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Synthesis of α,γ-Peptide Hybrids by Selective Conversion of Glutamic Acid Units

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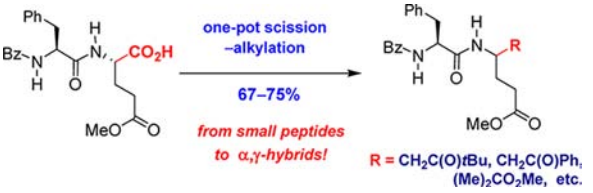
ABSTRACT



The site-selective modification of small peptides at a glutamate residue allows the ready preparation of α,γ-hybrids. In this way, a single peptide can be transformed into a variety of hybrid derivatives. The process takes place under very mild conditions, and good global yields are obtained.

The synthesis of α,γ-peptide hybrids has recently elicited much interest both from the synthetic and the pharmaceutical fields. These peptides display promising antibiotic, antiviral, antihypertensive, antimalaric, and anti-Alzheimer properties.[1] In addition, unlike natural peptides, they are resistant to in vivo degradation.

Thus, pepstatin **1** (Figure 1) is a potent inhibitor of aspartic acid protease and displays antibiotic activity,[1b] while the cyclic peptide **2** acts as an antagonist of the chemokine receptor at nanomolar concentrations and is a promising drug lead for the prevention of tumor metastasis.[1c] Other useful hybrid peptides or peptidomimetics are the antitumorals dolastatin, tamandarin A, and hapalosin, the anti-HIV drug indinavir, etc.[1a]

Traditionally, to obtain collections of these hybrids, each peptide is prepared de novo from the starting α- or γ-amino acids.[1,2] This method is time-consuming and also requires a supply of different and often expensive γ-amino acids.

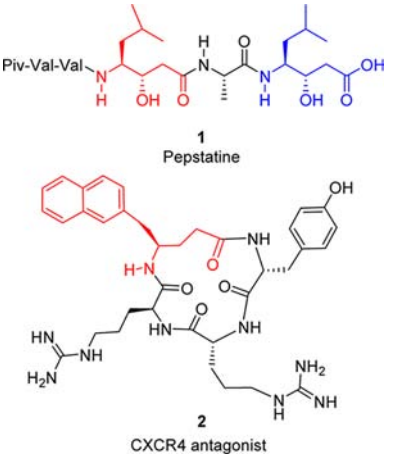


Figure 1. Bioactive α,γ-peptide hybrids.

An attractive alternative would start from a single α,γ-hybrid that could be selectively modified at one residue, converting it into a variety of unnatural γ-amino acids. However, the site-selective modification of peptides is usually very difficult[3] because of the similar reactivity of the amino acid units.[4]

In this work, we report an efficient method for the one-pot conversion of peptides **3** (Scheme 1) containing glutamic

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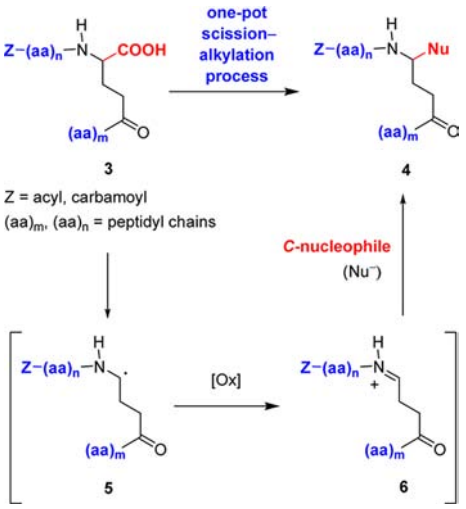
acid residues into α,γ-peptides **4** with unnatural γ-aminoacids. In this transformation, the α-carboxyl group from the glutamic residue is replaced by different alkyl chains. Since the starting peptides **3** are readily available and cheaper than the α,γ-hybrid derivatives **4**, this method allows the preparation of high-value products that can be used as drug leads.

