in statistical (1:1:2) ratio.[8] When **1** was heated with $CpRh(CO)_2$, an even more interesting exchange reaction took place which led to a mixture of **1** and the two other possible Rh/Co μ-methylene dimers **7** and **8**. These three complexes were separated by column chromatography on alumina. The homonuclear rhodium complex had been obtained earlier in elegant work by Herrmann and his group,[1c] and our sample of **7** was characterized by comparison of spectral data with those reported for Herrmann's complex. The new material **8** was characterized by conventional analytical and spectroscopic techniques and is apparently a very rare example of a heterobinuclear μ-methylene complex.[9]

Because it involves a relatively clear example of a binuclear methylene-transfer reaction, we examined the reaction of **1** with ethylene in somewhat more detail. When a solution of **1** in benzene-d_6 under 4.5 atm of C_2H_4 was heated to 61 °C for 20 h, NMR observation showed it had reacted completely, leading to propene in 65% yield along with a small amount (3%) of methane. The organometallic product of the reaction is a sensitive material which is stable in solution only under ethylene. On the basis of its IR and ^1H NMR spectra,[10] we assign to it the carbonyl/ethylene complex structure **9**; it is formed in 95% yield (NMR). Support for this assignment is provided by examination of the reaction between neutral dimer **3** and ethylene. This leads rapidly to the known compounds $CpCo(CO)_2$ and $CpCo(C_2H_4)_2$,[11] which then more slowly symproportionate to give **9**.

As reported for the corresponding reaction of μ-$CH_2Fe_2(CO)_8$ with ethylene,[3c] the rate of conversion of **1** to propene is strongly inhibited by CO. Although this qualitative result alone might be taken as evidence for an initial step involving dissociative CO loss, two pieces of evidence suggest that the nature of the inhibition is more complicated. First, the rate does not obey good first- or second-order kinetics. Second, *the reaction is also inhibited strongly by ligands other than CO* (see, for example, the effect of C_2F_4 shown in Figure 1), *but without the buildup of any detectable alkene complexes formed reversibly from* **1**. The only way such an inhibition can be operating is if the inhibitor is scavenging some material (e.g., a reactant involved in the propagation step of a chain reaction or a catalyst for the reaction) which is involved in the activation of one of the starting materials. Some indication as to what this "hidden" partner might be was provided by carrying out the reaction of **1** with ethylene in the presence of dimer **3**. Monitoring by NMR showed the initial transformation of **3** to $CpCo(C_2H_4)_2$ (**10**), as described above, followed by rapid conversion of **1** to propene. Addition of independently prepared **10** to the reaction produced a similarly dramatic acceleration in rate (Figure 1).

It seems clear from these experiments that the reaction of **1** with ethylene is autocatalytic, and the catalyst is coordinatively unsaturated $CpCo(C_2H_4)$ (**11**). This material is generated rapidly by ethylene loss from $CpCo(C_2H_4)_2$. We propose the pathway summarized in Scheme III as a likely mechanism for the autocatalytic reaction. Dissociation of ethylene from **10** gives **11**, and this species is capable of abstracting CO, in a bimolecular step,[12] from **1**. This leads to unsaturated binuclear complex **12**, which reacts with ethylene to give propene. It seems likely that this occurs by π complexation followed by insertion to give **14**, a coordinatively unsaturated relative[13] of metallacyclopentane **15**, as suggested by Pettit and his co-workers for the related iron system.[3c] The metal fragments are then scavenged by ethylene to regenerate **10** and a second molecule of **9**. Supporting evidence for this hypothesis is provided by additional experiments involving **15**. As reported earlier,[13] thermolysis of **15** leads to propene and cyclopropane in about a 4:1 ratio. Thermolysis of **15** in the presence of **3** leads to a significant increase in this ratio (propene/cyclopropane = 9.0), presumably because **3** increases (as it does with **1**) the amount of reaction proceeding by initial CO removal to give **14** (Scheme III).

