11a and **12a** (72:28),[16] and 10% of an unidentified substance of considerably longer retention time. Formation of the diastereomers clearly demonstrates that Cope rearrangement had occurred under the reaction conditions; however, there was no evidence for the desired tandem Cope–Claisen rearrangment. Since *O*- to *C*-silyl migration is not normally observed in the Claisen allyl silyl ketene acetal rearrangement,[17] it is especially noteworthy, and perhaps indicative of the energy barrier for Claisen rearrangement in this system.

The influence of a methyl substituent on the ketene acetal was examined by thermolysis of **1b**, X = $OSiMe_2$-*t*-Bu, 90:10 *E*/*Z* [0.3 M in 1,2,4-trichlorobenzene, 205 °C, 3.5 h, 10 equiv of *O*,*N*-bis(trimethylsilyl)acetamide, argon] followed by treatment with KF·$2H_2O$ in HMPA[11d] and extraction with 1 N KOH to give a mixture of carboxylic acids in 51% combined yield. ^{1}H NMR of this mixture showed a doublet of doublets (J = 15, 4 Hz) at δ 5.80 characteristic of a proton on a *trans*-alkene. Treatment with CH_2N_2 gave a mixture of three methyl esters (20:46:34), all of which showed parent ions at m/e 250 and similar fragmentation patterns on GC/MS analysis. Although the individual components have not yet been separated, the presence of **4b** (X = OMe, one or both α-substituted propionate diastereomers) as a major constituent is strongly suggested by spectral data [inter alia δ 5.60 (dm, J = 16 Hz)]. The formation of compound(s) containing a >C=CH_2 group via transannular cyclization[18] is also suggested [^{1}H NMR δ 4.67 (br s); IR 890 cm^{-1}].

In addition to the desired tandem Cope–Claisen rearrangement, the occurrance of *O*- to *C*-silyl migration was also detected by a separate experiment in which neutral byproducts were isolated and characterized. Thus, thermolysis of **1b** [86 mg in 2.5 mL of 1,2,4-trichlorobenzene, 214 °C, 2 h, 5 equiv of *O*,*N*-bis(trimethylsilyl)acetamide, argon], treatment with KF·$2H_2O$ in HMPA, and washing with 1 N KOH gave 58 mg of neutral products containing 55% of the diastereomers **15** and **16** (70:30) and 45% of distereomers **11b** and **12b** (76:24). A sample of *C*-silyl esters was obtained by flash chromatography.[8]

Our preliminary investigation concerning the influence of silyl ketene acetal substitution was culminated with the first successful isolation of an (*E*,*E*)-1,6-cyclodecadiene prepared by a tandem Cope–Claisen rearrangement. Thermolysis of **1c**, X = $OSiMe_2$-*t*-Bu [0.1 M in 1,2,4-trichlorobenzene, 214 °C, 2.0 h, 10 equiv of *O*,*N*-bis(trimethylsilyl)acetamide, argon], treatment with KF·$2H_2O$ in HMPA, and extraction with 1 N KOH gave a 50% yield of a 9:1 mixture of the (*E*,*E*)-1,6-cyclodecadiene **4c**,[19] X = OH, and an unidentified carboxylic acid.[20] Silylation of the above mixture ($ClSiMe_2$-*t*-Bu, imidazole, DMF) and purification by flash chromatography gave the (*E*,*E*)-1,6-cyclodecadiene **4c**, X = $OSiMe_2$-*t*-Bu, in 82% yield.[21]

In summary, we have demonstrated that the tandem Cope–Claisen rearrangement may be employed for the preparation of (*E*,*E*)-1,6-cyclodecadienes. This transformation appears to occur in a concerted manner through chair-like cyclodecadiene conformations since the (*E*,*E*)-1,6-cyclodecadiene produced is not the thermodynamically most stable isomer.[22] Further, the Claisen rearrangement, indeed the pivotal step in this reaction sequence, is markedly influenced by the substituents on the silyl ketene acetal.[23] The trend observed for **1a–c** may be both a reflection of an electronic effect in which the added methyl substituents accelerate the rate of the Claisen rearrangement[11d] and a result of steric factors in which the added methyl substituents decrease the tendency for *O*- to *C*-silyl migration.[17] Research directed toward the application of this strategy to the total synthesis of germacrane sesquiterpenes is currently in progress.

