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Stereocontrolled Synthesis of *Erythro* N-Protected α-Amino Epoxides and Peptidyl Epoxides.

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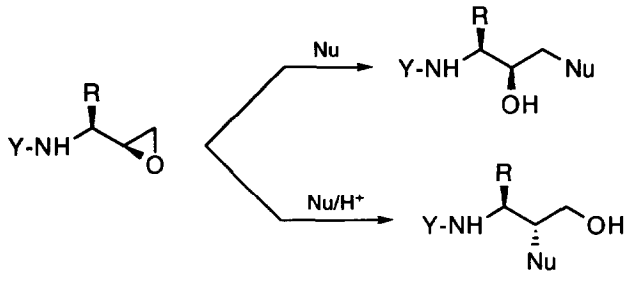
Abstract: N-protected α-amino epoxides of *erythro* configuration, derived from α-amino acids, were synthesized in a stereoselective manner. The *erythro* (2S,3S) configuration was achieved by the synthetic sequence: amino acid -> haloketone -> halohydrin -> epoxide. A mechanistic explanation for the observed stereoselectivity is presented. This stereoselective synthetic approach was applied to the synthesis of a variety of short peptidyl epoxides, bearing a predefined absolute configuration of the chiral epoxide moiety.

INTRODUCTION

α-Amino epoxides can serve as versatile chiral synthons, since they undergo regio- and stereoselective attack by various nucleophiles.[1,2] Thus, they will yield multifunctional group products of predetermined (stereo and regio) structures (eq. 1).[3,4,5]



(1)

The first synthesis of an α-amino epoxide (derived from an α-amino acid) was nonstereoselective, yielding a racemic mixture of the product.[4b] This procedure, based on direct epoxidation of an α-amino aldehyde by a sulfonium ylide, was later improved to produce preferentially the *threo* isomer of the α-amino epoxide.[6] A second approach, based on stereoselective epoxidation of allyl amines, yields the *threo* isomer in

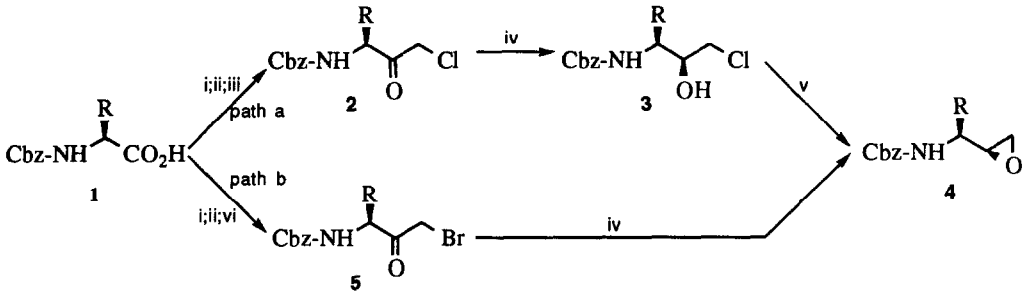
high enantiomeric excess, but in a poor to moderate yield.[3] This route has been extensively used for the synthesis of hydroxyethylene dipeptide isosters.[4e,7,8] Recently, we improved this route by a simple modification of the N-protecting group, and demonstrated its application to the synthesis of *threo* peptidyl epoxides.[9] On the other hand, an efficient general strategy for the synthesis of *erythro* α-amino epoxides has not been developed yet.[10]

As part of a project directed towards the development of novel specific protease inhibitors, we have devised such stereoselective synthesis of the *erythro* (2S,3S) isomer of α-amino epoxides. In this paper, we describe this synthetic approach, along with its application to the synthesis of *erythro* peptidyl epoxides.

RESULTS AND DISCUSSION

The general approach we have developed for the synthesis of the *erythro* isomer of N-protected α-amino epoxides utilizes the chirality of natural α-amino acids to induce a prefered configuration at the new adjacent chiral center. The key step of the synthetic scheme (Scheme 1) is a stereoselective reduction of a haloketone, leading to an *erythro* configuration of the alcohol and the subsequent epoxide products.

Synthesis of erythro α-amino epoxides (4)



a: R=Me
b: R=CH_2CHMe_2
c: R=CH_2Ph

[a](i) $ClCO_2CH_2CHMe_2$, N-methyl morpholine, THF; (ii) CH_2N_2, Et_2O; (iii) HCl (g); (iv) $NaBH_4$, EtOH; (v) NaOMe, MeOH; (vi) HBr (aq).

Scheme 1. Synthesis of *erythro* N-protected α-amino epoxides

The *erythro* isomer of N-protected α-amino epoxides (**4**) can be efficiently synthesized, either via chloromethyl ketone **2** (Scheme 1, path a) or its bromo analog **5** (Scheme 1, path b), starting from an N-protected α-amino acid. Thus, the N-protected α-amino chloromethyl ketones (**2**) were synthesized, in quantitative yields, from the corresponding carboxylic acids (**1**), in a one-pot three-step sequence through a mixed anhydride and diazoketone intermediates.[11,12] The chloroketones (**2**) were stereoselectively reduced by

$NaBH_4$ to the corresponding chlorohydrins (**3**). This reaction yields, preferentially, the *erythro* isomer ((2S,3S) 2-hydroxy-3-amino derivative; 50-100% de. See Table 1). The reduction step also produces varying amounts of the corresponding epoxides in low yield along with the chlorohydrins. The assignment of the stereochemistry around the newly formed chiral center is based on a comparison of ^1H NMR data of the final product - the epoxide (*vide infra*) - with published data.[3,4b,6] In addition, peptidyl epoxides that we synthesized via the haloketone route (*vide infra*) were compared to peptidyl epoxides of identical sequences that we previously synthesized through the olefin epoxidation method[9] (see Table 3). It is well established that the latter procedure yields the *threo* configuration preferentially.[3,8b,8c,13] Thus, we can safely assume that the haloketone route outlined above yields the *erythro* configuration.

Table 1. Product Ratio[a] and Total Yield[b] for the Synthesis of *Erythro* α-Amino Epoxides (**4**)

R	X=Cl (path a)			X=Br (path b)		
	erythro	*threo*	yield	*erythro*	*threo*	yield
Me	75	25	80%	67	33	58%
CH_2CHMe_2	80	20	88%	80	20	66%
CH_2Ph	>95[c]	<5	68%	80	20	73%

[a] Determined by ^1H NMR. [b] Yields from the corresponding α-amino acid. [c] Only one isomer was detected by ^1H and ^{13}C NMR.

This stereoselectivity can be explained in terms of Cram's rule for nucleophilic attacks on aldehydes and ketones (see Fig. 1).[14,15] For the purpose of this analysis of the reactive conformation, we assume that the side chain R is larger than the amido group - even in the case of the alanine derived chloromethyl ketone (which has the smallest residue, R=Me). This assumption is supported by a number of studies, including the energetic preference of such substituents on cyclohexane to be equatorial, rather than axial.[16,17] This conformation exposes the *re* face of the carbonyl to the incoming hydride, preferentially leading to *erythro* configuration of the product (Fig. 1).

