could rearrange to their more extensively delocalized isomers *E*, which on hydrolysis would lead to **16/18** or **17/20.** Cation D, probably an intermediate between B and E, might also cyclize further to F, and, provided that (*E*)-isosafrole is the starting olefin, afforded **21, 22,** or **23** with the stereochemistry indicated.

Several observations support this hypothesis. Condensation of ketal **10** with (*E*)-**12** (TsOH, CH_3CN, 20 °C, 1 h) gave a mixture of **17,** mp 169–172 °C, **20,** mp 150–154 °C (combined yield 25%), **15,** mp 130–131 °C (28%), and **24,** mp 151–152 °C (7%). The bicyclooctane **15** was stable under the conditions used for its generation but the secondary alcohol **24** was slowly, but quantitatively, converted to **17/20.** The latter mixture on the other hand was stable to trifluoromethanesulfonic acid in acetonitrile, conditions which caused nearly quantitative conversion of **15** to **17/20** showing that "burchellins" are more stable than "guianins". Secondly, isosafrole (**12**) recovered from condensations was found to be enriched in *Z* isomer because cycloadditions leading to C with two endo substituents are slower than those resulting in B with only one such destabilizing substituent. Finally, and most significantly, methanesulfonic acid promoted condensation (1 equiv, CH_3CN, 0 °C, 65 min) of pure (*Z*)-isosafrole (**12**) with ketal **9** followed by methylation of the crude mixture with methyl iodide (DMF, Ag_2O, 20 °C, 20 h) afforded racemic 2-epi,3a-epiburchellin (**3,** 10%), mp 140–142 °C, ^1H NMR δ 0.52 (d, 3, J = 7 Hz) identical with natural material ex *Aniba terminalis* as judged by spectral comparison[13] and 20% racemic futoenone (**4**), mp 242–246 °C. Identity with natural material rests on comparison of infrared, mass, ultraviolet, and 90-MHz NMR spectra as well as chromatographic behavior.

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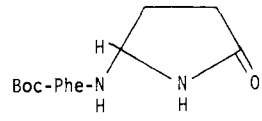
A General Approach to Retro-Isomeric Linear Peptide Synthesis

Sir:

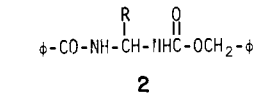
The topochemical approach for studying structure-activity relationships in linear peptides is still relatively new. A retro-isomer of a linear peptide is obtained through formal reversal of all the peptide bonds in the backbone, thus conserving the side-chain topology.[1] Synthesis of an absolute linear retro-isomer also requires solution of the "end-group" problem.[2] An absolute retro-isomer incorporates amino acids of the opposite chirality while preserving the same residues at each end of the peptide. The carboxyl end group problem can be solved by replacement of the C-terminal amino acid with an α-substituted malonic acid. However, conservation of the N-terminal amino acid is difficult, since an α,α-diamino residue is involved[3] (Figure 1).

Only a single case is known in the literature in which an α,α-diamino residue has been used to obtain the correct N terminus in a retro linear peptide. Morley replaced the pyroglutamyl residue by the 2-keto-5-pyrrolidinylamino residue (**1**), the α,α-diamino analogue. The synthesis of **1** was accomplished by a nonstereospecific hydrogenation of the 5-imino-2-pyrrolidinone precursor.[3]



1

In this paper we introduce a new application for a sequence of reactions, related to work carried out by Bergmann and Zervas[4] who dealt with stepwise degradation of polypeptides. They prepared doubly aminated aldehydes (*gem*-diamino compounds) of the general structure **2** through Curtius rearrangement of *N*-benzoylamino acids or *N*-benzoyl peptide hydrazides. The thermal rearrangement of the corresponding azides in the presence of benzyl alcohol yielded the appropriate benzylurethanes (structure **2**). The removal of the *N*-benzyloxycarbonyl group was accomplished by catalytic hydrogenation in the presence of hydrochloric acid followed by boiling in water which resulted in the corresponding aldehyde. The



2

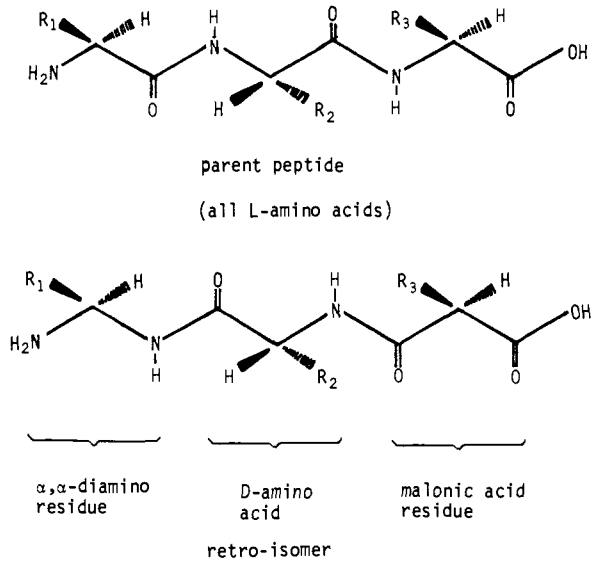


Figure 1.

Table I.[a] Analytical Results on *gem*-Diacyldiamino Compounds

Compd	X	R	Y	Empirical formula	% C Found	% C Calcd	% H Found	% H Calcd	% N Found	% N Calcd	Mp, °C
3a	Z	CH_3-	Boc	$C_{15}H_{22}N_2O_4$	61.42	61.21	7.55	7.53	9.42	9.52	149–150
3b	Boc	t-BuO_2CCH_2-	Z	$C_{20}H_{30}N_2O_6$	61.06	60.90	7.79	7.67	7.06	7.10	114–117
3c	Z	$PhCH_2O_2C$-	Boc	$C_{22}H_{26}N_2O_6$	63.73	63.76	6.36	6.32	6.93	6.76	129–130

[a] All compounds showed the expected NMR and IR spectra which confirmed the proposed structures.

latter was characterized as a 2,4-dinitrophenylhydrazone derivative.