Acknowledgment. This research was supported by a grant from the National Cancer Institutes, National Institutes of Health (CA 25977). GC/MS data was obtained on a VG 7070 GC/MS and associated VG 2035 F/B data system, funded by NIH Biomedical Research Development Grant 1 S08 RR 09082.

(16) Authentic sample isolated by preparative gas chromatography.

(17) For references concerning *O*- to *C*-silyl migration, see ref 10c. For alternative reaction pathways available to allyl silyl ketene acetals, see: (a) Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1980**, *45*, 891. (b) Reference 10d, 11f.

(18) Several studies on the transannular cyclization of 1,5-cyclodecadienes have appeared. (a) Reference 4b. (b) Sutherland, J. K. *Tetrahedron* **1974**, *30*, 1651. (c) Fisher, N. H.; Wiley, R. A.; Perry, D. L. *Rev. Latinoam. Quim.* **1976**, *7*, 87. (d) Hikino, H.; Konno, C.; Nagashima, T.; Kohama, T.; Takemoto, T. *Chem. Pharm. Bull.* **1977**, *25*, 6. For transannular cyclization of 1,6-cyclodecadienes, see: (e) Yosikara, K.; Ohta, Y.; Saki, T.; Hirose, Y. *Tetrahedron Lett.* **1969**, 2263.

(19) Salient spectral features indicative of the (*E*,*E*)-1,6-cyclodecadiene include the following: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.50 (br s, *trans*-CH_3C=CH), 4.77–5.20 (m, $CH(CH_3)CH$=C*H*), 5.02 (dm, J = 9 Hz, CH_3C=C*H*), 5.60 (dd, J = 14, 3.5 Hz, $CH(CH_3)CH$=CH), 10.9 (br s, CO_2H). The presence of a small amount of compound(s) containing a >C=CH_2 group[18] is also indicated: δ 4.65 (br s).

(20) Thermolysis of **1c** for longer times results in the formation of a larger percentage of this substance which is presumably a transannular cyclization[18] product.

(21) ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.25 (s, >Si(CH_3)$_2$, 0.95 (s, C(CH_3)$_3$), 1.02 s, C(CH_3)$_2CO_2$), 1.50 (br s, *trans*-CH_3C=CH), and 0.67–2.70 (m) (total 37 H), 5.0 (ddd, J = 16, 9, 2 Hz, $CH(CH_3)CH$=C*H*) and 5.02 (dm, J = 9 Hz, *trans*-CH_3C=C*H*) (total 2 H), 5.87 (dd, J = 16, 4 Hz, $CH(CH_3)C$-*H*=CH,1 H).

(22) (a) Dale, J.; Moussebois, C. *J. Chem. Soc. (C)* **1966**, 264. (b) Dale, J.; Ekeland, T.; Schang, J. *J. Chem. Soc., Chem Commun.* **1968**, 1477.

(23) For Claisen rearrangements facilitated by a substituent on the benzyl moiety, see: (a) Raucher, S.; Lui, A. S.-T. *J. Am. Chem. Soc.* **1978**, *100*, 4902. (b) Raucher, S.; Lui, A. S.-T.; Macdonald, J. E. *J. Org. Chem.* **1979**, *44*, 1885.

Electron-Transfer Photooxygenation. 6. Indirect Sensitized Photooxygenation of Aryl Olefins[1]

Dale S. Steichen and Christopher S. Foote*

Department of Chemistry, University of California Los Angeles, California 90024

Received October 6, 1980

Photooxygenation of aryl olefins sensitized by cyanoaromatics has been shown to proceed by an electron-transfer mechanism with initial formation of the radical anion of the sensitizer and radical cation of the olefin.[2] Quenching of the reaction by electron transfer from aromatic ethers to the substrate radical cation has also been reported.[2,3] Spada and Foote studied these reactions by laser-flash spectroscopy and showed that tetraphenylethylene (TPE) radical cation can also be formed indirectly by electron transfer from TPE to an initially formed *trans*-stilbene (TS) radical cation.[4] Schaap and co-workers made similar observations and showed that this electron transfer could result in the enhancement of reactivity of the donor olefin.[5]

We now report that photooxygenation of tetraphenylethylene and other aromatic olefins of low-oxidation potential can be sensitized by an indirect mechanism involving this type of process. When TS (0.05 M) is photooxygenated with 9,10-dicyanoanthracene (DCA) in oxygenated acetonitrile containing 0.005 M TPE, production of benzophenone (from oxidation of TPE) is enhanced (compared to TPE oxidation without TS), and the formation of benzaldehyde (from TS) is suppressed[6] (Table I).