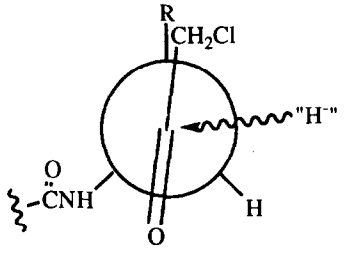
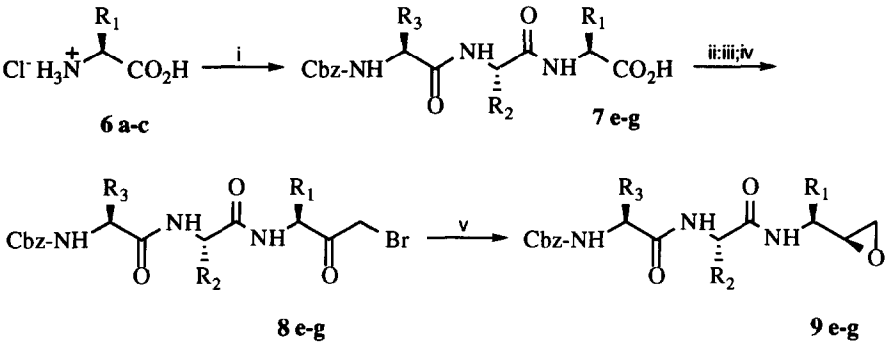


Fig. 1. Application of Cram's rule to the reduction of chiral chloroketones derived from α-amino acids

The stereoselectivity increases with the bulkiness of the side chain R (Table 1). Thus, the alanine derivative (R=Me, **2a**) exhibits a 3:1 *erythro:threo* ratio (50% de) in the product of the reduction step. This ratio increases slightly to 4:1 (60% de) in the reduction of leucine derived chloroketone (**2b**), whereas the reduction of the phenylalanine chloroketone (R=benzyl, **2c**) yields only the *erythro* isomer (based on NMR spectrum). Similar stereospecificity was also obtained during the reduction of valine derived chloroketone, with increased substitution at the β position; no traces of the *threo* isomer could be detected by NMR (unpublished results). The chiral chlorohydrin derivatives were transformed into the corresponding epoxides by treatment with base (NaOMe / MeOH).

Erythro epoxides **4** can also be generated via the bromoketone derivatives **5** (path b of Scheme 1) of the N-protected α-amino acids. The bromoketones were prepared from the corresponding diazoketones[11a] by treatment with one equivalent of 48% HBr (aq).[18] They were then reduced by $NaBH_4$, yielding the corresponding epoxides (**4**) directly. This direct reaction is not surprising, considering the higher reactivity of the bromide, relative to the chloride, as an SN2 leaving group. The reduction step exhibits the same trend of selectivity that was observed in the reduction of the corresponding chloroketones, namely, a larger side chain (R) leads to higher selectivity (see Table 1). The yields in the bromoketone synthesis, as well as the reduction step, are somewhat lower than the corresponding reactions of the chloro derivatives (Table 1). However this sequence is one step shorter and eliminates the necessary treatment with a strong base. This was found to be crucial for the synthesis of longer peptidyl epoxides (*vide infra*).

Synthesis of peptidyl epoxides bearing an erythro configuration (9)



6 a-c **7 e-g** **8 e-g** **9 e-g**

a: R_1=Me
b: R_1=CH_2CHMe_2
c: R_1=CH_2Ph
e: R_1=CH_2Ph, R_2=R_3=Me
f: R_1=Me, R_2=CH_2CHMe_2, R_3=H
g: R_1=CH_2Ph, R_2=CH_2CHMe_2, R_3=H

[a](i) Cbz-aa_3aa_2, DCC, NHS; (ii) $ClCO_2CH_2CHMe_2$, N-methyl morpholine, THF; (iii) CH_2N_2, Et_2O; (iv) HBr (aq); (v) $NaBH_4$, EtOH.

Scheme 2. Synthesis of *erythro* peptidyl epoxides

The synthesis of *erythro* peptidyl epoxides (**9**) follows the above sequence, starting with the corresponding peptide **7** (Scheme 2). The synthesis of chloromethyl ketone derivatives of longer peptides is completely analogous to that of the N-protected α-amino chloromethyl ketones derived from α-amino acids described above. This step, as well as the following $NaBH_4$ reduction, proceed in high yield. However, the subsequent basic epoxidation step proceeds in very low yield. This is probably due to deprotonation of the amide moieties (pK_a~16)[19] and subsequent side reactions of the anion thus formed. This problem was overcome by preparing the peptidyl bromoketones (**8**), which were then transformed directly into the corresponding epoxides (**9**), in high yield, by $NaBH_4$ reduction (see Table 2). This reduction was also stereoselective, yielding the expected *erythro* configuration preferentially (Table 2).

Table 2. Product Ratio[a] and Total Yield[b] for the Synthesis of *Erythro* Tripeptidyl Epoxides (9)

product	*erythro*	*threo*	yield
Cbz-Gly-Leu-Ala-epoxide	74	26	51%
Cbz-Ala-Ala-Phe-epoxide	79	21	61%
Cbz-Gly-Leu-Phe-epoxide	82	18	72%

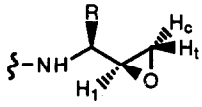
[a] Determined by ^{1}H NMR. [b] yields from the corresponding tripeptide.

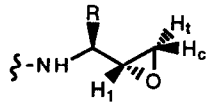
It is important to assess the degree of epimerization at the labile C_α of the peptidyl haloketones during purification and the subsequent $NaBH_4$ reduction. Thus, we further studied a peptide bearing the most labile residue - Cbz-Gly-Leu-Phe-epoxide. An authentic sample of Cbz-Gly-Leu-D-Phe-epoxide was synthesized (via a bromoketone intermediate) from D-phenylalanine, according to the procedure outlined above. ^{1}H NMR doping experiment (addition of small amounts of the purified Cbz-Gly-Leu-D-Phe-epoxide into a sample of the corresponding crude L isomer) reveals the presence of 3% of the D isomer in the crude L isomer product.

Nucleophilic (exo) attack on the optically pure *erythro* peptidyl epoxide would then yield the corresponding optically pure hydroxyethylene compound. This is in contrast to other approaches which yield a 1:1 mixture of isomers at this position.[20] Such nucleophilic attacks on α-amino epoxides and peptidyl epoxides are well documented in the literature.[6,8,20a]

The two isomers, *threo* [9] and *erythro* peptidyl epoxides, can be separated by reverse phase HPLC.[9] They could be easily distinguished by their ^{1}H-NMR spectrum: the *erythro* isomer displays a "compact" set of resonances of the epoxide protons, whereas the *threo* isomer has a more "spread out" and better resolved spectrum. This is clearly seen from Table 3.

Table 3. ^{1}H NMR Chemical Shifts[a,b] (in ppm) of Epoxidic Protons.





epoxide	*erythro*			*threo*		
	H_1	H_t	H_c	H_1	H_t	H_c
Cbz-Phe	2.918	2.777	2.815	3.013	2.540	2.658
Cbz-Leu	2.834	2.67	2.67	2.939	2.652[c]	2.512[c]
Cbz-Ala	2.921	2.74	2.74	2.980	2.583	2.718
Cbz-Gly-Leu-Phe[d]	2.943	2.766	2.786	3.008	2.475	2.623
Cbz-Gly-Leu-D-Phe	2.942	2.756	2.756	---	2.539	2.622
Cbz-Ala-Ala-Phe[d,e]	2.951	2.726	2.772	3.049	2.517	2.679
Cbz-Gly-Leu-Ala[d]	2.909	2.674	2.718	3.004	2.538	2.726
Cbz-Ala-Ala-Ala[f]	2.938	2.707	2.746	3.012	2.552	2.725

[a] In $CDCl_3$. [b] The *cis-trans* assignment is based on the vicinal J coupling.[21] [c] Note that the assignment in this case would be interchanged by comparison of chemical shifts. [d] Data for the *threo* isomer is from ref. 9. [e] In $CDCl_3/CD_3OD$. [f] From ref. 9.

