); 4.46(s, 2H). Elemental analysis for $C_{11}H_9NO_5$ (235.20): calcd. C 56.17%, H 3.86%, N 5.96%; found C 55.97%, H 3.89%, N 5.94%.

Compound **2e.** ^{1}H NMR: δ= 7.4-7.7(m, 5H); 5.07(dd, 1H, J= 4.0, 7.3); 1.8-2.0(m, 3H); 0.94(dt, 6H). Elemental analysis for $C_{14}H_{15}NO_4$ (261.28): calcd. C 64.36%, H 5.79%, N 5.36%; found C 64.42%, H 5.79%, N 5.34%.

General procedure for the preparation of U_2AA-Fs. U_2AA-OH (10 mmol), dissolved in dry CH_2Cl_2 (25 ml) in the presence of dry pyridine (10 mmol), was cooled to -50°C under argon. Cyanuric fluoride (10

mmol) was added in 5 portions over 5min. The temperature of the stirred reaction mixture was allowed to rise and was kept at -30°C for 1h and then at -10° to 0°C for 1h. The mixture, containing a precipitate, was diluted with cold CH_2Cl_2 and washed three times with ice cold water. After drying, the solvent was evaporated and the residual oil was further evacuated for 1h under high vacuum. ^1H NMR shows that the crude products (oil; ca. 95% yield) contain about 90% of the fluoride contaminated in equal parts by starting material and the corresponding Boc-NCA. The crude products were used as such in further syntheses. When possible, the fluorides were crystallized by leaving the product in the quoted solvent mixture (Table 1) for two days in the deep-freeze, decanting at -30°C the crystallization solvent and drying the crystals.

Compound **3a**. ^1H NMR: δ= 7.3(m, 5H); 5.7(m, 1H); 5.1(s, 2H); 3.2(dd, 1H, J= 17.0, 7.2); 2.8(ddd, 1H, J= 17.0, 6.2, 2.3); 1.4(s, 18H). ^{19}F NMR: δ= 24.6(dd, 1F, J= 5.2, 2.3). Elemental analysis for $C_{21}H_{28}FNO_7$ (425.46): calcd. C 59.28%, H 6.63%, N 3.29%; found C 59.26%, H 6.39%, N 3.37%.

Compound **3b**. ^1H NMR: δ= 7.3(m, 5H); 5.14(s, 2H); 4.5(dt, 1H, J= 4.7, 9.0); 3.56(t, 2H, J= 7.7); 1.6(m, 6H);1.41(s, 18H); 1.39(s, 9H). ^{19}F NMR: δ= 27.0(d, J= 4.7). Elemental analysis for $C_{29}H_{43}FN_2O_9$ (582.68): calcd. C 59.78%, H 7.44%, N 4.81%; found C 59.52%, H 7.21%, N 5.06%.

Compound **3c**. ^1H NMR: δ= 7.30(s, 5H); 5.19(s, 2H); 4.52(d, 2H, J= 3.7); 1.40(s, 9H). ^{19}F NMR: δ= 25.28(d, 1F, J= 3.7). Elemental analysis for $C_{15}H_{18}FNO_5$ (311.32): calcd. C 57.87%, H 5.83%, N 4.50%; found C 57.99%, H 5.90%, N 4.33%.

Compound **3d**. ^1H NMR: δ= 7.31(m, 5H); 5.19(q, 2H); 5.19(m, 1H); 2.0-2.5(m, 4H); 1.38(s,9H); 1.36(s, 9H). ^{19}F NMR: δ= 27.14(d, 1F, J= 4.7). Elemental analysis for $C_{22}H_{30}FNO_7$ (439.49): calcd. C 60.13%, H 6.88%, N 3.19%; found C 59.85%, H 6.59%; N 3.32%.

Compound **3e**. ^1H NMR: δ= 7.41(m, 5H); 5.23(m, 1H); 1.95(m, 2H); 1.68(m, 1H); 1.1(s, 9H); 0.94(dt, 6H). ^{19}F NMR: δ= 27.46(d, 1F, J=5.0). Elemental analysis for $C_{18}H_{24}FNO_4$ (337.40): calcd. C 64.08%, H 7.17%, N 4.15%; found C 64.33%, H 7.37%, N 4.11%.