Futher experiments will be required to determine whether this mechanism is correct in detail. However, it is clear from this work that the observation of qualitative inhibition of a reaction by the addition of excess ligand is *not* sufficient to establish a dissociative first step in its mechanism. In addition, it seems likely that other apparently straigtforward insertion and group-transfer processes may involve intermolecular activation by a second metal complex.

Acknowledgment. We are grateful to Professor W. A. Herrmann for helpful discussions and several useful exchanges of information. Financial support for this work was provided by the National Science Foundation (Grant CHE 78-08706).

(8) Data for **5**: mp 57.5–58.5 °C; IR (toluene) 1950 cm^{-1} (br s); ((KBr) 1978 (m), 1938 (br s) cm^{-1}; ^1H NMR (benzene-d_6) δ 6.80 (s, 2 H), 4.58–4.57 (q, 8 H), 1.75 (s, 6 H); MS (15 eV), m/e 346 (M^+). Anal. Calcd for $C_{15}H_{16}Co_2O_2$: C, 52.05; H, 4.66; Co, 34.05. Found: C, 52.44; H, 4.81; Co, 33.2. The mixed dimer **6** was identified by ^1H NMR, MS and HRMS analysis of the mixture formed on heating dimers **1** and **5**. Data for **6**: ^1H NMR (benzene-d_6) δ 6.85 (s, 2 H), 4.66 (s, 5 H), 4.55 (m, 4 H), 1.73 (s, 3 H); HRMS. Anal. Calcd for $C_{14}H_{14}O_2Co_2$: 331.9658. Found: 331.9659.

(9) Data for **8**: mp 67.5 °C, IR (toluene) 1977 (w), 1962 (br s) cm^{-1}; ^1H NMR (acetone-d_6) δ 6.84 (s, 2 H), 5.37 (d, 5 H, J_{HRh} = 0.62 Hz), 5.07 (s, 5 H) (trans isomer); 7.70 (q, 1 H, J_{HRh} = 3.24 Hz, J_{HH} = 0.34 Hz), 6.17 (q, 1 H, J_{HRh} = 1.13 Hz), 5.52 (d, 5 H, J_{HRh} = 0.52 Hz), 5.14 (s, 5 H) (cis isomer); MS (15 eV), m/e 362 (M^+) HRMS. Anal. Calcd for $C_{13}H_{12}O_2CORh$: 43.12; H, 3.34; Co, 16.3; M_r 391.9215. Found: C, 42.79; H, 3.35; Co, 16.0; M_r 361.9227.

(10) ^1H NMR (C_6D_6) δ 2.15 (br s, 2 H), 2.55 (br s, 2 H), 4.40 (s, 5 H); IR 1974 cm^{-1}.

(11) Jonas, K.; Kruger, C. *Angew. Chem.* **1980**, *92*, 513.

(12) A similar metal-assisted CO dissociation has recently been reported: Albers, M. O.; Coville, N. J.; Ashworth, T. V.; Singleton, E.; Swanepoel, H. E. *J. Chem. Soc., Chem. Commun.* **1980**, 489. Attempts to remove CO from **1** using trialkylamine oxides were inconclusive; oxidative decomposition of **1** occurred more rapidly than attack of the amine oxide at the CO ligand.

(13) Theopold, K. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5964.

Structure of Palytoxin

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Palytoxin, an extremely poisonous, water-soluble substance from marine coelenterates belonging to the genus *Palythoa*,[1] is cleaved into several compounds by sodium periodate. The structures of some of these degradation products have been recently described and indicate that partial structures **1a–f** are present in palytoxin (Scheme I).[2,3] The presence of unit **1g** in palytoxin from Okinawan *P. tuberculosa* is suggested from the structure of another periodate oxidation product.[4] This unit, however, appears to be slightly modified in the palytoxins from Hawaiian *P. toxica* and a *Palythoa* sp. from Tahiti.[3] We report here the structures of additional periodate oxidation products which show that units **1h** and **1i** are present in palytoxin from a Tahitian *Palythoa* sp. Units **1a–f**, **1h**, and **1i** account for the eight carbon–carbon double bonds, seven methyl groups, and three quaternary carbons indicated by the ^{13}C NMR spectrum. Also reported are the structures of several ozonolysis products which allow us to sequence these units into a total gross structure **1a** for this toxin.