Further extension of this developed methodology, as well as its utilization for synthesis of novel protease inactivators is currently under investigation in our laboratory, and will be reported separately.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 200 MHz and 75 or 50 MHz, respectively, in $CDCl_3$, unless otherwise specified. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or relative to solvent resonance in other solvents. All ^{1}H NMR assignments were supported by homonuclear decoupling experiments, while ^{13}C NMR assignments were supported by off-resonance heteronuclear decoupling or 2-D hetero COSY experiments. Mass spectra were recorded in CI mode with either iso-butane or ammonia as the reagent gas, unless otherwise indicated. TLC was performed on E. Merck 0.2 mm precoated silica gel F-254 plates, and viewed by Cl_2/KI-tolidine[22]. Flash column chromatography[23] was carried out on silica gel 60 (230-400 mesh ASTM, E. Merck). Molecular mechanics calculations were carried out using a PCMODEL program (Serena Software, Box 3076, Bloomington, IN 47402). Amino acids, protected amino acids, and protected peptides, all of the natural L (S) configuration, and (D)-Phenylalanine were purchased from Sigma Chemical Company. Anhydrous solvents were dried and freshly distilled (THF and ether from sodium/benzophenone, and CH_2Cl_2 from 4Å molecular sieves).

N-Protected α-amino chloromethyl ketones (2). A solution of N-protected α-amino acid (1 mmole) and N-methylmorpholine (1.1 mmole) in dry THF (5 ml), under argon atmosphere was cooled to -15±5°C. Isobutyl chloroformate (1 mmole) was added and after 5 min. the reaction mixture was quickly filtered and added to a precooled (-15°C) etherial solution of diazomethane (2 mmole) in a plastic vessel.[11a,12] The reaction was allowed to warm up to room temperature and, after about an hour, was cooled to 0°C and dry HCl

was slowly bubbled through it till the yellow color disappeared.[11b] Evaporation to dryness afforded a clean product which was used in the next reaction without further purification.

Cbz-alanyl chloromethane (2a) (93% yield). ^{1}H NMR δ 1.34 (d, J=7.3 Hz, 3H, CH_3), 4.23(d, J=16 Hz, 1H, CH_2Cl), 4.24 (d, J=16 Hz, 1H, CH_2Cl), 4.54 (quintet, J=7.3 Hz, 1H, CHα), 5.06 (d, J=13 Hz, 1H, CH_2Ph), 5.07 (d, J=13 Hz, 1H, CH_2Ph), 5.67 (bs, 1H, NH), 7.30 (s, 5H, Ph); ^{13}C NMR δ 17.17 (CH_3), 45.81 (CH_2Cl), 53.50 (Cα), 66.99 (CH_2Ph), 127.87, 128.07, 128.37, 135.99 (Ph), 155.58 (OCON), 201.31 (CO); MS *m/z* 273, 275 (MNH_4^+), 256, 258 (MH^+), 212, 214 (MH^+-CO_2), 108 ($PhCH_2OH$).

Cbz-leucyl chloromethane (2b) (99% yield). ^{1}H NMR δ 0.91 (d, J=6.3 Hz, 3H, CH_3), 0.96 (d, J=6.7 Hz, 3H, CH_3), 1.33-1.84 (m, 3H, CH_2β + CHγ), 4.25 (d, J=16.2 Hz, 1H, CH_2Cl), 4.29 (d, J=16.2 Hz, 1H, CH_2Cl), 4.58 (dt, J=8.2, 4.1 Hz, 1H, CHα), 5.081 (d, J=12.4 Hz, 1H, CH_2Ph), 5.083 (d, J=12.4 Hz, 1H, CH_2Ph), 5.56 (d, J=8.1 Hz, 1H, NH), 7.32 (s, 5H, Ph); ^{13}C NMR δ 21.26 (CH_3), 22.97 (CH_3), 24.62 (Cγ), 39.96 (Cβ), 46.50 (CH_2Cl), 56.19 (Cα), 66.98 (CH_2Ph), 127.85, 128.06, 128.37, 135.91 (Ph), 156.05 (OCON), 201.85 (CO); MS *m/z* 298, 300 (MH^+), 262 (MH^+-Cl), 254, 256 (MH^+-CO_2), 220 (MH^+-$HOCCH_2Cl$).

Cbz-phenylalanyl chloromethane (2c) (97% yield). ^{1}H NMR δ 3.00 (dd, J=13.6, 7.1 Hz, 1H, CH_2β), 3.10 (dd, J=13.6, 7.0 Hz, 1H, CH_2β), 3.97 (d, J=15.1 Hz, 1H, CH_2Cl), 4.15 (d, J=15.1 Hz, 1H, CH_2Cl), 4.76 (q, J=7.1 Hz, 1H, CHα), 5.07 (s, 2H, CH_2Ph), 5.46 (d, J=6.8 Hz, 1H, NH), 7.10-7.40 (m, 10H, Ph); ^{13}C NMR δ 37.20 (Cβ), 47.15 (CH_2Cl), 58.68 (Cα), 66.95 (CH_2Ph), 127.10, 127.82, 128.04, 128.33, 128.66, 128.93, 135.36, 135.86 (Ph), 155.68 (OCON), 200.74 (CO); MS *m/z* 349, 351 (MNH_4^+), 332, 334 (MH^+), 313 (MNH_4^+-HCl), 296 (MH^+-HCl), 288, 290 (MH^+-CO_2), 252 (MH^+-HCl-CO_2).

N-Protected α-amino chlorohydrins (3). To a solution of 0.65 mmole N-protected α-amino chloromethyl ketone (**2**) in ethanol (10 ml) was added 27 mg (0,72 mmole) $NaBH_4$. After 4 hours, water (20 ml) was added and the solution was extracted with CH_2Cl_2 (30 ml). The organic phase was dried over magnesium sulfate, followed by filtration and evaporation. The clean product was obtained (as a mixture of isomers) after flash chromatography.

Cbz-alanyl chlorohydrin (3a) (Eluted with hexane:ether:CH_2Cl_2 2:2:1. 90% yield). ^{1}H NMR δ (*erythro*) 1.14 (d, J=6.7 Hz, 3H, CH_3), 3.30 (d, J=4.3 Hz, 1H, OH), 3.46 (dd, J=11.2, 7.4 Hz, 1H, CH_2Cl), 3.52 (dd, J=11.2, 3.8 Hz, 1H, CH_2Cl), 3.83 (m, 1H, CHOH), 3.91 (m, J=8.1, 6.8, 2.6 Hz, 1H, CHα), 5.07 (d, J=12 Hz, 1H, CH_2Ph), 5.08 (d, J=12 Hz, 1H, CH_2Ph), 5.27 (d, J=8.1 Hz, 1H, NH), 7.33 (s, 5H, Ph); (*threo*) 1.221 (d, J=6.9 Hz, 3H, CH_3), 3.925 (m, 1H, CHα); ^{13}C NMR δ (*erythro*) 14.83 (CH_3), 46.64 (CH_2Cl), 49.16 (Cα), 66.89 (CH_2Ph), 74.00 (CHOH), 128.00, 128.13, 128.47, 136.16 (Ph), 156.04 (OCON); (*threo*) 18.28 (CH_3), 48.73 (Cα), 49.30 (CH_2Cl), 74.26 (CHOH); MS *m/z* 258, 260 (MH^+), 222 (MH^+-HCl), 214, 216 (MH^+-CO_2), 178 (MH^+-H_2OCHCH_2Cl), 91 ($C_7H_7^+$).

