of three modified amino acid residues containing an α,β-unsaturated amide group conjugated with an oxazole,12 as well as an α-keto-β-amino acid moiety constituting a homocyclic-like unit. Interpretation of the HMBC and NOESY spectral data provided evidences for the amino acid sequence of I. As a result, I was deduced to be composed of a cyclic moiety and a side chain. The cyclic moiety consisted of segment 4, Pro, Orn, and BhTrp connected in this sequence. The side chain was attached to the α-NH of the Orn residue and consisted of nVal and lle. The N-terminus of lle was shown to be protected by the 2-hydroxy-3-methylpentanoic acid group (Hmp).13 Further substantial evidence for the structure of keramamide B (1) was obtained by the FAB MS/MS spectrum of the (M + H)+ ion of 1 1 (m/z 1137), which afforded daughter ions corroborating well the amino acid sequence deduced from the NMR results. The chiral GC analysis (Chiral-Val, Alltech) of the N-trifluoracetyl/methyl ester derivatives of the hydrolysate of I revealed that all of the Aba,10 Pro, Orn, nVal, and lle residues of I bore the L configuration. The BhTrp residue in I was converted into aspartic acid (Asp) by ozonolysis of I followed by oxidation with CH3CO2H, while the C-11-N-14 moiety was converted into leucine (Leu) by treatment with H2O/NaOH. These Asp and Leu residues were determined to be L by the chiral GC method, revealing that the BhTrp and the β-amino amino acid in I were also L. Therefore, the structure of keramamide B was established to be that of I. Molecular formulas of keramamides C (2) and D (3) were determined to be C31H47O12N10Br and C29H47O12N10Br, respectively, by HRFABMS data. The amino acid analyses and FAB MS/MS results revealed that keramamide C (2) contained an Aba residue in place of the nVal residue in keramamide B (4). For keramamide D (3) the nVal in 1 was replaced by an Aba residue and the ethyl group attached to C-9 of segment 4 was substituted by a methyl group.16 Keramamides B-D (1-3; 5 × 104 M) inhibited the superoxide generation response of the human neutrophils17 elicited with a chemoattractant peptide, N-formyl-Met-Leu-Phe (fMLP), but did not inhibit that induced by phorbolmyristate acetate or immune complex.18 The mechanism of action is currently under investigation.19

Acknowledgment. We thank Mr. Z. Nagahama for his help in collecting the sponge and Professor T. Sasaki, Kanazawa University, for the cytotoxicity test.

Supplementary Material Available: Notes for spectral data and spectra of keramamides B-D (36 pages). Ordering information is given on any current masthead page.

(18) Human neutrophils are known to generate superoxide anion, when exposed to appropriate stimuli, such as phorbolmyristate acetate, ovulabumin complex of immunoglobulin G; antibody, and fMLP. Therefore the present results suggest that a certain factor inhibited by keramamides B-D (1-3) is involved in the intracellular signal transduction processes initiated by fMLP. (19) Keramamides B-D (1-3) exhibited no cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells in vitro at 10 μg/mL.

New Synthesis of Methyl 1,3-Butadiene-2-carboxylate by the Chelotropic Extrusion of Carbon Monoxide from 3-Carbomethoxy-3,4-pentadienial and a Study of Its Dimerization To Give Dimethyl Mikanecate (Dimethyl 4-Ethenyl-1-cyclohexene-1,4-dicarboxylate)

Michael E. Jung* and Craig N. Zimmerman
Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90024
Received June 12, 1991

For a synthetic approach to piaunoil B and C (1a,b), diterpene isolated from Croton subybratus Kurz which show anti peptic ulcer activity,1 we required an easy preparation of the 5-(3-furyl) allylic lactone 2a. A reasonably short route would involve the thermal [3,3]-sigmatropic rearrangement2 of the readily available 3-carbomethoxypropynyl ethenyl ether 3 to give the allylic acetaldehyde 4 followed by addition of an aryl anion and subsequent lactone formation. We report here the discovery of a novel thermal rearrangement of 3-carbomethoxy-3,4-pentadienial (4) to produce methyl 1,3-butaediene-2-carboxylate (5). In addition, we present the kinetic parameters for the very facile dimerization of 5 via a Diels-Alder cycloaddition.3

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Ester 3 was prepared from the readily available 2-propynyl ethenyl ether \( (\text{EtMgBr, THF, } \Delta) \) and trapping with methyl chloroformate. Flash vacuum pyrolysis of 3 was accomplished by introduction of a 0.5–1 M solution of 3 in benzene or toluene into a horizontal pyrolysis tube (i.d. = 1 cm) packed with glass helices heated to 390 °C at a vacuum of ~140 mm. Trapping the pyrolysatate at ~78 °C gave the desired 3-carbomethoxy-3,4-pentadienal (4) in 65–78% yield. Thus this is a good approach to allenic lactones of this sort. Alternatively, the pyrolysate could be handled normally and even chromatographed without extensive decomposition. The preparation of allenic lactones such as 2 from 4 proved straightforward. For example, addition of phenylmagnesium bromide in ether at ~78 °C to 4 followed by heating with catalytic toxic acid in benzene furnished the phenyl allenic lactone in 50–70% yield, was dimethyl mikanecate. This turns out to be a fairly convenient way of preparing this very reactive dienic ester.

Although the high propensity of 5 toward Diels–Alder dimerization has been known for some time, no good data are available on the kinetics of this process. We therefore carried out the dimerization of 5 to give 7 in toluene at several temperatures and measured the rate of cyclization. The rate data was used in both the Eyring and Arrhenius equations to produce the following kinetic parameters (at 298 K):

\[
E_a = 11.12 \pm 0.72 \text{ kcal/mol}
\]

\[
\Delta H^* = 10.67 \pm 0.95 \text{ kcal/mol}
\]

\[
\Delta S^* = -35.4 \pm 2.8 \text{ cal/(mol K)}
\]

Thus the dimerization of this diene has a lower activation energy than most other dienes. For example, the activation energy for the dimerization of cyclopentadiene at 20 °C in benzene is 16.4 kcal/mol. The reasons behind this very fast dimerization of 5 are not totally clear, but probably involve a strong polarization of the 1,2-double bond, thus making it a very good dienophile (much better than the 1,2-double bond of methyl 1,3-buta diene-1-carboxylate, for example, which is reluctant to dimerize). In addition, the E (s-cis) conformation of the diene, necessary for the Diels–Alder reaction, is probably more stable than the Z (s-trans), thus making it easier to achieve the transition-state geometry. We intend to carry out further calculations on this system to try to determine in a more precise way the underlying reasons for the rapid dimerization.

Finally, we have also shown that this two-step procedure for the synthesis of 2-substituted butadienes is useful for the preparation of other dienes. Thus pyrolysis of the readily available 3-(silyloxy)methylpropargyl vinyl ether 8 gives the substituted pentadienal 9, which can be further pyrolyzed at higher temperatures to give the 2-(silyloxy)methyl-1,3-buta diene-1-carboxylate, for example, which is reluctant to dimerize. Further studies on the dimerization of 5 and the use of allenic lactones such as 2a,b in the synthesis of the plau nols will be reported later.

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**Acknowledgment.** We thank the National Institutes of Health (GM-31349) for generous financial support and Professor Ken Houk and Dr. Michael Blanda for helpful discussions.