The transformation is achieved using a sequential radical decarboxylation–oxidation–alkylation process.[5] The radical decarboxylation is induced by treatment of the acid **3** (Scheme 1) with (diacetoxyiodo)benzene (DIB) and iodine, in the presence of visible light (sunlight or 80 W tungsten-filament lamps). The initial carboxyl radical undergoes scission to give a *C*-radical **5**. Under the reaction conditions, this radical is oxidized to an acyliminium ion **6**,[6,7] which can be trapped by carbon nucleophiles,[8] forming the α,γ-hybrids **4**.

The scission–alkylation process was studied first using simple glutamic acid derivatives **7**[9a] and **8**[9b,c] (Table 1). Different reaction conditions were tried, and the best results were obtained when the scission step proceeded at room temperature, using a ratio substrate/DIB/I_2 of 1/1.5/0.3, while the addition of the nucleophile was carried out at

Scheme 1



0 °C, using $BF_3 \cdot OEt_2$ as the Lewis acid. The process took place in good yields, affording products **9**–**14**, which present a variety of alkyl chains. Noteworthy, the mild reaction conditions were compatible with acid-labile groups, such as Boc.

The process was then tried with the known dipeptide **15**[10] (Scheme 2), which presents an *N*-terminal glutamate residue. Although side-reactions (such as chain scission) could take place in peptides, the process proceeded in good yield, generating the α,γ-hybrid peptides **16** and **17**. The modified residue is an aspartate analogue and can be used to extend the peptide chain in other direction.

The configuration of dipeptides **16** (*S*) and **17** (*R*) was assigned by chemical correlation to related compounds, as commented later.

Since the reacting position is away from stereogenic centers, a 1:1 mixture of the two possible diastereomers **16** and **17** was formed. The stereoselectivity should improve when the glutamic residue is placed at other positions in the peptide. For instance, in the dipeptide **18** (Scheme 3), the glutamate amino group is attached to a phenylalanine unit, which could act as a chiral auxiliary during the addition step.

In effect, when the decarboxylation–alkylation was carried out, the diastereomeric α,γ-dipeptides **19** and **20** were obtained (dr 2:1, 71% yield).[11] Their configuration was determined as commented later.

The introduction of other alkyl chains also took place satisfactorily (Scheme 4). Using 1-phenyl-1-(trimethylsiloxy)-ethene as the nucleophile, the diastereomeric peptide hybrids **21** and **22** were obtained in 2:1 ratio (75% global yield).

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(4) (a) The site-selective modification is particularly difficult when several units of the "convertible" amino acid (glycine, dehydro amino acids, etc.) are present in the peptide. For other approaches to this subject, see: Datta, S.; Kazmaier, U. *Org. Biomol. Chem.* **2011**, *9*, 872–880. (b) Franz, N.; Menin, L.; Klok, H. A. *Org. Biomol. Chem.* **2009**, *7*, 5207–5218. (c) Chapman, C. J.; Hargrave, J. D.; Bish, G.; Frost, C. G. *Tetrahedron* **2008**, *64*, 9528–9539. (d) Wan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9248–9252. (e) Dialer, H.; Steglich, W.; Beck, W. *Tetrahedron* **2001**, *57*, 4855–4861. (f) Ricci, M.; Madariaga, L.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 242–245.

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(9) (a) Trotter, N. S.; Brimble, M. A.; Harris, P. W. R.; Callis, D. J.; Sieg, F. *Bioorg. Med. Chem.* **2005**, *13*, 501–518. (b) Feng, X.; Edstrom, E. D. *Tetrahedron: Asymmetry* **1999**, *10*, 99–106. (c) Bavetsias, V.; Jackman, A. L.; Kimbell, R.; Gibson, W.; Boyle, F. T.; Bisset, G. M. F. *J. Med. Chem.* **1996**, *39*, 73–85.