Cbz-leucyl chlorohydrin (3b) (Eluted with ether:hexane 1:1. 96% yield). ^{1}H NMR δ 0.92 (d, J=6.5 Hz, 6H, CH_3), 1.26-1.43 (m, 2H, CH_2β), 1.63 (m, 1H, CHγ), 3.45-3.60 (m, 2H, CH_2Cl), 3.83 (m, 2H, CHOH + CHα), 5.09 (s, 2H, CH_2Ph), 7.33 (s, 5H, Ph); ^{13}C NMR δ (*erythro*) 21.37 (CH_3), 23.58 (CH_3), 24.56 (Cγ), 38.54 (Cβ), 46.82 (CH_2Cl), 52.16 (Cα), 66.95 (CH_2Ph), 74.48 (CHOH), 127.97, 128.14, 128.46, 136.23 (Ph), 156.51 (OCON); (*threo*) 22.01 (CH_3), 22.94 (CH_3), 24.38 (Cγ), 41.51 (Cβ), 47.53 (CH_2Cl), 52.10 (Cα), 66.95 (CH_2Ph), 73.56 (CHOH); MS *m/z* 317, 319 (MNH_4^+), 300, 302 (MH^+), 281 (MNH_4^+-HCl), 264 (MH^+-HCl), 256, 258 (MH^+-CO_2).

Cbz-phenylalanyl chlorohydrin (3c) (Eluted with ether:hexane 1:1. 75% yield). ^{1}H NMR δ (*erythro*) 2.95 (dd, J=14, 7 Hz, 1H, $CH_2\beta$), 2.99 (dd, J=14.0, 4.9 Hz, 1H, $CH_2\beta$), 3.55 (dd, J=11.4, 7.4 Hz, 1H, CH_2Cl), 3.65 (dd, J=11.4, 3.8 Hz, 1H, CH_2Cl), 3.85 (m, 1H, CHOH), 3.98 (m, 1H, CHα), 4.83 (d, J=7.2 Hz, 1H, NH), 5.03 (bs, 2H, CH_2Ph), 7.20-7.35 (m, 10H, Ph); ^{13}C NMR δ 35.72 (Cβ), 47.59 (CH_2Cl), 54.77 (Cα), 66.97 (CH_2Ph), 73.25 (CHOH), 126.72, 127.95, 128.16, 128.50, 128.61, 129.40, 137.04 (Ph); MS *m/z* 334, 336 (MH^+), 290, 292 (MH^+-CO_2), 226, 228 (MH^+-$PhCH_2OH$), 91 ($C_7H_7^+$).

N-Protected tripeptides (7) were prepared by standard DCC / NHS coupling. 2.5 mmole N-protected dipeptide, 2.75 mmole (584 mg) dicyclohexyl carbodiimide (DCC), and 5.0 mmole (575 mg) N-hydroxysuccinimide (NHS) were dissolved in 30 ml dry THF and stirred for 4 hours. An aqueous solution (30 ml) of an α-amino acid · HCl salt (3 mmole) and K_2CO_3 (500 mg, 3 mmole) was added, and the reaction was further stirred for ~20 hours (followed by t.l.c. to completion). Water (50 ml) and ether (40 ml) were added, and the phases were separated. The aqueous phase was acidified by 32% HCl to pH 1. A white precipitate was formed, and crystallized upon storage in the refrigerator over night. The crystals were washed with water and desiccated under reduced pressure.

Cbz-alanyl-alanyl-phenylalanine (7e). (64% yield). ^{1}H NMR (in CD_3OD) δ 1.33 (d, J=7.1 Hz, 6H, Ala-CH_3), 3.06 (dd, J=13.9, 7.4 Hz, 1H, Phe-$CH_2\beta$), 3.22 (dd, J=13.9, 5.2 Hz, 1H, Phe-$CH_2\beta$), 4.18 (q, J=7.1 Hz, 1H, Ala-CHα), 4.39 (q, J=7.1 Hz, 1H, Ala-CHα), 4.68 (m, 1H, Phe-CHα), 5.08 (d, J=12.5 Hz, 1H, Cbz-CH_2), 5.12 (d, J=12.5 Hz, 1H, Cbz-CH_2), 7.15 (d, J=7.3 Hz, Ala-NH), 7.15-7.40 (m, 10H, Ph), 7.93 (d, J=7.3 Hz, Phe-NH), 8.06 (d, J=7.0 Hz, Ala-NH); ^{13}C NMR δ 18.00 (Ala-CH_3), 18.34 (Ala-CH_3), 38.14 (Phe-Cβ), 50.00 (Ala-Cα), 51.66 (Ala-Cα), 54.70 (Phe-Cα), 67.64 (Cbz-CH_2), 127.59, 128.59, 129.20, 137.67 (Ph), 174.09 (CON), 174.19 (CON), 174.82 (CO_2H); MS *m/z* 459 (MNH_4^+), 442 (MH^+), 423 (MH^+-H_2O), 415 (MNH_4^+-CO_2), 398 (MH^+-CO_2), 351 (MH^+-CO_2-HCO_2), 334 (MH^+-$PhCH_2OH$), 308 (Ala-Ala-PheH$^+$).

Cbz-glycyl-leucyl-alanine (7f). (80% yield). ^{1}H NMR (in CD_3OD) δ 0.90 (d, J=5.2 Hz, 3H, Leu-CH_3), 0.93 (d, J=5.2 Hz, 3H, Leu-CH_3), 1.38 (d, J=7.3 Hz, 3H, Ala-CH_3), 1.50-1.70 (m, 3H, Leu-$CH_2\beta$ + CHγ), 3.76 (d, J=16.9 Hz, 1H, Gly-CH_2), 3.89 (d, J=16.9 Hz, 1H, Gly-CH_2), 4.37 (q, J=7.3 Hz, 1H, Ala-CHα), 4.50 (dd, J=8.8, 5.7 Hz, 1H, Leu-CHα), 5.13 (d, J=12.7 Hz, 1H, Cbz-CH_2), 5.14 (d, J=12.7 Hz, 1H, Cbz-CH_2), 7.32 (s, 5H, Ph); ^{13}C NMR δ 17.50 (Ala-CH_3), 22.06 (Leu-CH_3), 23.41 (Leu-CH_3), 25.70 (Leu-CHγ), 42.01 (Leu-$CH_2\beta$), 44.93 (Gly-CH_2), 49.26 (Leu-Cα), 52.81 (Ala-Cα), 67.83 (Cbz-CH_2), 128.79, 128.96, 129.42, 137.95 (Ph), 158.94 (OCON), 171.96 (CON), 174.27 (CON), 175.66 (CO_2H); MS *m/z* 411 (MNH_4^+), 394 (MH^+), 376 (MH^+-H_2O), 367 (MNH_4^+-CO_2), 350 (MH^+-CO_2), 240 (MNH_4^+-CH_3CHCO_2H), 323 (MNH_4^+-Ala), 303 (MH^+-$PhCH_2OH$).