Oxidation of palytoxin, hexadecahydropalytoxin, or *N*-(*p*-bromobenzoyl)palytoxin with excess $NaIO_4$ in water at 0 °C for

(1) (a) Moore, R. E.; Scheuer, P. J. *Science (Washington, D.C.)* **1971**, *172*, 495. (b) Moore, R. E.; Dietrich, R. F.; Hatton, B.; Higa, T.; Scheuer, P. J. *J. Org. Chem.* **1975**, *40*, 540.

(2) Moore, R. E.; Woolard, F. X.; Sheikh, M. Y.; Scheuer, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 7758.

(3) Moore, R. E.; Woolard, F. X.; Bartolini, G. *J. Am. Chem. Soc.* **1980**, *102*, 7370.

(4) Hirata, Y.; Uemura, D.; Ueda, K.; Takano, S. *Pure Appl. Chem.* **1979**, *51*, 1875.

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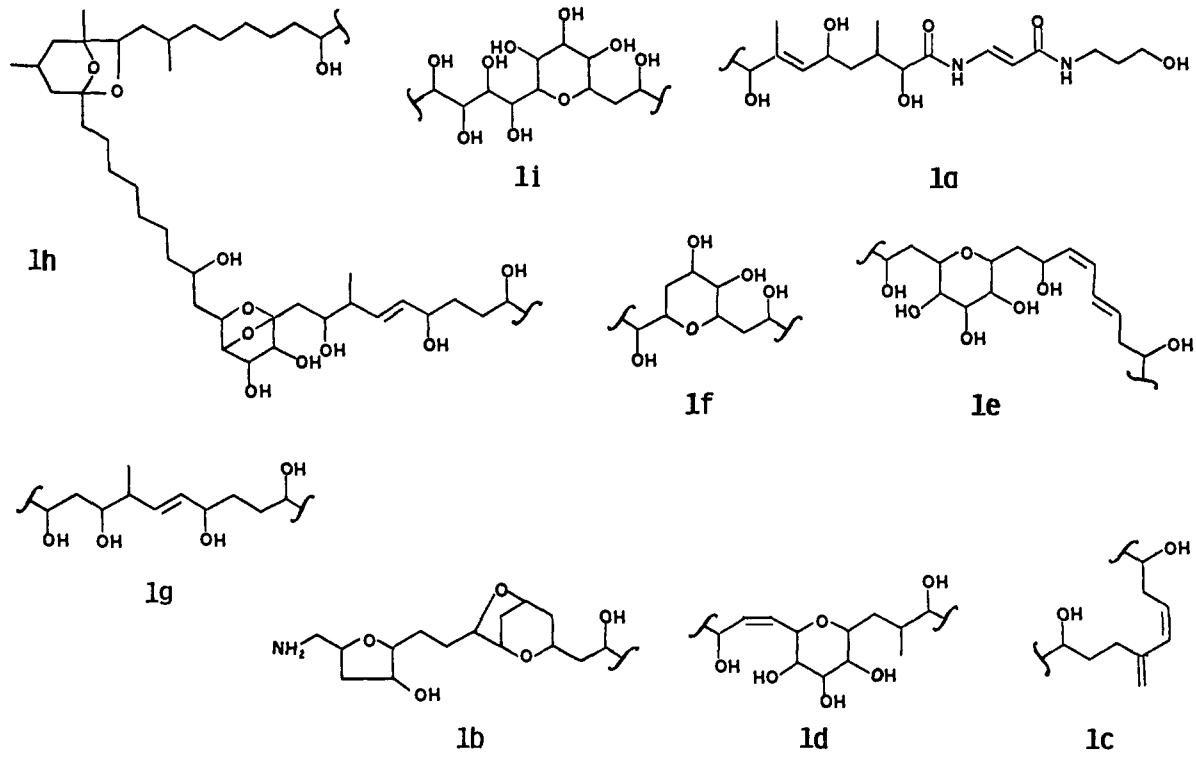
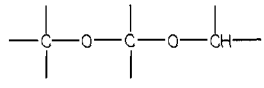
Scheme I



