the chiral side chain promised to result in decomposition of the cyanohydrin,[11] an acid-catalyzed method was developed (0.6% p-TsOH·H_2O in 2:1 dioxane/H_2O, reflux, 16 h), which effected conversion of **4** into (*R*)-mandelonitrile (**5**, 93% yield),[6a,7a] $[\alpha]^{25}_D$ +43.5° (*c* 5, $CHCl_3$).[12] The optical purity of **5** was confirmed to be 92.5% by conversion to the MTPA ester[13] (1.5 molar equiv MTPACl, pyridine, 3.5 h, 25 °C). Treatment of **4** with methanolic hydrogen chloride (3:1 Et_2O/MeOH saturated with HCl, 4 °C, 16 h) afforded (*R*)-methyl mandelate (**6**)[6a] mp 52.5–54 °C (97% yield from **4**), $[\alpha]^{25}_D$ −168° (*c* 0.8, C_6H_6).[14]

The reduction of cyanohydrins and derivatives to provide β-amino alcohols is well documented.[15] We decided therefore to explore the possibility of converting the chiral ethers **3** into β-amino alcohols while retaining the stereochemical integrity of the carbinol group. In the event, treatment of ethers **3a** and **3c** with borane (1.5 molar equiv BH_3·THF,[3] reflux 4 h) led respectively to the amino ethers **7** and **8**.[7a] Substance **7** was formylated[16] to give **9** in 85% overall yield,[6b,7] and the GC of the corresponding *tert*-butyldimethylsilyl ether showed two peaks in the ratio 96:4, confirming that no detectable epimerization had occurred during reduction.[17] The chiral auxilliary was removed[2] by oxidation to the ketone (Jones reagent), followed by base-catalyzed β-elimination[10] to produce **11**[6b,7] (89% yield from **9**). The configuration of **11** was shown to be *R* by its transformation[18] into the known quarternary iodide **14**.[19]

Ether **3c** was also reduced as described above, and the product **8** was converted[20] into the *tert*-butoxycarbonyl derivative **10**[6,7a] in 90% yield. Removal of the chiral auxilliary[2,9,10] afforded **12**,[6,7a] the optical purity of which was shown to be 91.5% by conversion to the MTPA ester,[13] thus confirming that little, if any, racemization occurred during the reduction step. Deprotection of **12** (TFA/H_2O (3:1), 25 °C, 0.5 h) afforded the known 2(*R*)-hydroxy-2-phenylethylamine (**13**), monohydrate[6,7a] in 80% yield (from **10**), $[\alpha]^{25}_D$ −60° (*c* 2, $CHCl_3$).[21]

The study described above illustrates the suitability of chiral cyanohydrin ethers of type **3** as precursors to optically active cyanohydrins, β-amino secondary alcohols, and α-hydroxy esters. A particularly noteworthy aspect of our methodology for the preparation of ethers **3** is that it permits the easy access to either antipodal form at the newly generated chiral center (Scheme I) dependent, in a reliable manner, upon the choice of an acetal **1** derived from (2*R*,4*R*)- or (2*S*,4*S*)-pentane-2,4-diol.[22-24]

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research.