Cbz-glycyl-leucyl-phenylalanine (7g). (87% yield). ^{1}H NMR (in CD_3OD) δ 0.86 (d, J=6.3 Hz, 3H, Leu-CH_3), 0.89 (d, J=6.6 Hz, 3H, Leu-CH_3), 1.45-1.70 (m, 3H, Leu-$CH_2\beta$ + CHγ), 2.99 (dd, J=13.5, 8.4 Hz, 1H, Phe-$CH_2\beta$), 3.17 (dd, J=13.5, 5.0 Hz, 1H, Phe-$CH_2\beta$), 3.75 (bs, 2H, Gly-CH_2), 4.43 (dd, J=9.1, 5.6 Hz, 1H, Leu-CHα), 4.62 (dd, J=8.3, 5.3 Hz, 1H, Phe-CHα), 5.08 (bs, 2H, Cbz-CH_2), 7.17-7.38 (m, 10H, Ph), 7.94 (d, J=8.2 Hz, Leu-NH), 8.12 (d, J=8.0 Hz, Phe-NH); ^{13}C NMR δ 22.05 (Leu-CH_3), 23.31 (Leu-CH_3), 25.69 (Leu-Cγ), 38.26 (Phe-Cβ), 41.79 (Leu-Cβ), 44.91 (Gly-CH_2), 52.95 (Phe-Cα), 54.99 (Leu-Cα), 67.89 (Cbz-CH_2), 127.69, 128.76, 128.98, 129.33, 129.40, 130.28, 138.09 (Ph), 159.0 (OCON), 171.82 (CO_2), 174.16 (CON), 174.53 (CON); MS *m/z* 488 (MNH_4^+), 470 (MH^+), 453 (MH^+-OH), 379 (MH^+-$C_7H_7^+$), 362 (MH^+-$PhCH_2OH$).

Cbz-glycyl-leucyl-D-phenylalanine (7h). ^{1}H NMR (in CD_3OD) δ 0.81 (bs, 6H, Leu-CH_3), 1.25-1.55 (m, 3H, Leu-CH_2β + CHγ), 2.93 (dd, J=13.6, 9.8 Hz, 1H, Phe-CH_2β), 3.23 (dd, J=13.8, 4.7 Hz, 1H, Phe-CH_2β), 3.77 (bs, 2H, Gly-CH_2), 4.43 (t, J=6.5 Hz, 1H, Leu-CHα), 4.68 (q, J=4.8 Hz, 1H, Phe-CHα), 5.08 (s, 2H, Cbz-CH_2), 7.15-7.40 (m, 10H, Ph); ^{13}C NMR δ 22.01 (Leu-CH_3), 23.33 (Leu-CH_3), 25.63 (Leu-Cγ), 38.26 (Phe-Cβ), 41.95 (Leu-Cβ), 45.02 (Gly-CH_2), 52.79 (Phe-Cα), 54.85 (Leu-Cα), 67.89 (Cbz-CH_2), 127.77, 128.84, 128.99, 129.43, 130.29, 138.24 (Ph), 159.0 (OCON), 171.88 (CO_2), 174.30 (CON), 174.31 (CON)

Peptidyl bromoketones were prepared from the corresponding peptides, in a 1 mmole scale. The peptides were first transformed into the corresponding diazoketones,[11a,12] and the latter, dissolved in ether, were treated with 1 eq. of 48% HBr (aq)[18] to yield the respective products. They were purified by flash chromatography (Elution with step gradients of 1:2 and up to 3:1 of ether:hexane).

N-Cbz-alanyl bromomethane (5a). (65% yield). ^{1}H NMR δ 1.34 (d, J=7.2 Hz, 3H, CH_3), 4.02 (d, J=14 Hz, 1H, CH_2Br), 4.05 (d, J=14 Hz, 1H, CH_2Br), 4.57 (quintet, J=7.1 Hz, 1H, CHα), 5.05 (d, J=13 Hz, 1H, CH_2Ph), 5.09 (d, J=13 Hz, 1H, CH_2Ph), 5.77 (d, J=6.8 Hz, 1H, NH), 7.31 (s, 5H, Ph); ^{13}C NMR δ 17.29 (CH_3), 31.56 (CH_2Br), 53.50 (Cα), 66.86 (CH_2Ph), 127.83, 128.02, 128.32, 135.88 (Ph), 155.60 (OCON), 200.95 (CO); MS *m/z* 300, 302 (MH^+), 256, 258 (MH^+-CO_2), 178 (M^+-$COCH_2$Br), 152 ($PhCH_2OCONH_3^+$), 91 ($C_7H_7^+$). A sample was crystallized from ether. m.p. 83-84°C. Anal calcd for $C_{12}H_{14}NO_3Br$: C 48.00, H 4.67, N 4.67. Found C 48.20, H 4.45, N 4.71.

N-Cbz-leucyl bromomethane (5b). (83% yield). ^{1}H NMR δ 0.93 (d, J=6.3 Hz, 3H, CH_3), 0.96 (d, J=6.0 Hz, 3H, CH_3), 1.44 (ddd, J=13.2, 9.2, 4.0 Hz, 1H, CH_2β), 1.61 (td, J=8.9, 4.0 Hz, 1H, CH_2β), 1.57-1.71 (m, 1H, CHγ), 4.04 (d, J=13.6 Hz, 1H, CH_2Br), 4.08 (d, J=13.6 Hz, 1H, CH_2Br), 4.62 (ddd, J=13.2, 7.9, 4.0 Hz, 1H, CHα), 5.09 (s, 2H, CH_2Ph), 5.42 (d, J=7.9 Hz, 1H, NH), 7.33 (s, 5H, Ph); ^{13}C NMR δ 21.44 (CH_3), 23.09 (CH_3), 24.78 (Cγ), 32.10 (CH_2Br), 40.53 (Cβ), 56.42 (Cα), 67.13 (CH_2Ph), 127.97, 128.18, 128.47, 135.98 (Ph), 156.06 (OCON), 201.31 (CO); MS *m/z* 359, 361 (MNH_4^+), 342, 344 (MH^+), 298, 300 (MH^+-CO_2), 281 (MNH_4^+-Br+H), 264 (MH^+-Br+H), 220 (M-$COCH_2$Br).

N-Cbz-phenylalanyl bromomethane (5c). (82% yield). ^{1}H NMR δ 3.10 (dd, J=13.9, 6.1 Hz, 1H, CH_2β), 3.49 (dd, J=13.9, 7.3 Hz, 1H, CH_2β), 3.82 (d, J=13.8 Hz, 1H, CH_2Br), 3.94 (d, J=13.8 Hz, 1H, CH_2Br), 4.79 (q, J=7.2 Hz, 1H, CHα), 5.02 (d, J=12.6 Hz, 1H, CH_2Ph), 5.09 (d, J=12.6 Hz, 1H, CH_2Ph), 5.52 (d, J=7.6 Hz, 1H, NH), 7.10-7.38 (m, 10H, Ph); ^{13}C NMR δ 32.79 (CH_2Br), 37.88 (Cβ), 58.78 (Cα), 67.11 (CH_2Ph), 127.21, 127.92, 128.14, 128.42, 128.76, 129.00, 135.45, 135.93 (Ph), 155.69 (OCON), 200.20 (CO); MS *m/z* 393, 395 (MNH_4^+), 376, 378 (MH^+), 332, 334 (MH^+-CO_2), 313 (MNH_4^+-HBr), 296 (MH^+-HBr). A sample was crystallized from ether. m.p. 99-101°C. Anal calcd for $C_{18}H_{18}NO_3Br$: C 57.45, H 4.79, N 3.72. Found C 57.75, H 4.80, N 3.75.