3 h led to a mixture of lipophilic aldehydes, at least one of which was a formate ester and another a hemiacetal. Further oxidation of this mixture of aldehydes with $NaIO_4/KMnO_4$ led to palyoic acid (**2**, $C_{25}H_{44}O_6$) which formed a dimethyl ester **3** on treatment with diazomethane (Scheme II). The ^{13}C NMR spectrum of palyoic acid indicated that (1) both carboxylic acid groups are attached to methylene chains that are longer than three methylenes; (2) the remaining two oxygens and the two quaternary carbons are present in a subunit A;



A

(3) no more than five methylenes are connected to branched carbon atoms; and (4) the two secondary methyl groups are attached to methines which are β to branched carbon atoms. The ^1H NMR spectrum of palyoic acid showed that the A unit is present in a 6,8-dioxabicyclo[3.2.1]octane system, and spin–spin decoupling experiments, with the aid of difference spectroscopy, indicated that one of the secondary methyl groups is located in an equatorial position on C-3 and that the other one is on a side chain carbon β to C-7. The number of carbons separating the carboxylic acid groups and the bicyclic system and the positions of the two CO_2H-containing side chains was decided by mass spectrometry. The mass spectrum of **2** (also **3–12**, **21**, **29**) showed three intense peaks for fragment ions **a–c**, a fragmentation pattern that was essentially the same as that shown in the mass spectrum of *exo*-brevicomin.[5]

One of the aldehydes was **4**, which eliminated formic acid on sublimation to give **5** and formed a triacetate **6**[6] on reduction with $NaBH_4$ and acetylation. Short-term oxidation of *N*-(*p*-bromobenzoyl)palytoxin[3] followed by $NaBH_4$ reduction and acetylation produced a mixture of **6**, **7**,[6] **8–10**. The trideuterated compounds **11** and **12**, however, were formed when the toxin was treated with D_2O at 55 °C prior to periodate oxidation. These data suggested that unit **1h** is present in palytoxin.

The only other product in the periodate oxidation[3] was a mixture of related acyclic ethers (**13–20**) which was analyzed by GC–MS. The most intense peaks in the mass spectra of the ethers were due to ions resulting from fission of the ether C–O bonds. The structure of compound **13**, one of the major components, was confirmed by ^1H NMR spectroscopy. These compounds suggested the presence of unit **1i** in palytoxin.

N-(*p*-Bromobenzoyl)palytoxin or acetylated *N*-(*p*-bromobenzoyl)palytoxin was treated with excess ozone in aqueous ethanol at 0 °C. The octaozonide was decomposed with sodium borohydride, and the resulting mixture of polyols was acetylated with acetic anhydride in pyridine. Separation of the corresponding polyacetates was achieved by LC on silica gel with 50% CH_2Cl_2 in EtOAc, EtOAc, and 5% EtOH in EtOAc. Several compounds [e.g., several C-2, C-41, C-42 diastereomers of gross structure **21**, **22–27**, and two C-14 epimers of gross structure **28** (Scheme III)] were isolated and identified. The molecular weights of the compounds were determined by field desorption mass spectrometry (FDMS), and the structures were elucidated by extensive ^1H NMR studies in $CDCl_3$, C_6D_6, and $CDCl_3$–C_6D_6 mixtures at 360 and 600 MHz. The structures of these ozonolysis products clearly showed that Tahitian palytoxin has structure **1A** (Scheme IV).