(1) (a) Paper 5: J. Eriksen and C. S. Foote, *J. Am. Chem. Soc.*, **102**, 6083 (1980); (b) work supported by National Science Foundation Grant CHE 77-21560.

(2) Reference 1a.

(3) K. A. Brown-Wensley, S. L. Mattes, and S. Farid, *J. Am. Chem. Soc.*, **100**, 4162 (1978).

(4) L. T. Spada and C. S. Foote, *J. Am. Chem. Soc.*, **102**, 391 (1980).

(5) A. P. Schaap, *J. Am. Chem. Soc.*, **102**, 389 (1980).

(6) Photooxygenations were carried out with a Hanovia 1200 W medium-pressure mercury vapor lamp in a water-cooled immersion well surrounded with a 1-cm filter solution consisting of 30.0 g of $NaNO_2$ in 1 L of H_2O. Solutions were contained in 15- × 125-mm Pyrex tubes fitted with septa which were oxygenated by bubbling for 1 min prior to irradiation. Solutions were irradiated 35 min while rotating around the light source on a merry-go-round. $E_{1/2}$ (ox) vs. SCE: TPE = 1.33 V; TS = 1.51 V.

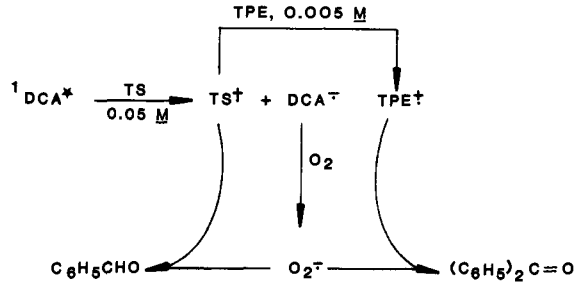
0002-7863/81/1503-1855$01.25/0

Table I. Direct and Indirect Photooxidation of Tetraphenylethylene (TPE) Sensitized by DCA[a]

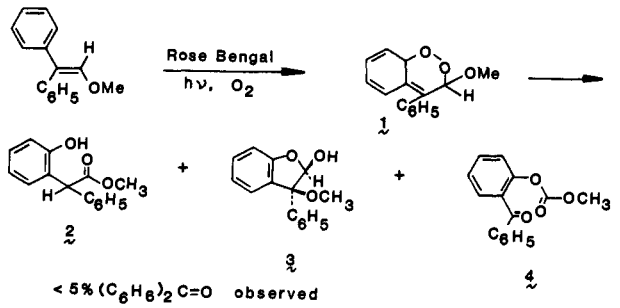
[initial substrate], M		TPE	[product], M	
TPE	TS	conversion, %	$(C_6H_5)_2C=O$[b]	C_6H_5CHO[c]
0.005		6	3×10^{-4}	
	0.05			6.4×10^{-3}
0.005	0.05	50	2.5×10^{-3}	3.2×10^{-3}

[a] [DCA] = 2×10^{-4} M. [b] Product from TPE. [c] Product from TS.

Scheme I



Scheme II



These results and the laser-flash results reported previously suggest that the photooxygenation of TPE under these conditions proceeds via initial formation of $TS^{+}\cdot$ followed by electron transfer from TPE to $TS^{+}\cdot$ (Scheme I).

The reaction of TPE is more efficient with 0.05 M TS than with TPE (0.005 M) alone, because both trapping of ^{1}DCA* by the high concentration of TS and electron transfer from TPE to $TS^{+}\cdot$ are efficient.

An even more interesting operation of this mechanism occurs with the enol ether 1,1-diphenyl-2-methoxyethylene (DPME), which (unlike TS and TPE) reacts with singlet oxygen.[7] The product formed on Rose Bengal sensitization (with oxygen) was reported to be endoperoxide **1**,[8] which subsequently rearranged to give isolable products **2**–**4**. Dioxetane cleavage product benzophenone was formed in <5% yield with Rose Bengal (Scheme II).