Cbz-alanyl-alanyl-phenylalanyl bromomethane (8e). (67% yield). ^{1}H NMR δ 1.27 (d, J=7.4 Hz, 3H, Ala-CH_3), 1.30 (d, J=7.1 Hz, 3H, Ala-CH_3), 2.98 (dd, J=14.1, 7.8 Hz, 1H, Phe-CH_2β), 3.13 (dd, J=14.1, 6.3 Hz, 1H, Phe-CH_2β), 3.82 (d, J=13.8 Hz, 1H, CH_2Br), 3.96 (d, J=13.8 Hz, 1H, CH_2Br), 4.25 (m, 1H, Ala-CHα), 4.46 (quintet, J=7.1 Hz, 1H, Ala-CHα), 4.90 (q, J=7.3 Hz, 1H, Phe-CHα), 5.05 (d, J=12.3 Hz, 1H, Cbz-CH_2), 5.10 (d, J=12.3 Hz, 1H, Cbz-CH_2), 5.71 (d, J=7.0 Hz, 1H, Ala-NH), 7.12 (d, J=8.0 Hz, 1H, Ala-NH), 7.25 (d, J=7.1 Hz, 1H, Phe-NH), 7.16-7.35 (m, 10H, Ph); ^{13}C NMR δ 17.75 (Ala-CH_3), 18.35 (Ala-CH_3), 33.11 (CH_2Br), 37.19 (Phe-Cβ), 48.98 (Ala-Cα), 50.78 (Ala-Cα), 57.45 (Phe-Cα), 67.18 (Cbz-CH_2), 127.20, 127.98, 128.24, 128.53, 128.76, 129.03, 135.84, 136.04 (Ph), 156.19 (OCON),

172.10 (CON), 172.42 (CON), 199.91 (CO); MS *m/z* 535, 537 (MNH_4^+), 518, 520 (MH^+), 457 (MNH_4^+-H+Br), 440 (MH^+-H+Br), 438 (MH^+-HBr). A sample was crystallized from ethyl acetate-hexane and recrystallized from CH_2Cl_2-ether. m.p. 165-166°C. Anal calcd for $C_{24}H_{28}N_3O_5Br$: C 55.60, H 5.41, N 8.11. Found C 55.89, H 5.28, N 8.31.

Cbz-glycyl-leucyl-alanyl bromomethane (8f). (60% yield). ^1H NMR δ 0.89 (d, J=5.1 Hz, 3H, Leu-CH_3), 0.92 (d, J=5.4 Hz, 3H, Leu-CH_3), 1.35 (d, J=7.1 Hz, 3H, Ala-CH_3), 1.48-1.69 (m, 3H, Leu-$CH_2\beta$ + CHγ), 3.85 (dd, J=16, 6 Hz, 1H, Gly-CH_2), 3.90 (dd, J=16, 6 Hz, 1H, Gly-CH_2), 4.05 (s, 2H, CH_2Br), 4.51 (m, 1H, Leu-CHα), 4.72 (quintet, J=7.0 Hz, 1H, Ala-CHα), 5.10 (s, 2H, Cbz-CH_2), 5.80 (bt, J=6 Hz, 1H, Gly-NH), 6.97 (d, J=8.1 Hz, 1H, Leu-NH), 7.25 (d, J=5 Hz, 1H, Ala-NH), 7.34 (bs, 5H, Ph); ^{13}C NMR δ 16.91 (Ala-CH_3), 21.91 (Leu-CH_3), 22.77 (Leu-CH_3), 24.75 (Leu-Cγ), 31.88 (CH_2Br), 40.92 (Leu-Cβ), 44.63 (Gly-CH_2), 51.77 (Leu-Cα), 52.35 (Ala-Cα), 67.31 (Cbz-CH_2), 128.03, 128.26, 128.54, 136.03 (Ph), 156.87 (OCON), 169.68 (CON), 172.17 (CON), 200.65 (CO); MS *m/z* 487, 489 (MNH_4^+), 470, 472 (MH^+), 409 (MNH_4^++H-Br), 408 (MNH_4^+-Br), 392 (MH^++H-Br), 390 (MH^+-HBr). A sample was crystallized from ethyl acetate-hexane and recrystallized from CH_2Cl_2. m.p. 100-102°C.

Cbz-glycyl-leucyl-phenylalanyl bromomethane (8g). (76% yield). ^1H NMR δ 0.90 (d, J=7.1 Hz, 3H, Leu-CH_3), 0.92 (d, J=7.1 Hz, 3H, Leu-CH_3), 1.30-1.57 (m, 3H, Leu-$CH_2\beta$ + CHγ), 2.98 (dd, J=12.5, 7.0 Hz, 1H, Phe-$CH_2\beta$), 3.14 (dd, J=12.5, 7.2 Hz, 1H, Phe-$CH_2\beta$), 3.70 (bs, 2H, Gly-CH_2), 3.85 (d, J=12.1 Hz, 1H, CH_2Br), 3.98 (d, J=12.1 Hz, 1H, CH_2Br), 4.45 (m, 1H, Leu-CHα), 4.94 (q, J=7.1 Hz, 1H, Phe-CHα), 5.15 (s, 2H, Cbz-CH_2), 5.70 (bt, J=4 Hz, 1H, Gly-NH), 6.76 (d, J=8.0 Hz, 1H, Leu-NH), 7.13-7.37 (m, 11H, Phe-NH + Ph); ^{13}C NMR δ 22.00 (Leu-CH_3), 22.75 (Leu-CH_3), 24.80 (Leu-Cγ), 33.10 (CH_2Br), 37.24 (Phe-Cβ), 40.57 (Leu-Cβ), 44.73 (Gly-CH_2), 51.82 (Leu-Cα), 57.38 (Phe-Cα), 67.43 (Cbz-CH_2), 127.26, 128.11, 128.35, 128.62, 128.88, 129.16, 135.91, 136.10 (Ph), 156.79 (OCON), 169.50 (CON), 172.20 (CON), 199.97 (CO); MS *m/z* 563, 565 (MNH_4^+), 546, 548 (MH^+), 485 (MNH_4^++H-Br), 468 (MH^++H-Br), 466 (MH^+-HBr), 377 (MNH_4^+-Br-$PhCH_2O$), 360 (MH^+-Br-$PhCH_2O$). A sample was crystallized from ethyl acetate-hexane and recrystallized from CH_2Cl_2-ether. m.p. 136-138°C. Anal calcd for $C_{26}H_{32}N_3O_5Br$: C 57.14, H 5.86, N 7.69. Found C 57.34, H 5.58, N 7.87.

Cbz-glycyl-leucyl-D-phenylalanyl bromomethane (8h). ^1H NMR δ 0.83 (d, J=5.2 Hz, 6H, Leu-CH_3), 1.30-1.60 (m, 3H, Leu-$CH_2\beta$ + CHγ), 2.97 (dd, J=13.9, 8.3 Hz, 1H, Phe-$CH_2\beta$), 3.16 (dd, J=13.9, 6.7 Hz, 1H, Phe-$CH_2\beta$), 3.82 (d, J=13.8 Hz, 1H, CH_2Br), 3.83 (d, J=5.3 Hz, 2H, Gly-CH_2), 4.00 (d, J=13.8 Hz, 1H, CH_2Br), 4.39 (dt, J=5.6, 8.2 Hz, 1H, Leu-CHα), 4.91 (q, J=7.4 Hz, 1H, Phe-CHα), 5.12 (s, 2H, Cbz-CH_2), 5.54 (t, J=5.7 Hz, 1H, Gly-NH), 6.58 (d, J=8.1 Hz, 1H, Leu-NH), 7.05 (d, J=6.9 Hz, 1H, Phe-NH), 7.10-7.40 (m, 10H, Ph); ^{13}C NMR δ 22.00 (Leu-CH_3), 22.72 (Leu-CH_3), 24.69 (Leu-Cγ), 33.28 (CH_2Br), 37.21 (Phe-Cβ), 40.53 (Leu-Cβ), 44.75 (Gly-CH_2), 51.64 (Leu-Cα), 57.56 (Phe-Cα), 67.43 (Cbz-CH_2), 127.29, 128.10, 128.31, 128.57, 128.84, 129.09, 135.78, 135.97 (Ph), 156.73 (OCON), 169.37 (CON), 171.93 (CON), 200.24 (CO); MS *m/z* 546, 548 (MH^+), 502, 504 (MH^+-CO_2), 468 (MH^++H-Br), 466 (MH^+-HBr), 305 (Z-glycyl-leucyl$^+$).