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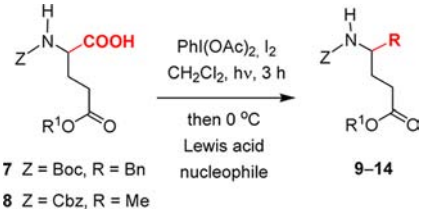
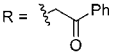
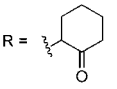
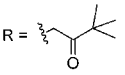
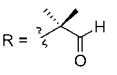
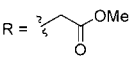
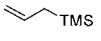
(11) (a) For related compounds with known stereochemistry, see: Subasinghe, N.; Schulte, M.; Chan, M. Y. M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1990**, *33*, 2734–2744. (b) Manesis, N. J.; Goodman, M. *J. Org. Chem.* **1987**, *52*, 5342–5349.

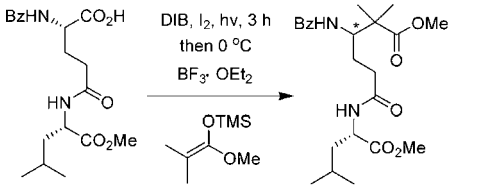
Table 1. One-Pot Scission–Alkylation[a]



entry	substrate	nucleophile	product (%)[b]
1	7		 **9** (66)
2	7		 **10** (68)
3	**8**		 **11** (67)
4	**8**		 **12** (70)
5	**8**		 **13** (73)
6	**8**		R = CH_2-CH=CH_2 **14** (84)

[a] DIB (1.5 equiv), I_2 (0.3 equiv), hν, 25 °C, 3 h; then 0 °C, $BF_3 \cdot OEt_2$ (2 equiv), nucleophile (3 equiv), 0 → 25 °C, 3 h. [b] Yields for products purified by chromatography.

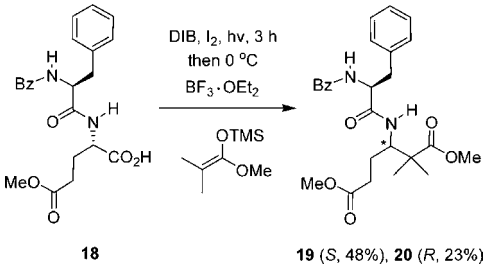
Scheme 2



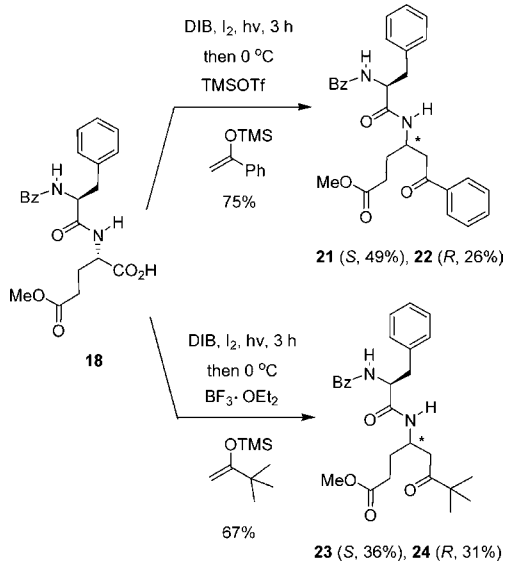
When the reaction was carried out with 1-*tert*-butyl-1-(trimethylsiloxy)ethene as the nucleophile, a separable mixture of dipeptides **23** and **24** was formed (67% overall yield, dr 6:5).

The formation of both diastereomers could be useful in medicinal chemistry studies to determine structure–activity relationships. Therefore, it was necessary to confirm the stereochemistry of both isomers.

Scheme 3



Scheme 4



In order to determine the configuration of the scission–addition products, the solid compounds **21** and **22** were crystallized, but the crystals proved unsuitable for X-ray analysis. Therefore, a chemical correlation with related α,γ-hybrids was explored. Thus, compound **7** underwent the Arndt–Eistert homologation[12] to give compound **25**, which was transformed in four steps into the α,γ-dipeptide **26** (Scheme 5). The $[\alpha]_D$ of this compound ($[\alpha]_D = -48$) was very similar to the optical rotation of compound **16** ($[\alpha]_D = -40$) but quite different than that of compound **17** ($[\alpha]_D = +37$). The other spectroscopic data were also very similar for **26** and **16**. Therefore, we propose the (*S*) configuration for compound **16**.