The use of the *gem*-diamino compounds for the synthesis of linear peptides, retro-isomers, requires two different amino protected groups which could be removed selectively. We used a modified Curtius reaction,[5] employing a saturated solution of nitrosyl chloride in dry tetrahydrofuran. The azide which formed was allowed to rearrange to the corresponding isocyanate by heating in toluene at 80 °C. Addition of either *tert*-butyl alcohol or benzyl alcohol to the reaction mixture yielded the following N,N′-diprotected *gem*-diamino compound of the general formula **3**. Microchemical analyses and melting points are listed in Table I.

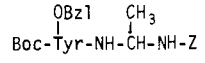
XN_α-CH(R)-NHY

3

The deprotection of compounds **3a–c** can be followed by immediate acylation using dicyclohexylcarbodiimide as a coupling agent. We have found that, although acidolysis is a practical deprotective reaction for *tert*-butyloxycarbonyl groups, the preferred approach wherever possible involves hydrogenation of benzyloxycarbonyl groups.

In Scheme I we outline the first application of the deprotected α,α-diamino analogues (above) to the synthesis of a linear retro-isomer of a dipeptide sweetener—α-DL-aminomalonyl-DL-phenylalanine methyl esters. The amine obtained from deprotection of compound **3c** was coupled to 2-benzylmalonic acid monomethyl ester to yield the fully protected linear retro-isomer **4**, mp 145–147 °C. Microchemical anal. Calcd for $C_{28}H_{28}N_2O_7$: C, 66.66; H, 5.59; N, 5.55. Found: C, 66.39; H, 5.72; N, 5.80. Deprotection of compound **4** by a catalytic hydrogenation under atmospheric pressure was carried out in methanol in the presence of 0.7 equiv of triethylamine, using a vortex shaker to induce rapid mixing. We could identify compound **5** as the only product. Its ^1H NMR spectrum taken in Me_2SO-d_6 showed the following bands: δ (ppm) 8.95, 8.88 (2 d, 1 H, NH), 7.25 (m, 5 H, arom), 4.71 (overlapping d, 1 H, NCHN), 3.95 (m, 1 H, CCHC), 3.54 (s, 3 H, OCH_3), 3.03 (m, 2 H, $-CH_2-$). An assignment was carried out by using homonuclear spin decoupling. The IR spectrum of the free retro-isomer **5** shows the following bands: ν_{max}^{KBr} (cm^{-1}) 3280, 1720, 1670 (sh), 1643, 1510. This compound was not sufficiently stable to be sent for microchemical analysis. The inherent instability originates from the diaminated glyoxylic acid structure.

We have also applied the same approach to the reversal of the peptide backbone in the middle of a peptide sequence related to the enkephalins, resulting in peptide analogues with only partial retrostructure. *tert*-Butyloxycarbonyl-*O*-benzyl-L-tyrosyl-D-alanylhydrazide was subjected to the reactions described above to yield 60% *N*-*tert*-butyloxycarbonyl-*O*-benzyl-L-tyrosyl)-*N*′-benzyloxycarbonyl-α,α-diaminoethane (**6**).



6

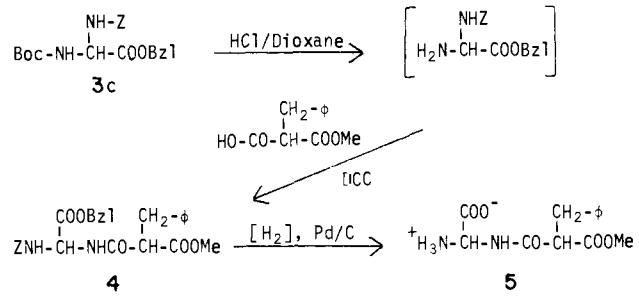
The crystalline compound **6**, had mp 170 °C, $[\alpha]^{21}_D$ −17.86 (*c* 2.01, DMF). Microchemical anal. Calcd for $C_{31}H_{37}N_3O_6$: C, 67.98; H, 6.81; N, 7.67. Found: C, 67.79; H, 6.80; N, 7.70. This general synthetic method can be used to obtain a variety of partial retro-analogues, with the retrosequence starting at various positions in the peptide chain and extending to include any desired number of residues.

The new application of the old "carbobenzoxy degradation"[4] provides the first solution to the synthesis of true retro-analogues of linear peptides. In our work, a topochemical approach requires us to modify a peptide in a manner such that the general features of spatial structure remain identical with those in the parent peptide but the direction of the peptide bonds is reversed. These modifications may result in an increased resistance toward inactivation by proteolytic enzymes which could give rise to prolonged biological activity.[1]

This chemistry was applied by us for the synthesis of retro-analogues of luteinizing hormone releasing factor (LRF). The synthesis was commenced with monomalonamide followed by D-amino acid residues and terminated with 5-amino-2-pyrrolidinone residue. Using our method we have been able to prepare 5-benzyloxycarbonylamino- and 5-*tert*-butyloxycarbonylamino-*N*-benzyloxycarbonylpyrrolidin-2-one (closely related compounds to structure **1**) in high yields from benzyloxycarbonyl-l-pyroglutamic acid hydrazide. Our results on the synthesis of retro-isomer of the LRF will be reported elsewhere.[6]

We are continuing work on improving the synthetic methods, optimizing yields, establishing methods for purification, and checking optical purity at different stages of the synthesis. This methodology is being applied to other biologically active peptides, including hormones and tastants.

Scheme I



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