(11) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287.
(12) Lit. $[\alpha]^{20}_D$ +39° (*c* 5, $CHCl_3$), ref 15b.
(13) Determined by GC analysis (base-line separation) of (*R*)-(+)-MTPA esters. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
(14) Lit. mp 54–55 °C, $[\alpha^{20}_D$ −176° (*c* 0.83, C_6H_6). Noe, C. R. *Chem. Ber.* **1982**, *115*, 1591–1606.
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(16) The substrate was heated to 60 °C with excess HCO_2H/Ac_2O (1:1) for 1 h, and then the crude formate ester was isolated and saponified by stirring with K_2CO_3, MeOH, H_2O.
(17) Epimerization of **3a**, A/B 95:5 (LDA, THF, −78 °C;[11] H_2O) gave a sample of **3a**, A/B 51:49 (GC coinjection and ^1H NMR spectroscopy). This sample was transformed into the *tert*-butyldimethylsilyl ether of **9**, which showed two GC peaks, ratio 49:51, of identical retention times (coinjection) with the sample mentioned above (ratio 95:5).
(18) Amide **11** was converted (37% aqueous $HCHO/HCO_2H$ (1:1), reflux 12 h) into the tertiary amine,[7a] which was further methylated (MeI, MeOH, reflux 16 h) to give **14**; mp 178–180 °C, $[\alpha]^{25}_D$ −10.9° (*c* 1, EtOH), [reported[19] mp 170–172 °C, $[\alpha]^{25}_D$ −12.23° (*c* 1, EtOH)].
(19) Coke, J. L.; Richon, A. B. *J. Org. Chem.* **1976**, *41*, 3516–3517.
(20) Di-*tert*-butyl dicarbonate,[3] THF, reflux, 45 min. Cf. Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730–732.
(21) Lit. $[\alpha]^{20}_D$ −71° (*c* 5, $CHCl_3$), ref 15b.
(22) For a theoretical discussion of the origins of diastereoselectivity in these processes, see ref 2.
(23) For the preparation of both (2*R*,4*R*)- and (2*S*,4*S*)-pentane-2,4-diol, via asymmetric hydrogenation of acetylacetone, see: Ito, K.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3367–3368.
(24) During the course of this work, Ito et al. [Ito, Y.; Kato, H.; Imai, H.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 6449–6450] reported the reaction of a dimethyl acetal with *tert*-butyl isocyanide in the presence of $TiCl_4$ to give a cyanohydrin *O*-methyl ether. When chiral acetal **1b** was treated with *t*-BuNC under conditions otherwise identical with those employed for Me_3SiCN, **3b** was formed, quantitatively, with a diastereomeric ratio A/B 96:4 (GC coinjection and ^1H NMR spectroscopy).

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Peptide Decomposition in the Neutral pH Region via the Formation of Diketopiperazines

Summary: In the neutral pH region, the decomposition of the tripeptides Leu-Gly-Gly and Gly-Leu-Gly at 130 °C and the hexapeptide Phe-Gly-Leu-Gly-Val-Gly at 100 °C has been found to involve the formation of diketopiperazines from the N-terminal position of the peptides.

Sir: Although the decomposition of peptides in strongly acidic and basic solutions has been extensively investigated,[1] there have been few studies of peptide decomposition at neutral pH. Peptide hydrolytic mechanisms in the neutral pH region would be important to establish since they could be used to elucidate the pathways of protein decomposition in fossils and sediments.[2] Previous results from this laboratory have shown that in the range pH 5–8 dipeptides undergo extensive reversible cyclization to their diketopiperazines.[3] This transformation is accompanied by extensive racemization due to the rapid rate of racemization of amino acid residues in diketopiperazines.[3] In earlier investigations with dipeptide methyl esters and amides, it was demonstrated that internal aminolysis to form the diketopiperazine was much faster than the hydrolysis of the ester or amide functionality.[4] We were thus interested in the possiblity that decomposition of larger peptides would proceed via formation of diketopiperazines at the N-terminal position according to reaction mechanism 1.[5] To test this possiblity, the decomposition of the tripeptides Leu-Gly-Gly,

(1) Hill, R. L. *Adv. Protein Chem.* **1965**, *20*, 37.
(2) Bada, J. L.; Man, E. H. *Earth-Sci. Rev.* **1980**, *16*, 21. Ho, M.-S.; Bada, J. L.; Yan, Z.; Liu, D. In "Aquatic and Terrestrial Humic Materials"; Christman, R. F., Gjessing, E. T., Eds.; Ann Arbor Sci.: Ann Arbor, MI 1983; p 429.
(3) Steinberg, S.; Bada, J. L. *Science (Washington, D.C.)* **1981**, *213*, 544.
(4) Purdie, J. E.; Benoiton, N. L. *J. Chem. Soc., Perkin Trans. 2* **1973**, *13*, 1845.
(5) The continuation of the peptide chain is denoted by ~.