Young's tests of racemization. *Tests using* **2e**: To HCl·H-Gly-OEt (1 mmol) in DMF or CH_2Cl_2 (5ml) was added NEt_3 or NMM (1 mmol) followed by N-Benzoyl-L-Leu-NCA **2e** (1 mmol). The mixture was stirred for 2h at 2O°C and after dilution with AcOEt the solution was washed successively with water (2x), sat. aq. $NaHCO_3$ (2x), N HCl (2x), and with water to neutrality. After drying, evaporation of the solvent gave Bz-Leu-Gly-OEt as a solid which was dried to constant weight. Yields and e.e.% are given in Table 2.

Tests using **3e**: The coupling of N-Benzoyl-,N-Boc-L-Leu-F **3e** (1 mmol) with HCl·H-Gly-OEt (1mmol) was performed as above, but in the presence of 2 eq. (2 mmol) of NEt_3 or NMM. The usual work-up gave (Boc,Bz)-Leu-Gly-OEt as an oil which was treated with TFA (3ml) at 20°C for 45min. After evaporation, the resulting oil was dissolved in AcOEt and was washed with sat. aq. $NaHCO_3$, N HCl, and water. Drying and evaporation of the solvent gave Bz-Leu-Gly-OEt. Yields and e.e.% are reported in Table 2.

1-(Boc_2-phenylalanyl)-2-pyrrolecarboxylic acid benzyl ester (5a). Benzyl 2-pyrrolecarboxylate[26] (1mmol) in dry THF (1ml) was added under argon to NaH (1mmol; 60% dispersion in mineral oil). To the cooled mixture (0°C) was added a solution of Boc_2Phe-F[4] (1mmol) in THF (4ml) over 15min. The mixture was left to stir at 0°C 30min and at room temperature overnight. After dilution with AcOEt the solution was washed with 2M $KHSO_4$, with water, and dried. On evaporation of the solvent, 125mg of the resulting oil (523mg) were dissolved in CH_2Cl_2, applied to preparative TLC plates and developped in solvent B. The band at R_{fB} 0.78 (followed by R_{fB} 0.57 = benzyl 2-pyrrolecarboxylate) was eluted with CH_2Cl_2 and the solvent evaporated to dryness. The product (oil; 88mg) gave an analysis calcd for $C_{31}H_{36}N_2O_7$ (548.64): C 67.87%, H 6.61%, N 5.11%; found C 67.58%, H 6.64%, N 4.85%. ^{1}H-NMR: δ= 1.24(s, 18H); 3.35(oct, 2H, J= 14.2, 10, 5.7); 5.21(q, 2H); 5.86(q, 1H); 6.11(t, 1H); 6.90(m, 1H); 7.12-7.33(m, 11H, $2C_6H_5$+pyrrole).

1-(Boc,Cbz-phenylalanyl)-2-pyrrolecarboxylic acid t-butyl ester (5b). t-Butyl 2-pyrrolecarboxylate (1mmol) was treated with NaH (1mmol) and with Boc,CbzPhe-F[4] (1mmol) in the same manner as described for the preparation of **5a** to give an oil (495mg). Application of 160mg of this oil on preparative TLC plates and development in solvent B, gave, after elution of the band at R_{fB}0.71, an oil (125mg). Elemental analysis for $C_{31}H_{36}N_2O_7$ (548.64): calcd. C 67.87%, H 6.61%, N 5.11%; found C 67.57%, H 6.64%, N 4.83%. ^{1}H-NMR: δ= 1.19(s, 9H); 1.47(s, 9H); 3.31(oct, 2H, J= 14.1, 10, 5.5); 4.99(s, 2H); 5.92(q, 1H); 6.04(t, 1H); 6.77(m, 1H); 7.14(m, 11H, $2C_6H_5$+pyrrole).

1-(Boc_2-phenylalanyl)-2-formyl-pyrrole (6). 2-Formyl-pyrrole (1mmol) was acylated in the presence of NEt_3 (1mmol) in the same manner as described for the preparation of **5a** to give an oil (362mg). Application of 150mg of this oil on preparative TLC plates and development in CH_2Cl_2/AcOEt 20:1 gave, after elution of the band at R_f0.64, an oil which crystallized. Recrystallization in n-hexane gave **6** (88mg), mp 105-107°C. Elemental analysis for $C_{24}H_{30}N_2O_6$ (442.52): calcd. C 65.14%, H 6.83%, N 6.33%; found C 65.19%, H 6.87%, N 6.36%. ^{1}H NMR: δ= 10.10(s, 1H); 7.1-7.3(m, 7H); 6.21(t, 1H); 5.59(dd, 1H, J= 10.0, 5.4); 3.48(dd, 1H, J= 5.4, 14.3); 3.25(dd, 1H, J= 10.0, 14.3); 1.25(s, 9H).