Peptidyl epoxides (*erythro* isomer).

a. From chlorohydrins. To the N-protected α-amino chlorohydrin (**3**, 0.3 mmole) in methanol (5 ml) was added 1 ml of 0.3 M NaOMe in MeOH. After stirring for ~1.5 hours, water (10 ml) was added, and the solution was extracted with 10 ml CH_2Cl_2. The organic phase was dried over magnesium sulfate, filtered and evaporated to dryness. Flash chromatography afforded the pure product, as a mixture of isomers.

N-Cbz-alanyl epoxide (4a) (Eluted with CH_2Cl_2:hexane 2:1. *erythro:threo* 3:1. 95% yield). ^1H NMR δ (*erythro*) 1.16 (d, J=6.8 Hz, 3H, CH_3), 2.74 (bs, 2H, CH_2O), 2.92 (bs, 1H, CHO), 3.71 (m, J=6 Hz, 1H, CHα), 4.94 (bs, 1H, NH), 5.08 (d, J=12.3 Hz, 1H, CH_2Ph), 5.11 (d, J=12.3 Hz, 1H, CH_2Ph), 7.36 (s, 5H, Ph); (*threo*) 1.27 (d, J=6.9 Hz, 3H, CH_3), 2.58 (dd, J=4.6, 2.7 Hz, 1H, CH_2O), 2.72 (t, J=4.5 Hz, 1H, CH_2O), 2.98 (dt, J=4.5, 2.7 Hz, 1H, CHO), 4.03 (m, 1H, CHα), 4.83 (bs, 1H, NH), 5.1 (bs, 2H, CH_2Ph), 7.4 (s, 5H, Ph); ^{13}C NMR δ (*erythro*) 16.35 (CH_3), 45.95 (CH_2O), 47.90 (Cα), 54.34 (CHO), 66.74 (CH_2Ph), 128.03, 128.08, 128.46, 136.31 (Ph), 155.71 (OCON); MS *m/z* 239 (MNH_4^+), 222 (MH^+), 178 (MH^+-CO_2), 169 (MNH_4^+-$CH_2CHCHOCH_2$), 108 ($PhCH_2OH$), 91 ($C_7H_7^+$). A sample was crystallized from $CHCl_3$-hexane, yielding fine white needles. m.p. 74-75°C. Anal calcd for $C_{12}H_{15}NO_3$: C 65.16, H 6.79, N 6.34. Found

N-Cbz-leucyl epoxide (4b) (Eluted with hexane:ether 2:1. *erythro:threo* 4:1. 92% yield). ^1H NMR (in CD_3OD) δ (*erythro*) 0.88 (d, J=6.8 Hz, 3H, CH_3), 0.92 (d, J=6.7 Hz, 3H, CH_3), 1.37 (ddd, J=14.1, 8.4, 5.0 Hz, 1H, $CH_2β$), 1.48 (ddd, J=14.1, 9.7, 5.0 Hz, 1H, $CH_2β$), 1.70 (octet, J=6.8 Hz, 1H, CHγ), 2.67 (bs, 2H, CH_2O), 2.83 (dt, J=6.0, 3.1 Hz, 1H, CHO), 3.52 (ddd, J=9.7, 6.0, 5.0 Hz, 1H, CHα), 5.05 (s, 2H, CH_2Ph), 7.31 (s, 5H, Ph); (*threo*) 2.51 (dd, J=4.8, 2.6 Hz, 1H, CH_2O), 2.65 (t, J=3 Hz, 1H, CH_2O), 2.94 (dt, J=6.7, 4.0 Hz, 1H, CHO), 3.73 (m, 1H, CHα); ^{13}C NMR δ (*erythro*) 22.10 (CH_3), 23.73 (CH_3), 25.63 (Cγ), 41.79 (Cβ), 45.93 (CH_2O), 51.97 (CHO), 55.24 (Cα), 67.45 (CH_2Ph), 128.72, 128,96, 129.45, 138.45 (Ph), 158.58 (OCON); (*threo*) 45.61 (CH_2O), 51.00 (CHO), 65.24 (CH_2Ph), 127.98, 128.24 (Ph); MS *m/z* 320 ($MC_4H_9^+$), 302 ($MC_3H_3^+$), 264 (MH^+), 220 (MH^+-$HCHOCH_2$), 188 ($MC_3H_3^+$-CH(i-Bu)$CHOCH_2$), 91 ($C_7H_7^+$).

N-Cbz-phenylalanyl epoxide (4c) (Eluted with hexane:ether 2:1. only the *erythro* isomer was detected. 68% yield). ^1H NMR δ 2.74-2.79 (bs, 2H, CH_2O), 2.87-2.97 (m, 2H, CHO + $CH_2β$), 2.99 (dd, J=9.1, 5.3 Hz, 1H, $CH_2β$), 3.77 (m, 1H, CHα), 4.78 (d, J=8.5 Hz, 1H, NH), 5.02 (s, 2H, CH_2Ph), 7.15-7.40 (m, 10H, Ph); ^{13}C NMR δ 37.58 (Cβ), 46.78 (CH_2O), 53.05 (CHO), 53.23 (Cα), 66.84 (CH_2Ph), 126.83, 128.02, 128.15, 128.51, 128.65, 129.39, 136.4, 137.5 (Ph), 155.8 (OCON); MS *m/z* 315 (MNH_4^+), 298 (MH^+), 254 (MH^+-CO_2), 207 (MH^+-$C_7H_7^+$). A sample was crystallized from ether. m.p. 94-95.5°C. Anal calcd for $C_{18}H_{19}NO_3$: C 72.73, H 6.40, N 4.71. Found C 72.46, H 6.28, N 4.75.

b. From bromoketones. 12 mg (0.33 mmole) $NaBH_4$ were added to a solution of 0.3 mmole bromoketone in 7 ml ethanol. After 4 hours, water (10 ml) was added, and the solution was extracted with 15 ml CH_2Cl_2. The organic phase was dried over magnesium sulfate, filtered and evaporated to dryness. Flash chromatography (elution of N-protected α-amino epoxides with 2:1 hexane:ether, and peptidyl epoxides with 1:2 hexane:ether) afforded the clean product as a mixture of isomers.

N-Cbz-alanyl epoxide (4a) (*erythro:threo* 2:1. 89% yield).

N-Cbz-leucyl epoxide (4b) (*erythro:threo* 4:1. 80% yield).

N-Cbz-phenylalanyl epoxide (4c) (*erythro:threo* 4:1. 81% yield).

