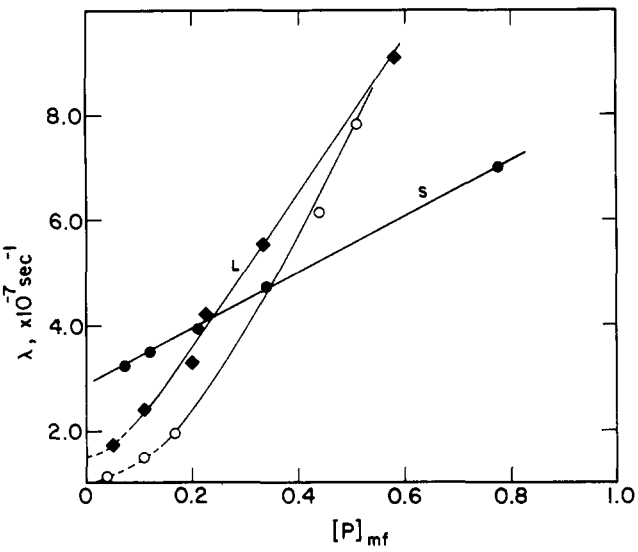

Figure 3. Plots of pseudo-first-order apparent excimer decay rates vs. mole fraction of PDecA in DSP (S), DOP (O), and DLP (L). Measurements were taken at surface pressures of 5 dyn/cm.

Here the time course of apparent excimer emission decay at high probe concentration may be related to excimer behavior via the expression

$$1/\tau = \lambda = k_m + k_{md} + k_{dm}[Py]$$

where τ is the measured lifetime, k_m is the rate constant for excited monomer emission, k_{md} is excimer dissociation, and k_{dm} is the formation rate constant. It follows that

$$d\lambda/d[Py] = k_{dm}$$

at high concentrations of PDecA. The plots in Figure 3 of λ vs. [PDecA] provide essentially linear relationships over most of the data although some curvature is implied at the lowest concentrations used. The intercepts for these plots fall within the region reported in Birk's early pyrene–hexane systems where λ as $C \rightarrow 0$ is taken to reflect the sum of all rate constants for disappearance of excimer. In none of these systems have we been able to suitably measure the monomer lifetime (spectral studies have shown that the contribution of monomer fluorescence is very small in these systems).

For comparison to other systems, we have applied the simple relationship of Sackmann[3] ($D_p \approx {}^1/_4\, k_{dm}$) and utilized areas per molecule found in Figure 1. With this relationship and k_{dm} in cm^2 $molecule^{-1}$ s^{-1}, one arrives at diffusion coefficients of 0.5, 2.4, and 2.2×10^{-7} cm^2 s^{-1} for PDecA in DSP, DOP, and DLP, respectively. The diffusion constant found here in DSP is comparable to that reported by Sackmann for PDecA in dipalmitoylphosphatidylcholine bilayer and monolayer vesicles (8×10^{-8} cm^2 s^{-1})[7]. The values for the DOL system are, as expected, somewhat lower than for PDodecA in an oleic acid monolayer determined eariler by steady-state methods and application of Monte Carlo simulations to the data (lower limit = 9×10^{-7}).[8] Although these measurements were conducted at low surface pressure, it might be considered somewhat surprising that the DSP monolayer exhibited a k_{dm} so comparable with those obtained in the other lipids which incorporate *cis* methylene interrupted double bonds. However, photobleaching studies by Tancrede, et al. indicate a limited dependence on the nature of the lipid alkyl chains alone.[9] Additionally, one may not disregard the perturbations in the lipid packing generated by the presence of the pyrene (or other) probe. While such diffusion constants are not meant to be taken strictly as a measure of lipid fluidity in a pure lipid monolayer, they do demonstrate a rather simple means for characterizing interaction of the probe and provide an insight into spread monolayer behavior at the molecular level. A comprehensive study of temperature, compression, and probe structure effects in such systems is in progress.

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(8) Loughran, T.; Hatlee, M. D.; Patterson, L. K.; Kozak, J. J. *J. Chem. Phys.* **1980**, *72* (11), 5791–5797.
(9) (a) Tancrede, P.; Teissie, J.; Tocanne, J. F. *Biophys. J.* **1984**, *45*, 336. (b) Tancrede, P., private communication.