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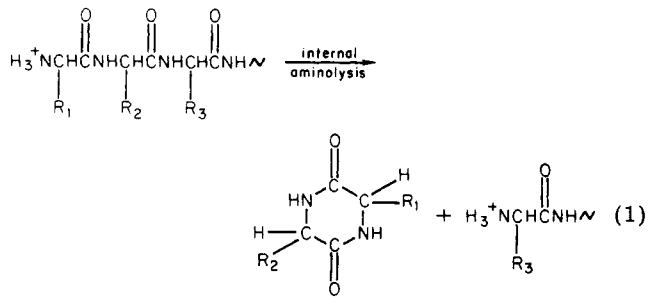

(1)

Gly-Leu-Gly, and Gly-Gly-Leu and the hexapeptide Phe-Gly-Leu-Gly-Val-Gly were investigated in the neutral pH region at elevated temperatures (100 and 130 °C).

Solutions (1 μM) of each peptide were prepared in phosphate buffer;[6] aliquots in Pyrex test tubes were sealed under vacuum and heated at elevated temperatures for various lengths of time. Peptide fragments produced by heating were separated and quantified by high-pressure liquid chromatography.[8,9]

The results of the heating experiments with Leu-Gly-Gly and Gly-Leu-Gly at 130 °C are shown in Table I; similar results[9] were observed at 100 °C. The principle decomposition route of Leu-Gly-Gly and Gly-Leu-Gly was found to be the internal aminolysis reaction, i.e., eq 1, producing the diketopiperazine c-(-Leu-Gly-). In addtion to diketopiperazine formation, the tripeptides also underwent a reversible sequence inversion reaction, apparently through a cyclic tripeptide intermediate. Thus, the heated solutions of Leu-Gly-Gly contained c-(-Leu-Gly-), Gly-Leu-Gly, and a trace of Gly-Gly-Leu. Likewise, Gly-Leu-Gly decomposed to c-(-Leu-Gly-) and underwent extensive sequence inversion to Leu-Gly-Gly and trace amounts of Gly-Gly-Leu. Hydrolysis of the diketopiperazines yielded dipeptides in all heating experiments. The rate of formation of diketopiperazines from Leu-Gly-Gly and Gly-Leu-Gly increased with decreasing pH. Dipeptides were formed at a much slower rate than the rate of decompositon of the tripeptides or the rate of diketopiperazine formation. It is thus apparent that the dipeptides are formed from the decomposition of the diketopiperazines and not from hydrolysis of the tripeptides.

The importance of the hydrolysis of the Leu–Gly peptide bond in the decomposition of Leu-Gly-Gly was determined by measuring the production of free leucine in the initial stages of heating.[10] At pH 7.4 only 2% of the tripeptide decomposed as a result of hydrolysis at the Leu–Gly bond. It was not possible to quantify the importance of hydrolysis at the Gly–Gly bond for Leu-Gly-Gly. However, because only very little Leu-Gly was observed during the initial heating periods, it is inferred that hydrolysis of this bond is very much slower than formation of the diketopiperazine.

The decomposition of Gly-Gly-Leu was notably different than that of the other two tripeptides. From the appearance of Gly-Leu during the initial stages of heating, it was estimated that 60% of the Gly-Gly-Leu decomposed via hydrolysis of the Gly–Gly peptide bond. For this tripeptide, hydrolysis at the Gly–Gly peptide bond competes effectively with the formation of the diketopiperazine c-(-Gly-Gly-).

The most surprising observation in the tripeptide heating experiments is the tripeptide sequence inversion. This reaction presumably proceeds via formation of a cyclic tripeptide intermediate, although alternative bicyclic intermediates may also be possible. Sequence inversion of Leu-Gly-Gly was approximately as fast as diketopiperazine formation at pH 7.4 (see Table I). The instability of the nine-membered ring of cyclic tripeptides is well documented.[11] This may explain why we were not able to isolate or detect a cyclic tripeptide in these heating experiments.

The decomposition of the hexapeptide Phe-Gly-Leu-Gly-Val-Gly was investigated at 100 °C and pH 7.26. Because the diketopiperazines produced from the decomposition of the hexapeptide were not always clearly resolved by the analytical method,[8] they were quantified after separation from the heated solutions by chromatography[3] on Dowex-50X8. The separated diketopiperazines were then hydrolyzed in 6 N HCl and the amino acids quantified.[3,12]