Cbz-alanyl-alanyl-phenylalanyl epoxide (9e) (*erythro:threo* 3.7:1. 91% yield).[24] ^1H NMR δ 1.24 (d, J=7.0 Hz, 3H, Ala-CH_3), 1.29 (d, J=7.1 Hz, 3H, Ala-CH_3), 2.74 (dd, J=4.9, 2.9 Hz, 1H, CH_2O), 2.76 (t, J=4.8 Hz, 1H, CH_2O), 2.87 (dd, J=14.3, 8.5 Hz, 1H, Phe-$CH_2β$), 2.94 (dd, J=14.3, 7.1 Hz, 1H, Phe-$CH_2β$), 2.99 (td, J=4.7, 2.9 Hz, 1H, CHO), 4.04 (m, 1H, Phe-CHα), 4.12 (q, J=7.2 Hz, 1H, Ala-CHα), 4.28 (q, J=7.1 Hz, 1H, Ala-CHα), 5.08 (d, J=12.2 Hz, 1H, Cbz-CH_2), 5.12 (d, J=12.2 Hz, 1H, Cbz-CH_2), 7.17-7.39 (m, 10H, Ph); ^{13}C NMR δ 17.39 (Ala-CH_3), 17.92 (Ala-CH_3), 37.05 (Phe-Cβ), 45.73

(CH_2O), 49.39 (Cα), 50.59 (Cα), 51.31 (Cα), 52.85 (CHO), 66.88 (Cbz-CH_2), 126.38, 127.69, 127.98, 128.21, 128.28, 128.94, 135.95, 136.81 (Ph), 156.5 (OCON), 172.20 (CON), 172.75 (CON); MS *m/z* 457 (MNH_4^+), 440 (MH^+), 349 (MNH_4^+-$PhCH_2OH$), 332 (MH^+-$PhCH_2OH$), 306 (MH^++H-$PhCH_2OCO$). A sample was crystallized from ethyl acetate-hexane and recrystallized from CH_2Cl_2-ether. m.p. 150-152°C. Anal calcd for $C_{24}H_{29}N_3O_5$: C 65.60, H 6.61, N 9.57. Found C 65.32, H 6.86, N 9.72.

Cbz-glycyl-leucyl-alanyl epoxide (9f) (*erythro:threo* 2.8:1. 85% yield).[24] ^1H NMR δ 0.89 (d, J=6.4 Hz, 3H, Leu-CH_3), 0.91 (d, J=5.7 Hz, 3H, Leu-CH_3), 1.10 (d, J=6.5 Hz, 3H, Ala-CH_3), 1.5-1.7 (m, 3H, Leu-CH_2β + CHγ), 2.67 (dd, J=4.4, 2.6 Hz, 1H, CH_2O), 2.72 (t, J=4.4 Hz, 1H, CH_2O), 2.91 (ddd, J=5.0, 4.0, 2.6 Hz, 1H, CHO), 3.86 (d, J=12.0 Hz, 2H, Gly-CH_2), 3.99 (m, J=6.5 Hz, 1H, Ala-CHα), 4.48 (m, 1H, Leu-CHα), 5.11 (s, 2H, Cbz-CH_2), 5.84 (bs, 1H, Gly-NH), 6.82 (d, J=6.7 Hz, 1H, Ala-NH), 6.94 (d, J=8.1 Hz, 1H, Leu-NH), 7.31 (s, 5H, Ph); ^{13}C NMR δ 15.72 (Ala-CH_3), 21.17 (Leu-CH_3), 22.84 (Leu-CH_3), 24.85 (Leu-Cγ), 41.30 (Leu-Cβ), 44.68 (Gly-CH_2), 45.73 (CH_2O), 46.10 (Ala-Cα), 51.96 (Leu-Cα), 54.09 (CHO), 67.30 (Cbz-CH_2), 128.09, 128.30, 128.59, 136.14 (Ph), 156.69 (OCON), 169.33 (CON), 171.65 (CON); MS *m/z* 392 (MH^+), 91 ($C_7H_7^+$).

Cbz-glycyl-leucyl-phenylalanyl epoxide (9g) (*erythro:threo* 4.4:1. 95% yield).[24] ^1H NMR δ 0.85 (d, J=4.9 Hz, 3H, Leu-CH_3), 0.90 (d, J=7.6 Hz, 3H, Leu-CH_3), 1.30-1.45 (m, 1H, Leu-CH_2β), 1.45-1.65 (m, 2H, Leu-CH_2β + CHγ), 2.76 (dd, J=4.8, 2.7 Hz, 1H, CH_2O), 2.79 (dd, J=4.8, 3.8 Hz, 1H, CH_2O), 2.83 (dd, J=14.2, 8.9 Hz, 1H, Phe-CH_2β), 2.94 (q, J=3 Hz, 1H, CHO), 3.04 (dd, J=14.2, 4.6 Hz, 1H, Phe-CH_2β), 3.71 (dd, J=16, 7 Hz, 1H, Gly-CH_2), 3.79 (dd, J=16, 6 Hz, 1H, Gly-CH_2), 4.07 (m, 1H, Phe-CHα), 4.34 (dt, J=6.0, 8.3 Hz, 1H, Leu-CHα), 5.14 (s, 2H, CBZ-CH_2), 6.30 (bt, 1H, Gly-NH), 6.19 (d, J=8.2 Hz, 1H, Leu-NH), 6.37 (d, J=7.5 Hz, 1H, Phe-NH), 7.15-7.45 (m, 10H, Ph); ^{13}C NMR δ 22.01 (Leu-CH_3), 22.80 (Leu-CH_3), 24.76 (Leu-Cγ), 37.14 (Phe-Cβ), 40.13 (Leu-Cβ), 44.68 (Gly-CH_2), 46.47 (CH_2O), 51.39 (Phe-Cα), 51.69 (Leu-Cα), 53.09 (CHO), 67.43 (CBZ-CH_2), 126.64, 128.11, 128.37, 128.46, 128.60, 129.26, 135.93, (Ph), 168.99 (CON), 171.28 (CON); MS *m/z* 485 (MNH_4^+), 468 (MH^+), 452 (MH^+-O), 360 (MH^+-$PhCH_2OH$), 334 (MH^+-$PhCH_2OH$-O), 322 (MH^+-$CH_2OCHCHCHPh$), 91 ($C_7H_7^+$). A sample was crystallized from ethyl acetate-hexane and recrystallized from THF-hexane. m.p. 134-135°C. Anal calcd for $C_{26}H_{33}N_3O_5$: C 66.81, H 7.07, N 8.99. Found C 66.55, H 6.87, N 9.27.

Cbz-glycyl-leucyl-D-phenylalanyl epoxide (9h). ^1H NMR δ 0.78 (d, J=6.0 Hz, 3H, Leu-CH_3), 0.79 (d, J=5.8 Hz, 3H, Leu-CH_3), 1.2-1.4 (m, 3H, Leu-CH_2β + CHγ), 2.76 (d, J=3.5 Hz, 2H, CH_2O), 2.80 (dd, J=14.3, 9.0 Hz, 1H, Phe-CH_2β), 2.94 (q, J=3.3 Hz, 1H, CHO), 3.03 (dd, J=14.3, 5.4 Hz, 1H, Phe-CH_2β), 3.82 (d, J=5.6 Hz, 1H, Gly-CH_2), 3.83 (d, J=5.7 Hz, 1H, Gly-CH_2), 4.07 (m, 1H, Phe-CHα), 4.28 (q, J=8.2 Hz, 1H, Leu-CHα), 5.12 (s, 2H, CBZ-CH_2), 5.36 (bt, 1H, Gly-NH), 6.06 (d, J=9.3 Hz, 1H, Phe-NH), 6.35 (d, J=8.6 Hz, 1H, Leu-NH) 7.15-7.40 (m, 10H, Ph); ^{13}C NMR δ 22.12 (Leu-CH_3), 22.69 (Leu-CH_3), 24.70 (Leu-Cγ), 37.19 (Leu-Cβ), 41.03 (Phe-Cβ), 44.78 (CH_2O), 46.48 (Gly-CH_2), 51.58 (Cα), 51.87 (Cα), 53.00 (CHO), 67.42 (CBZ-CH_2), 126.88, 128.11, 128.32, 128.59, 128.65, 129.25, 136.59, (Ph), 169.53 (CON); MS *m/z* 485 (MNH_4^+), 468 (MH^+), 360 (MH^+-$PhCH_2OH$), 305 (Z-glycyl-leucyl$^+$), 128, 108 ($PhCH_2OH$).

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