A New Class of Amino Acid Based Sweeteners

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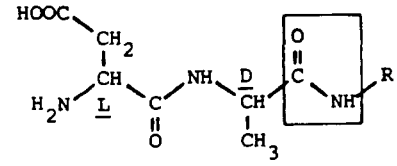
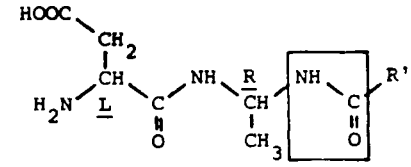
We wish to report the synthesis of a novel class of sweeteners based on the "retro-inverso" peptide modification. It has been reported that certain L-aspartyl-D-alanine amides I are sweet.[1,2]



(I)



(II)

Since the routes to reverse the direction of amide bonds in peptide backbones are now being developed,[3] we utilized this approach to prepare the *N*-(L-aspartyl)-1,1-diaminoalkane-based sweeteners II.[4] In these derivatives, the C-terminal amide bond in the structure I has been formalistically reversed. This was accomplished with complete maintainance of optical purity at the asymmetric center of the diaminoalkane residue. The taste characteristics of these molecules are strikingly similar in quality to sucrose and depend on the nature of the group R′ of the carboxylic acid used to acylate the 1,1-diaminoalkane. The properties of a small selection of a large number of these compounds which have been synthesized and where the nature of the group, R′, of the terminal amide is varied are summarized in Table I. The chirality of the aspartyl residue in these derivatives is L, while the chirality of the 1,1-diaminoalkane is *R*.

The synthesis of these 1,1-diaminoalkane derivatives is outlined in Scheme I. The protected dipeptide III was prepared by using standard peptide chemical techniques. The key step in the synthesis of these novel sweeteners, the Hofmann rearrangement of compound III, was accomplished by using a mild oxidizing agent from the class of iodobenzene compounds, such as [bis(trifluoroacetoxy)iodo]benzene.[5] The monoacylated 1,1-diaminoalkane salt IV was then acylated, under basic conditions, by the

* University of California.
(1) Sukehiro, M.; Minematsu, H.; Noda, K. *Seikatsu Kagaku* **1977**, *11*, 9–16; *Chem. Abstr.* **1977**, *87*, 168407*h*.
(2) Brennan, T. M.; Hendrick, M. E. U.S. Patent 4411925, 1983.
(3) Chorev, M.; Goodman, M. *Int. J. Peptide Protein Res.* **1983**, *21*, 258–268. Chorev, M.; MacDonald, S. A.; Goodman, M. *J. Org. Chem.* **1984**, *49*, 821–827.
(4) Verlander, M. S.; Fuller, W. D.; Goodman, M. European Patent Application, Publication 0128654, 1984; *Chem. Abstr.* **1985**, *102*, 185492*c*.
(5) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272–4276; **1984**, *49*, 4277–4284.