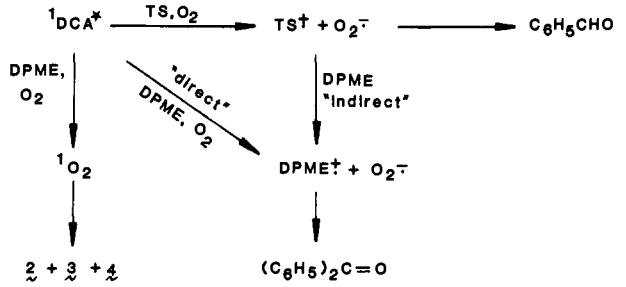
^{1}DCA*-sensitized photooxygenation of DPME produces a product mixture similar to that formed on Rose Bengal sensitization. The only difference is that significant amounts of benzophenone (5–50%) are formed in addition to **2**–**4**.[9] However, when TS is present in high concentrations so that the photooxygenation of DPME can proceed by way of the indirect mechanism, benzophenone formation is greatly enhanced, as shown by the results in Table II. In fact, benzophenone formation can

Table II. Products of DCA Sensitized Photooxygenation of 1,1-Diphenyl-2-methoxyethylene (DPME). Effect of Added *trans*-Stilbene (TS)[a-d]

solution	[DPME] × 10^3, M	[TS] × 10^2, M	product yields, relative %	
			2 + 3 + 4	$(C_6H_5)_2C=O$
1	1.0		>95	<5
2	3.0		94	6
3	5.0		92	8
4	7.0		87	13
5	9.0		82	18
6	1.0	5.0	<5	>95
7	3.0	5.0	11	89
8	5.0	5.0	16	84
9	7.0	5.0	28	72
10	9.0	5.0	33	67

[a] Yields determined by reverse-phase high-performance LC. [b] All solutions irradiated 0.25 h on a merry-go-round after 1-min oxygenation by bubbling. Conversion of DPME in solutions 1–5 varied from 50 to 100%, conversion in solutions 6–10 varied from 70 to 100%. [c] Final yields of benzaldehyde in solutions 6–10 were erratic, probably due to autoxidation processes. Yields of benzaldehyde were significantly lower than in a solution containing only TS irradiated under the same conditions. [d] Absolute yields of products from DPME were typically 40–50%.

Scheme III



be made nearly quantitative at sufficiently high TS/DPME ratios. The results suggest that a mechanism such as that shown in Scheme II occurs, with [2 + 4] products deriving from a singlet oxygen mechanism, but olefin cleavage products (presumably via dioxetane) deriving from radical cation–$O_2^{-}\cdot$ reaction (Scheme III). (While there is no clear evidence that dioxetanes are actual intermediates in the above photooxidations, benzophenone is not derived from endoperoxide **1**, since its decomposition under ^{1}DCA*-sensitized conditions yields less than 5% benzophenone. We have also observed both products of dioxetane cleavage (benzaldehyde and methyl benzoate) in approximately equal concentrations in the indirect photooxygenation of α-methoxy-*trans*-stilbene with diphenylacetylene radical cation as the initiator.)

The results suggest that the direct route gives mainly singlet oxygen products. As the ratio of TS/DPME increases, the fraction of singlet oxygen products decreases. We have evidence from other experiments that singlet oxygen can be produced from DCA on interaction with olefins and can give product distributions identical with those from Rose Bengal sensitized reactions.[10]

Singlet oxygen may be formed in ^{1}DCA*-sensitized photooxidations by a number of pathways. Aromatic excimers have been shown[11] to sensitize singlet oxygen, although no examples of sensitization by exciplexes or charge-transfer complexes have been reported to our knowledge. Singlet states of highly fluorescent molecules have been shown to produce singlet oxygen directly.[12-14] Recombination of radical ions has been shown to

(7) TS and TPE are essentially inert toward singlet oxygen under the conditions of these reactions: L. E. Manring, J. Eriksen, and C. S. Foote, *J. Am. Chem. Soc.*, **102**, 4275 (1980).

(8) D. S. Steichen and C. S. Foote, *Tetrahedron Lett.*, 4363 (1979).

(9) Yields of benzophenone from DPME [$(E_{1/2}$ (ox) vs. SCE = 1.12 V] are variable under ^{1}DCA*-sensitized conditions. Initial concentration of oxygen and DPME appear to be important. ^{1}DCA* sensitized photooxygenation of a 0.02 M solution of DPME in oxygenated acetonitrile produces a ~50% relative yield of benzophenone as determined by high-performance LC.

(10) Y. Araki, T. E. Goyne, K. Lee, D. S. Steichen, J. Eriksen, and C. S. Foote, to be published.