The hexapeptide was also found to decompose[9] by successive formation of diketopiperazines; c-(-Phe-Gly-), c-(-Leu-Gly-), and c-(-Val-Gly-) were detected in the heated hexapeptide solutions. The dipeptides Phe-Gly, Gly-Phe, Leu-Gly, Gly-Leu, Val-Gly, and Gly-Val were also identified.[8,9] These are the expected dipeptides if the hexapeptide decomposed via the formation of diketopiperazines, followed by their hydrolysis to the dipeptides. The ratios Phe-Gly/Gly-Phe and Leu-Gly/Gly-Leu remained constant at 2.4 ± 0.1 and 2.5 ± 0.1, respectively, during the course of the heating of the hexapeptide. This observation is consistent with the formation of the dipeptide pairs Phe-Gly, Gly-Phe and Leu-Gly, Gly-Leu in their equilibrium ratios from the hydrolysis of the di-

(6) The peptides Leu-Gly-Gly, Gly-Leu-Gly, Gly-Gly-Leu, Phe-Gly-Leu-Gly, and Val-Gly were purchased from Vega Chemicals. The hexapeptide Phe-Gly-Leu-Gly-Val-Gly was prepared by Dr. Russell Doolittle, Department of Chemistry, University of California, San Diego. The diketopiperazines c-(-Leu-Gly-), c-(-Phe-Gly-), and c-(-Val-Gly-) were synthesized from the dipeptides by the method of Fischer.[7] Phosphate buffers (0.1 M) were prepared with analytical-grade $NaH_2PO_4 \cdot H_2O$ and titrated to the desired pH with 2 M NaOH. The ionic strength was adjusted to 0.5 by the addition of NaCl. The pH values at 100 and 130 °C were calculated from the equations given by Bates (Bates, R. G. "Determination of pH"; Wiley: New York, 1964; p 76).

(7) Fischer, E. *Chem. Ber.* **1906**, *39*, 2893.

(8) The HPLC was carried out by using an Altex Model 310 gradient liquid chromatograph. Peptides were detected by monitoring the column effluent at 210 nm with an Altex 155-OOUV-VIS spectrophotometer. The column was a Sperisorb S-5-ODS (0.46 × 25 cm). Leucine-containing peptides, from the tripeptide heating experiments, were separated at a flow rate of 1 mL/min with a mobile phase consisting of 97.5% 0.05 M KH_2PO_4 (titrated to pH 3 with H_3PO_4) and 2.5% acetonitrile. Dipeptides formed from the hexapeptide were separated at a flow rate of 1 mL/min with a gradient from 100% 0.05 M KH_2PO_4 (pH 3/0% acetonitrile) to 90% 0.05 M KH_2PO_4 (pH 3/10% acetonitrile) over a 20-min period. The hexapeptide and Leu-Gly-Val-Gly were not eluted under these conditions. The identity of the various peptide fragments was established by comparison of their retention times with those of standards. In addition, the various peptides eluting from the HPLC column were collected, hydrolyzed, and their amino acid composition determined by using the procedures described below.[12]

(9) Steinberg, S. Ph.D. Thesis, University of California, San Diego, 1982.

(10) Leucine was analyzed by using the *o*-pthaldialdehyde (OPT)–amino acid technique described elsewhere.[3,9]

(11) Rothe, M.; Theysohn, R.; Mühlhauser, D.; Eisenbeiss, R.; Schindler, W. In "Chemistry and Biology of Peptides"; Meienhofer, J., Ed.; Ann Arbor Sci.: Ann Arbor, MI 1972; p 51.

(12) Amino acids produced from the hydrolyzed diketopiperazines and dipeptides were separated and quantified as their dansyl derivatives [Wilkenson, S. M. *J. Chromatogr. Sci.* **1978**, *16*, 547. Tapuhu, Y.; Schmidt, D. G.; Linder, W.; Karger, B. L. *Anal. Biochem.* **1981**, *115*, 123]. A 1-mL aliquot of 0.5 M Li_2CO_3 (pH 9.6) was added to the desiccated HCl hydrolysate. Dansyl chloride in acetonitrile (0.5 mL of 2 mg/mL) was added and the sample was allowed to react for 2 h at room temperature. The reaction was terminated with 50 μL of 0.5 M methylamine hydrochloride. The instrumentation and reversed-phase column was the same as that specified previously.[8] The mobile phase consisted of a gradient mixture of 0.5 M NaH_2PO_4 (pH adjusted to 7.2) and acetonitrile. All separations were carried out at a flow rate of 1 mL/min. The solvent was maintained at 10% acetonitrile for 5 min after injection at which time a 10-min gradient at 20% acetonitrile was initiated. After completion of the gradient, the mobile phase was maintained at 20% acetonitrile for 10 min and then increased linearly to 50% over 30 min.