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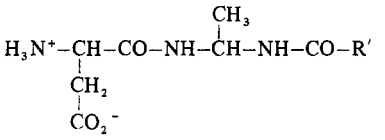
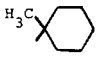
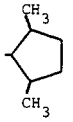
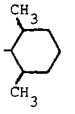
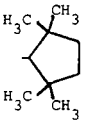
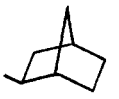
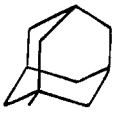
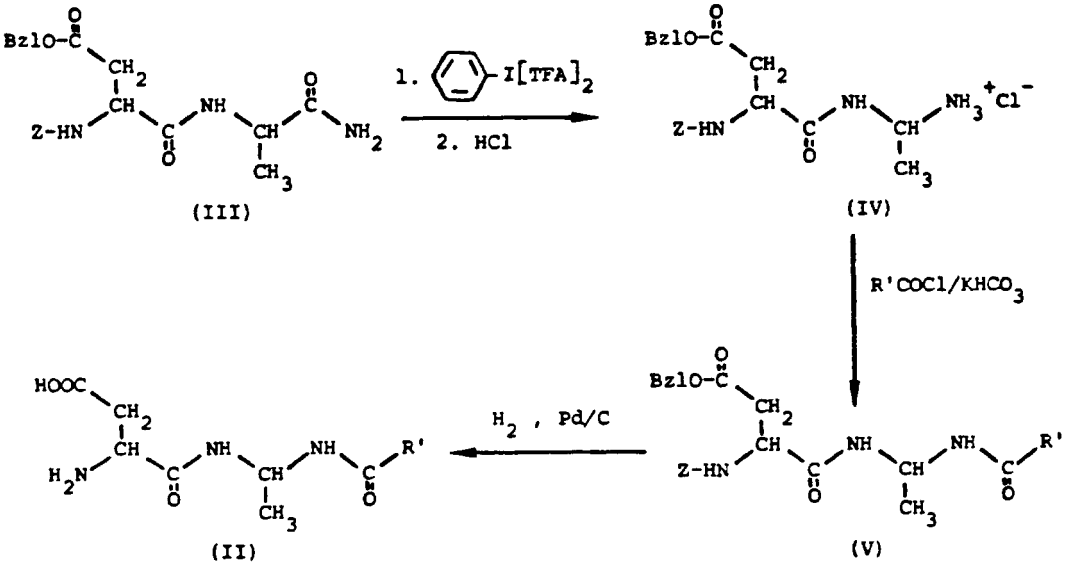
Table I. Properties of 1,1-Diaminoalkane-Derived Sweeteners



R′	sweetness[a]	microchemical anal.[b]	R′	sweetness[a]	microchemical anal.[b]
$-C(CH_3)_3$	75–100	C, H, N ($0.5H_2O$)		50–75	C, H, N ($0.75H_2O$)
	500–700	C, H, N ($0.75H_2O$)		35–50	C, H, N ($1.0H_2O$)
	75–100	C, H, N ($0.5H_2O$)		150–250[c]	C, H, N ($0.75H_2O$)
	300–400[c]	C, H, N ($0.5H_2O$)		150–200[c]	C, H, N ($1.25H_2O$)
	800–1000	C, H, N ($1.25H_2O$)		75–100	C, H, N ($1.0H_2O$)
"	600–800[d]	C, H, N ($1.5H_2O$)		5–15	C, H, N ($1.75H_2O$)
	5–20	C, H, N ($0.75H_2O$)			

[a] Values determined relative to sucrose by an expert taste panel available to the Cumberland Packing Corporation using established tasting protocols. [b] Values were within ±0.4% of the theoretical values for the elements indicated; samples contained varying amounts of water as indicated by the values in parentheses. [c] Mixture of cis and trans isomers. [d] Derived from *N*-(L-aspartyl)-(*S*)-1,1-diaminoethane.

Scheme I



appropriate acid chloride to yield the fully protected sweetener derivative V. Finally, compound V was deprotected under standard conditions to give the L-aspartyl-1,1-diaminoalkane sweetener II. In this series of compounds, the analogue *N*-(L-aspartyl)-*N*′-[(2,2,5,5-tetramethylcyclopentyl)carbonyl]-(*S*)-1,1-diaminoethane is also sweet, with a taste intensity of about 600–800 times sucrose.[6] This is most unexpected since analogous diastereomers in the dipeptide ester series, such as L-aspartyl-D-phenylalanine methyl ester and L-aspartyl-L-alanine benzyl ester, are bitter.

The compounds listed in Table I are extremely stable toward hydrolysis[6] and cannot form diketopiperazines. Thus, through use of a fundamental topochemical structural modification, we have designed an important, new class of synthetic sweetener molecules. A more complete description of these compounds will be published in a future report.[6]

Acknowledgment. We thank the Cumberland Packing Corporation for their financial support of this research, which was carried out at BioResearch, Inc.

Supplementary Material Available: Experimental section for II–V including TLC, optical rotation, and elemental analyses (4 pages). Ordering information is given on any current masthead page.

(6) Fuller, W. D.; Goodman, M.; Verlander, M. S., manuscript in preparation.