In a similar way, compound **25** was transformed into compound **27**, precursor of the α,γ-dipeptide **28**, whose optical rotation ($[\alpha]_D = -11$) matches that of compound

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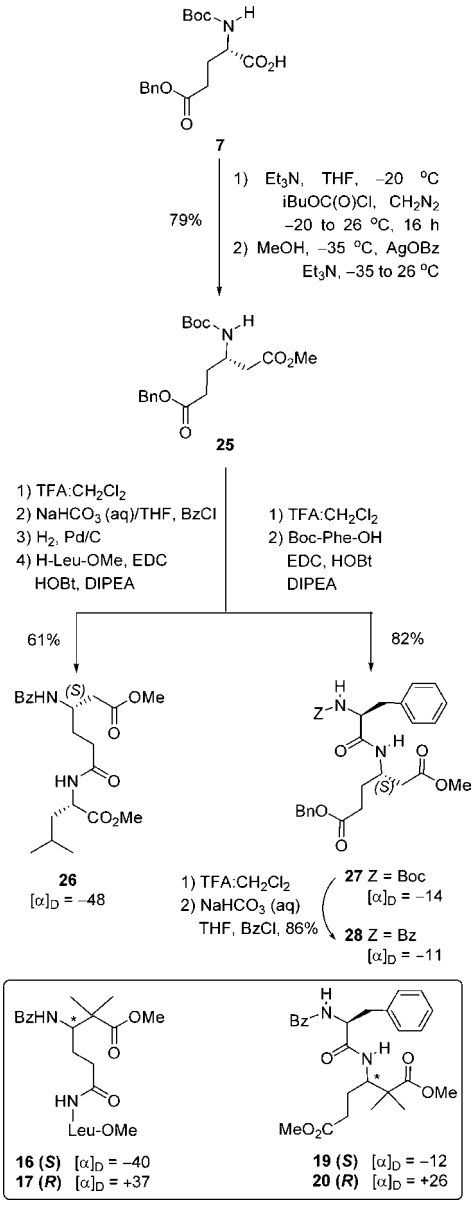
Scheme 5



19 ($[\alpha]_D = -12$) but differs from the one of isomer **20** ($[\alpha]_D = +26$). Compounds **19** and **20** were then assigned the *S* and *R* configurations, respectively.

Finally, compounds **21** and **23** were also assigned the *S* configuration because of the optical and spectroscopical similarities with respect to isomers **19** and **28**.

It should be pointed out that the Arndt–Eistert homologation allows the generation of α-unsubstituted or α-monosubstituted amino esters but not α,α-disubstituted derivatives. In those cases, the present methodology is a useful alternative to the Arndt–Eistert homologation. Moreover, as shown by compounds **21**–**24**, a variety of other alkyl chains can be introduced in a straightforward way.

In summary, the one-pot decarboxylation–alkylation process allows the efficient conversion of peptides with glutamic acid residues into α,γ-peptide hybrids with unnatural γ-amino acids. The process takes place under mild conditions in good yields. From a single peptide a collection of α,γ-peptide hybrids can be obtained in good global yield. Although epimer mixtures are generated, the isomers can be readily separated, which is quite useful to study structure–activity relationships. The dr could also be improved by using chiral catalysts, as will be reported in due course.

Nevertheless, this is the first reported site-selective peptide modification that allows the preparation of α,γ-hybrids. The use of the glutamate unit to generate diversity is particularly interesting. Since the carboxyl group of the glutamic units can be protected with different orthogonal groups, the starting peptide could contain several glutamic residues, but only the unprotected one(s) would be modified. For further modifications, the orthogonal protecting groups could be sequentially removed. The application of this methodology to the synthesis of bioactive or catalytic α,γ-hybrids is very promising.

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Supporting Information Available. Procedures for the synthesis of compounds **9**–**14**, **16**–**28**, the precursors of the scission substrates **30** and **31**, and their ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.