(11) D. M. Shold, *J. Photochem.*, **8**, 39 (1978).

(12) B. Stevens and R. D. Small, Jr., *Chem. Phys. Lett.*, **61**, 233 (1979).

(13) K. C. Wu and A. M. Trozzolo, *J. Phys. Chem.*, **83**, 2823 (1979).

(14) B. Stevens and J. A. Ors, *J. Phys. Chem.*, **80**, 2164 (1976).

produce triplets[15] (which could presumably sensitize singlet oxygen) and also singlet oxygen directly.[16] All attempts to observe, via flash spectroscopy, triplets or singlet oxygen production by trapping with β-carotene in ^{1}DCA*-sensitized photooxidations have thus far proved unsuccessful.[17]

(15) H. Schomberg, H. Staerk, and A. Weller, *Chem. Phys. Lett.*, **21**, 433 (1973).
(16) A. Mayeda and A. J. Bard, *J. Am. Chem. Soc.*, **95**, 6223 (1973).
(17) L. T. Spada, D. S. Steichen, and C. S. Foote, unpublished results. Unfortunately, β-carotene and other singlet oxygen quenchers are too rapidly destroyed in this system to be useful in product studies.

Structures of the Didemnins, Antiviral and Cytotoxic Depsipeptides from a Caribbean Tunicate[1]

Kenneth L. Rinehart, Jr.,* James B. Gloer, and J. Carter Cook, Jr.

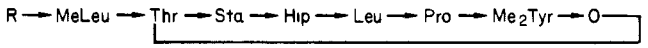
School of Chemical Sciences, University of Illinois Urbana, Illinois 61801

Stephen A. Mizsak and Terrence A. Scahill

The Upjohn Company Kalamazoo, Michigan 49001

Received September 26, 1980

We have recently discovered a class of depsipeptides in a Caribbean tunicate of the family Didemnidae (a species of the genus *Trididemnum*)[2] and have reported their isolation, separation, and biological properties elsewhere.[3] In brief, the didemnins inhibit the growth of both RNA and DNA viruses, are highly cytotoxic to L1210 leukemic cells, and protect mice against P388 leukemia and B16 melanoma. For example, didemnin A shows 50% inhibition of Coxsackie virus and equine rhinovirus (both RNA) and *Herpes simplex*, type 2 (DNA), at 1.5 μg/mL and *Herpes simplex*, type 1, at 3 μg/mL, while didemnin B has ID_{50} = 0.0011 μg/mL vs. L1210 leukemic cells, T/C up to 199 vs. P388 leukemia, and T/C 160 vs. B16 melanoma. We report here the structures of these very promising new compounds **1-3**, where Hip is hydroxyisovalerylpropionyl, O-CH[CH(CH$_3$)$_2$]COCH(CH$_3$)-CO.



1 (didemnin A), R = H

2 (didemnin B), R = $CH_3CHOHCO$—N(CH$_2$CH$_2$CH$_2$)—CH—CO—

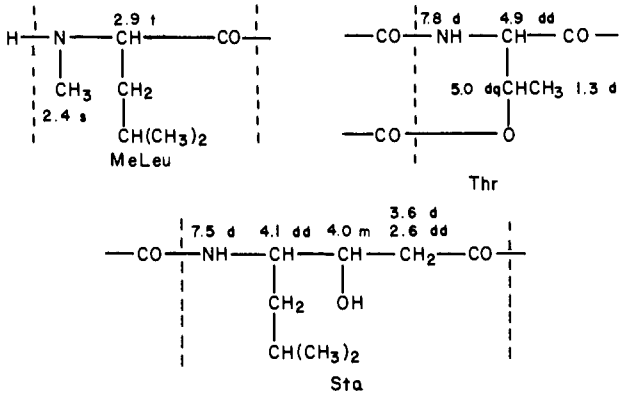
3 (didemnin C), R = $CH_3CHOHCO$—

The didemnins were separated over silica gel and assigned molecular weights of 942 (didemnin A, major component), 1111 (B, minor component), and 1014 (C, trace component) from their field desorption (FD) mass spectra. Initial structural efforts centered on didemnin A, as the simplest and most abundant component. Didemnin A was concluded to be a peptide from its ^{1}H NMR spectrum, with broad doublets (NH) at 8.3, 7.8, and 7.5 ppm. Hydrolysis with 6 N hydrochloric acid gave 1 mol each of *N*-methylleucine (MeLeu), threonine (Thr), leucine (Leu), proline (Pro), *N,O*-dimethyltyrosine (Me_2Tyr),[4] and statine (Sta).[5]