Table I. Products Detected in Neutral pH Aqueous Solutions of Leu-Gly-Gly and Gly-Leu-Gly Heated at 130 °C[a]

pH at 130 °C	heating time, h	Leu-Gly-Gly, %	c-(-Leu-Gly-),[b] %	Gly-Leu-Gly, %	Leu-Gly, %	Gly-Leu, %
			Leu-Gly-Gly			
7.40	1.0	68	14	14	0.8	0
	3.0	41	21	19	12	0.4
	5.2	23	26	14	22	13
6.96	1.0	66	21	11	0	0
	3.0	25	42	12	9.3	6.5
	5.0	15	49	9	17	11
6.10	1.0	45	41	6.6	0	0
	3.0	10	82	5	5	4
	5.0	4	87	2.8	6.5	5.5
			Gly-Leu-Gly			
7.40	1.1	19	5.5	75	2.2	0.4
	3.8	33	9.8	34	11	5.2
	5.8	32	12	27	21	8.9
6.77	1.0	17	18	65	2.5	0
	3.1	20	41	25	5.5	4.2
	5.2	11	47	9.1	14.5	9
6.10	1.1	9	39	53	2.6	0
	3.8	3.6	78	5.2	4.4	1.1
	5.8	1.5	80	2	8.6	4.5

[a] The quantities of other constituents (i.e., Gly, Leu, Gly-Gly-Leu, etc.) were found to be negligible. The values have an accuracy of ca. ±5%. [b] 3-(2-Methylpropyl)-2,5-piperazinedione.