1-(Boc,Cbz-phenylalanyl)-pyrrol-2-ylcarbonyl-α-oxy-isovaleric acid t-butyl ester (7). Pyrrole-2-carboxylic acid chloride[27] (5mmol) in CH_2Cl_2 (10ml) was added at 20°C over 1h to a solution of α-hydroxy-isovaleric acid t-butyl ester[28] (5mmol) and of DMAP (5mmol) in CH_2Cl_2 (10ml). The mixture was left to stir overnight, the DMAP hydrochloride formed was filtered off and the solvent evaporated to dryness. A small amount of the cyclic dimer of the acid chloride (Pyrocoll)[27] was removed by precipitation in n-hexane. After evaporation of the solvent, the resulting oil was heated under vacuum (60°C/3x10^{-3}mm Hg) to remove any unreacted t-butyl ester of α-hydroxy-isovaleric acid. (1mmol) of the obtained (oil, 53% yield), crude pyrrol-2-ylcarbonyl-α-oxo-isovaleric acid t-butyl ester [^{1}H NMR: δ= 9.4(s, 1H); 6.92(m, 2H); 6.20(q, 1H); 4.85(d, 1H, J= 4.4); 2.24(m, 1H); 1.40(s, 9H); 0.98(d, 6H, J= 6.9)] and Boc,CbzPhe-F (1mmol) were treated in the same manner as described for the preparation of **5a** to give an oil (503mg). Application of 155mg of this oil on preparative TLC plates and development in toluene/CH_3CN 32:1 gave, after elution with AcOEt of the band at R_f0.33, the compound **7** as an oil (62mg). Elemental analysis for $C_{36}H_{44}N_2O_9$·1/2AcOEt (646.77 + 44.05): calcd. C 65.88%, H 6.98%, N 4.32%; found C 65.81%, H 6.99%, N 4.19%. ^{1}H NMR: δ= 6.97-7.27(m, 12H); 6.10(t, 1H); 5.87(dd, 1H, J= 5.4, 9.7); 5.03(q, 2H); 4.86(d, 1H, J=

4.4); 3.34(dd, 1H, J= 5.4, 14.3); 3.21(dd, 1H, J= 9.7, 14.3); 2.21(m, 1H); 1.41(s, 9H); 1.21(s, 9H); 0.98(d, 6H).

Boc_2Phe-Leu-OBn. To a solution of Ts-OH·H-Leu-OBn (1.97g, 5mmol) in CH_2Cl_2 (30ml) was added NMM (2eq., 1.1ml, 10mmol) and Boc_2Phe-F[4] (crude product, 1.84g, 5mmol) in CH_2Cl_2 (5mmol). The mixture was stirred at room temperature for 1h, the solvent evaporated and the residue dissolved in AcOEt. After washing with 2M $KHSO_4$, M $KHCO_3$ and water, the organic phase was dried and evaporated to dryness to give an oil which solidified: 2.47g (87%), mp 55-59°C, R_{fA}0.62. Recrystallization from MeOH-H_2O gave 2.24g (79%), mp 62-64°C, $[\alpha]_D^{25}$= -68.7°(1; MeOH). Lit.[5]: mp 62.5-63°C; $[\alpha]_D^{25}$= -68° (0.98; MeOH).

Boc_2Phe-OSu (8). N-Hydroxysuccinimide (1.15g; 10mmol) and Boc_2Phe-OH[29] (3,65g; 10mmol) were dissolved in CH_3CN (30ml), cooled to -5°C and a cold solution of DCC (2.06g; 10mmol) in CH_3CN (10ml) was added. The mixture was stirred 30min at -5°C and overnight at room temperature. The dicyclohexylurea formed was filtered off, the solvent evaporated to dryness and the resulting oil triturated in isopropanol. The crystalline product (3.93g; 85%) had an mp 127-128°C, $[\alpha]_D^{25}$= -61.7° (1.1, dioxane). Elemental analysis for $C_{23}H_{30}N_2O_8$ (462.50): calcd. C 59.73%, H 6.54%, N 6.06%; found C 59.84%, H 6.58%, N 6.04%. ^{1}H-NMR: δ 1.35(s, 18H); 2.77(br s, 4H); 3.34(oct, 2H, J= 14.0, 10.2, 6.1); 5.48(q, 1H); 7.19(m, 5H).