(1) Presented in part at the 3rd International Symposium on Marine Natural Products (International Union of Pure and Applied Chemistry and Société Chimique de Belgique), Brussels, Sept 16, 1980.
(2) Identification as family Didemnidae was carried out by Dr. Charles C. Lambert, California State College, Fullerton, and identification as a *Trididemnum* species by Dr. Françoise Lafargue, Laboratoire Arago, Banyuls-sur-mer, France.
(3) K. L. Rinehart, Jr., J. B. Gloer, R. G. Hughes, Jr., H. E. Renis, J. P. McGovren, E. B. Swynenberg, D. A. Stringfellow, S. L. Kuentzel, and L. H. Li, *Science (Washington, D.C.)*, in press.
(4) F.-J. Marner, R. E. Moore, K. Hirotsu, and J. Clardy, *J. Org. Chem.*, **42**, 2815-2818 (1977).

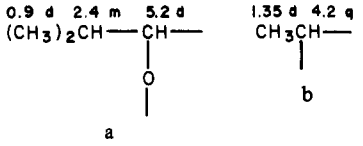
The amino acids were identified by FD mass spectrometry (FDMS) of the mixture, with M + H peaks at *m/z* 146 (MeLeu), 132 (Leu), 116 (Pro), and 210 (Me_2Tyr), an M - H_2O peak at *m/z* 101 for Thr, and M at *m/z* 175 for Sta. They were also identified by gas chromatography/mass spectrometry (GC/MS) of the amino acids' trifluoroacetyl *n*-butyl ester derivatives. In addition, they were quantitated by GC, and their identities confirmed by coinjection with derivatives of authentic samples. Statine was assigned as the allo (erythro) isomer by its coelution with the synthetic *R,S* isomer,[5] while gas chromatography on an optically active column[6] indicated Leu, MeLeu, Pro, Thr, and Me_2Tyr to have the L configuration.

The individual amino acids were characterized in the ^{1}H NMR spectrum of didemnin A by extensive spin decoupling, which established MeLeu as N-terminal, Thr as O- as well as N-acylated, and the hydroxyl group of Sta to be free, as shown. Didemnin



A reacts with acetic anhydride on the methylamino group of MeLeu and the hydroxyl group of Sta to give a diacetyl derivative, as judged by the product's molecular weight of 1026, two new $COCH_3$ groups at 1.9 and 2.1 ppm, and the shift of the appropriate protons to 2.8 (-N(Ac)-CH_3, MeLeu), 5.1 (AcNCH<, MeLeu) and 5.3 ppm (AcO-CH<, Sta).

Addition of the formulas for the amino acids' aminoacyl units (MeLeu, $C_7H_{14}NO$; Thr, $C_4H_6NO_2$; Sta, $C_8H_{15}NO_2$; Me_2Leu, $C_{11}H_{13}NO_2$; Pro, C_5H_7NO; Leu, $C_6H_{11}NO$) gave $C_{41}H_{66}N_6O_9$, 786.4891. The high resolution electron impact (HREI) mass spectrum of didemnin A gave a molecular ion peak at 942.5678. Subtraction of the two numbers yielded 156.0787 ($C_8H_{12}O_3$) as the unaccounted-for residue of didemnin A. The $C_8H_{12}O_3$ unit can be identified in the ^{1}H NMR spectrum as containing the units a and b and in the ^{13}C NMR spectrum as containing one ketone



carbon (205.1 ppm) and one carboxyl-type carbon (one of seven near 175 ppm, in addition to the six of the amino acids). The only reasonable combination of a and b with a keto and a carboxyl carbon in a $C_8H_{12}O_3$ unit is as a hydroxyisovalerylpropionyl (Hip) group. All the carboxyl carbons occur as amides or esters since didemnin A does not react with diazomethane.

The order of linkage of these seven units was assigned by partial hydrolysis of didemnin A in base and acid, followed by HRFDMS

(5) D. H. Rich, E. T. Sun, and A. S. Boparai, *J. Org. Chem.*, **43**, 3624-3626 (1978).
(6) R. C. Pandey, J. C. Cook, Jr., and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **99**, 8469-8483 (1977).

0002-7863/81/1503-1857$01.25/0