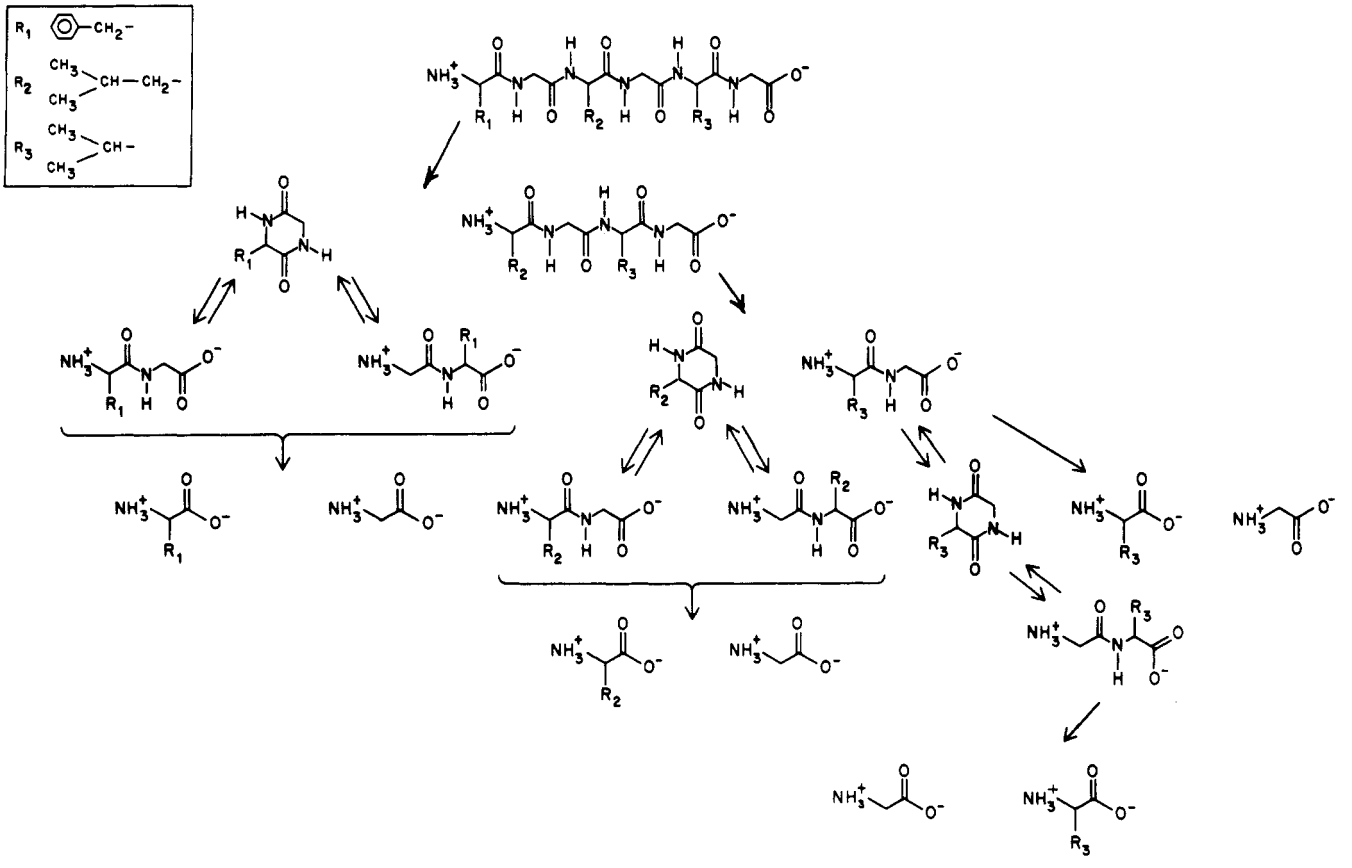

Figure 1. Hydrolysis pathway of the hexapeptide Phe-Gly-Leu-Gly-Val-Gly at pH 7.26 and 100 °C.

ketopiperazines c-(-Phe-Gly-) and c-(-Leu-Gly-), respectively. The diketopiperazine c-(-Val-Gly-), however, would be produced from the cyclization of Val-Gly, which should be the end product if the hexapeptide decomposes by the successive formation of the diketopiperazines. It would thus be expected that the Val-Gly/Gly-Val should undergo a large change during the heating of the hexapeptide solution. The ratio Val-Gly/Gly-Val was observed to decrease smoothly from 2.8 to 1.0 during the heating experiment. On the basis of the products detected, the decomposition pathways of the hexapeptide can be summarized as shown in Figure 1.

These results demonstrate the importance of internal aminolysis, giving rise to diketopiperazines during the decomposition of peptides. It is therefore proposed that diketopiperazine formation is also an important decomposition mechanism for the proteinaceous material in fossils. Moreover, the formation of diketopiperazines during protein decomposition and the rapid rate of racemization that accompanies diketopiperzine formation may explain the complex amino acid racemization kinetics observed in calcareous fossils.[2,13]

The first event in the diagenesis of proteins in fossils is likely the cleavage of labile peptide bonds,[14] i.e., those involving sterically unhindered residues, and hydroxy and acidic amino acid residues. After these initial cleavages, peptide decomposition should proceed largely by successive formation of diketopiperazines according to eq 1. The liberated diketopiperazines then undergo hydrolysis to dipeptides, which are in turn hydrolyzed to free amino acids. Rapid racemization occurs in the diketopiperazine intermediate.[3] The subsequent hydrolysis of the diketopiperazines into dipeptides and eventually free amino acids would thus yield the highly racemized low molecular weight peptides and free amino acids that are observed in calcareous fossils.[2,13,15]

In addition to the geochemical implications, the diketopiperazine hydrolysis mechanism for peptides may also have implications for the thermal processing of food proteins, where the rapid rate of racemization accompanying diketopiperazine formation could produce significant amounts of D-amino acids. Several diketopiperazines have been identified in aged and heated foods and in protein hydrolysates.[16] The presence of D-amino acids in foods has important nutritional consequences.[17]

Acknowledgment. This work was supported in part by a grant from the Alfred P. Sloan Foundation. We thank R. Doolittle for synthesizing the hexapeptide.

Registry No. Leu-Gly-Gly, 1187-50-4; Gly-Leu-Gly, 2576-67-2; Phe-Gly-Leu-Gly-Val-Gly, 85864-65-9; c-(-Leu-Gly-), 5845-67-0; c-(-Gly-Gly-), 106-57-0; c-(-Phe-Gly-), 10125-07-2; c-(-Val-Gly-), 16944-60-8.