N(Boc_2-L-Phenylalanyl)-L-Proline and N(Boc_2-D-Phenylalanyl)-L-Proline dicyclohexylammonium salts (9a and 9b). To a suspension of L-proline (1.27g; 11mmol) in DMF (15ml) was added NEt_3 (1.53ml; 11mmol) followed by (**8**) (4.62g; 10mmol) and the reaction mixture was stirred at room temperature (48h) until most of the suspended proline went into solution. This solution was diluted with AcOEt, washed with 2M $KHSO_4$, with water, and dried. Evaporation of the solvent gave an oil (4.48g; 97%), R_{fC}0.32, which proved to be (see below) a diastereoisomeric mixture of the required dipeptide **9**. The proportion of the L-L (63%) and D-L (37%) isomers was measured on the ^{1}H-NMR spectrum by integration of either the Pro H_αs or the Boc groups [L,L isomer: H_αPro δ = (d) 3.99, Boc δ = (s) 1.30; D,L isomer: H_αPro δ = (t) 4.49, Boc δ = (s) 1.23]. The oil, containing the two diastereoisomers, was dissolved in ether and dicyclohexylamine (DCHA) (1.1 eq., 2.12ml, 10.6mmol) was added. Boc_2-D-Phe-L-Pro-OH DCHA (**9b**) crystallized out, was filtered off, washed with ether and recrystallized in AcOEt. Yield 1.80g (29%), mp 184-186°C. Elemental analysis for $C_{36}H_{57}N_3O_7$ (643.88): calcd. C 67.16%, H 8.92%, N 6.53%; found C 66.93%, H 8.81%, N 6.47%.

The above ethereal mother liquor, left after the elimination of the D-L isomer, was evaporated to dryness. On trituration of the residue in n-hexane, the Boc_2-L-Phe-L-Pro-OH DCHA (**9a**) crystallized out. Recrystallization from n-hexane gave 2.85g (46%), mp 134-136°C. Elemental analysis for $C_{36}H_{57}N_3O_7$ (643.88): calcd. C 67.16%, H 8.92%, N 6.53%; found C 67.02%, H 8.78%, N 6.43%.

***cyclo*-(L-Phe-L-Pro).**[18] **9a** (1.93g; 3mmol), obtained above, was suspended in AcOEt, washed with 2M $KHSO_4$, with water, and the organic layer dried. Evaporation of the solvent gave the dipeptide with a free C-terminal carboxyl: oil, 1.33g (96%), ^{1}H-NMR: δ= 1.30(s, 18H); 1.6-2.4(m, 4H); 3.27(oct, 2H, J= 14.5, 10.1, 5.3); 3.40(m, 2H); 3.99(d, 1H); 5.07(q, 1H, J= 10.1, 5.3); 7.08(m, 5H).

After treating this dipeptide in ether with diazomethane in the usual manner, the obtained methyl ester Boc_2-L-Phe-L-Pro-OMe 1.36g, R_{fC} 0.69, was left to stir at room temperature in 98% formic acid (50ml) for

3h, to remove the Boc protecting groups.[30] After evaporation of the solvent, the dipeptide ester formate (oil) was left overnight under vacuum in the presence of KOH pellets. The oil was dissolved in EtOH and refluxed for 6h, the solvent was evaporated to dryness and the residue was recrystallized twice from AcOEt to give *c*-(L-Phe-L-Pro) 0.43g (62%), mp 131-133°C, $[\alpha]_D^{25}$= -84.0° (0.2; H_2O), R_{fC} 0.40. ^{1}H-NMR: δ= 2.73(q, 1H, $H_{\beta A}$Phe, $J_{H\beta AH\alpha}$= 10.3); 3.53(q,1H, $H_{\beta B}$Phe, $J_{H\beta BH\alpha}$= 3.8). Lit.[18] mp 134-136°C, $[\alpha]_D^{25}$= -82.3° (0.2; H_2O. ^{1}H-NMR:δ= 2.79(1H_βPhe, $J_{H\beta H\alpha}$= 10.5); 3.61(1H_βPhe, $J_{H\beta H\alpha}$= 4.O).

***cyclo*-(D-Phe-L-Pro).**[18] **9b** was freed from its DCHA salt as described for the L-L isomer. The free acid gave ^{1}H-NMR: δ= 1.23(s, 18H); 1.5-2.5(m, 4H); 3.16(oct, 2H, J= 14.2, 8.9, 6.0); 3.29(m, 2H); 4.49(t, 1H); 4.92(q, 1H, J= 6.0, 8.9); 7.06(m, 5H).

The esterification with diazomethane, the removal of the Boc groups and the cyclization to the diketopiperazine proceeded as described for the preparation of the L-L isomer. The *c*-(D-Phe-L-Pro) obtained after two recrystallizations from AcOEt (33% yield) had a mp 146-148°C, $[\alpha]_D^{25}$= -96.6° (0.2; H_2O), R_{fC} O.22, ^{1}H-NMR: δ= 2.98(q, 1H, $H_{\beta A}$Phe, $J_{H\beta AH\alpha}$= 4.3); 3.12(q, 1H, $H_{\beta B}$Phe, $J_{H\beta BH\alpha}$= 5.8). Lit.[18] mp 150-153°C, $[\alpha]_D^{25}$= - 94.2° (0.2; H_2O). ^{1}H-NMR: δ= 3.02(1H_βPhe, $J_{H\beta H\alpha}$= 4.5); 3.19(1H_βPhe, $J_{H\beta H\alpha}$= 5.5).

t-Butyloxycarbonylation of Boc_2Phe-Leu-OBn. Formation of 10 and 11. To Boc_2Phe-Leu-OBn (853mg; 1.5mmol) in dry CH_3CN (4ml) was added DMAP (18mg; O.15mmol) and $(Boc)_2O$ (360mg; 1.65mmol). The mixture was stirred at 20°C and the progress of the reaction followed by TLC in solvent (D). After 24h, more DMAP (6mg) and $(Boc)_2O$ (75mg) was added and the mixture was further stirred for 24h. Beside the starting material R_{fD}0.12, two major spots R_{fD}0.28 and 0.45 were visualized, the faster moving possibly increasing with time. After addition of a little water and stirring for 30min to decompose any excess of $(Boc)_2O$, the solvent was exchanged for AcOEt and the organic solution was washed with M $KHSO_4$, with water, dried and evaporated. The resulting oil (780mg), dissolved in toluene, was applied to a silica gel column and eluted with toluene-CH_3CN 32:1. Chromatographically pure **10**, R_{fD}0.28 (330mg), and **11**, R_{fD}0.45 (120mg), were secured as oils which spontaneously crystallized.

Two recrystallizations from n-hexane and one from MeOH of **10**, gave 198mg, mp 88-90°C. Elemental analysis for $C_{28}H_{34}N_2O_6$ (494.60): calcd. C 68.00%, H 6.93%, N 5.66%; found C 68.08%, H 7.02%, N 5.63%. IR (Nujol): 1785, 1715cm^{-1}(C=O). ^{1}H-NMR: δ= 0.42(m, 1H); 0.66(q, 6H); 1.61(s, H); 1.65(m, 1H); 1.92(m, 1H); 3.38(oct, 2H, J= 14.1, 5.3, 2.8); 4.63(q, 1H, J= 11.5, 4.5); 4.69(q, 1H, J= 5.3, 2.8); 5.1(q, 2H). MS m/e: 494(M^+), major peaks 479, 438, 421, 394, 338, 303.

Two recrystallizations from CH_2Cl_2/n-hexane of **11** gave 21mg, mp 135-137°C. IR (Nujol): 3300 (N-H), 1780(w), 1760(w), 1740, 1705cm^{-1}(C=O). ^{1}H-NMR: δ= 0.79(m, 6H); 0.85(m, 1H); 1.41(s, 9H); 1.75(m, 1H); 2.12(m, 1H); 3.23(q, 2H, J= 13.8); 4.67(q, 1H, J= 11.7, 4.1); 5.12(q, 2H); 5.83 (s, 1H); 7.14-7.35(m, 10H). MS m/e: 495(M^++H), major peaks 439, 394, 338, 303. A crystal from CH_2Cl_2/n-hexane was selected for X-ray analysis and gave the structure **11**.

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