(13) Wehmiller, J. F.; Hare, P. E. *Science (Washington, D.C.)* **1971**, *173*, 907. Bada, J. L.; Schroeder, R. A. *Earth Planet. Sci. Lett.* **1972**, *15*, 1. Schroeder, R. A.; Bada, J. L. *Earth-Sci. Rev.* **1976**, *12*, 347.
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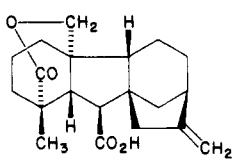
A New Strategy for C_{20} Gibberellin Synthesis: Total Synthesis of (±)-Gibberellin A_{38} Methyl Ester[†,1]

Summary: The extension of the strategy used for C_{19} gibberellin synthesis to include the C_{20} gibberellins has been realized through elaboration of the common intermediate **7** to give aldehyde **10** and then a novel intramolecular conjugate addition of an anionic ester species via a six-membered transition state, **3** → **4**, followed by the intramolecular aldol cyclization, **5** → **6**.

Sir: The molecular basis for the biological activity of the gibberellin phytohormones has yet to be established, while many questions relating to their biosynthesis also remain unanswered.[3] Reasonably practical access to the gibberellins through total synthesis has recently been established[4] for the C_{19} compounds, e.g., gibberellic acid, but only one of the simplest C_{20} gibberellins, (±)-GA_{15} (1), has



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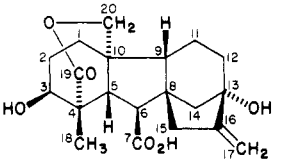

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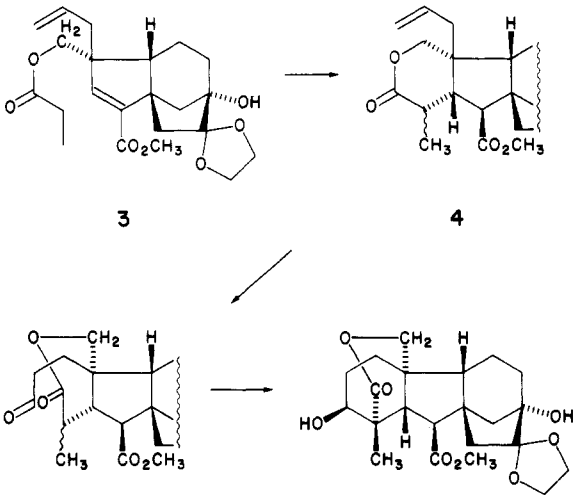
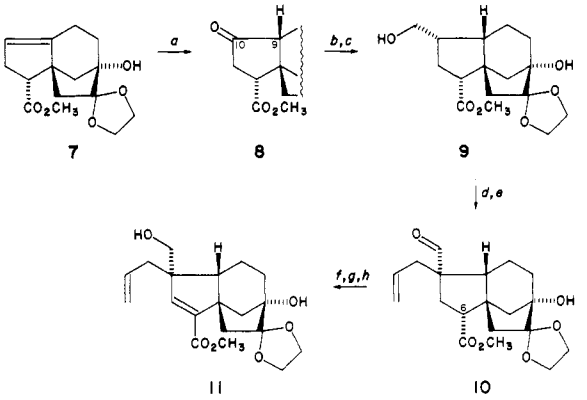
been prepared by total synthesis, and then from an arduous 45-step sequence.[5]

Chart I



3 4 5 6

Chart II



7 8 9 11 10

Reagents: [a] BH_3.DMS; CrO_3.2Py. [b] Zn, $TiCl_4$, CH_2Br_2. [c] Thexylborane; H_2O_2, Na_2HPO_4. [d] CrO_3.2Py. [e] LDA; CH_2=$CHCH_2Br$, HMPA. [f] KH, Ph_2Se_2. [g] $NaBH_4$. [h] H_2O_2, 2,6-lutidine.

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(1) This work was described at the Seventh National Convention of the R.A.C.I., Canberra, Australia, Aug 1982.
(2) Queen Elizabeth II Fellow.

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