The gross structures of the two palytoxins from *P. toxica* are proposed to have structures **1B** and **1C**. The same degradation

(5) In the mass spectrum of *exo*-brevicomin the three most intense fragment ions are *m/e* (relative intensity, ion) (100, $CH_3C{\equiv}O^+$), 85 (22, $CH_2{=}CHC{=}(OH^+)CH_2CH_3$ or M – $CH_2{=}C{=}O$ – C_2H_5), and 114 (18, $CH_3CH_2CH_2CH{=}C(OH^+\cdot)CH_2CH_3$ or M – $CH_2{=}C{=}O$) which are analogous to ions **a**, **c**, and **b**. The mass spectrum of the endo isomer is significantly different. Silverstein, R. M. *J. Chem. Ed.* **1968**, *45*, 794.

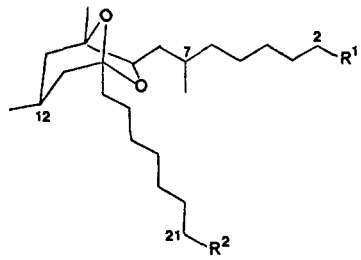
(6) Uemura et al. (Uemura, D.; Ueda, K.; Hirata, Y.; Katayama, C.; Tanaka, J. *Tetrahedron Lett.* **1980**, *21*, 4857, 4861) have recently reported the degradation of palytoxin from Okinawan *P. tuberculosa* to compounds **6** and **7**.

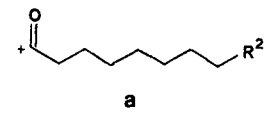
(7) The composition is similar to the equilibrium anomeric mixture in aqueous D-fructose. Doddrell, D.; Allerhand, A. *J. Am. Chem. Soc.* **1971**, **93**, 2779.

(8) Macfarlane, R. D.; Uemura, D.; Ueda, K.; Hirata, Y. *J. Am. Chem. Soc.* **1980**, **102**, 875.

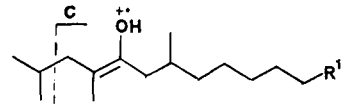
(9) Acetylation of palytoxin from Hawaiian *P. tuberculosa*, followed by ozonolysis, $NaBH_4$ reduction, and acetylation, leads to several diastereomers of gross structure **29** in addition to the several compounds of structure **21**. During the acetylation reaction β elimination of the acetoxyl group on C-57 from the C-55 keto form of the **1B** and **1C** toxins presumably occurs. Ozonolysis of the resulting α,β-unsaturated ketone ultimately leads to the **29** compounds.

Scheme II





a



b

2 $R^1 = R^2 = COOH$

3 $R^1 = R^2 = COOCH_3$

4 $R^1 = CHO$; $R^2 = CH(OCHO)CH_2CHO$

5 $R^1 = CHO$; $R^2 = CH{=}CHCHO$

6 $R^1 = CH_2OAc$; $R^2 = CHOAcCH_2CH_2OAc$

7 $R^1 = CH_2OAc$; $R^2 = CHOAcCH_2CHOAcCH_2OAc$

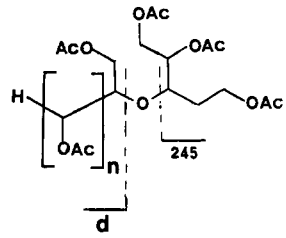
8 $R^1 = CH_2OAc$; $R^2 = CHOAcCH_2CHOAcCHOAcCH_2OAc$

9 $R^1 = CH_2OAc$; $R^2 = CHOAcCH_2CH(OCOCH_2CHOAcCHCH_3CH{=}CHCHOAcCH_2CH_2CH_2OAc)CHOAcCHOAcCH_2OAc$

10 $R^1 = CH_2OAc$; $R^2 = CHOAcCH_2CHOAcCH(OCOCH_2CHOAcCHCH_3CH{=}CHCHOAcCH_2CH_2CH_2OAc)CHOAcCH_2OAc$

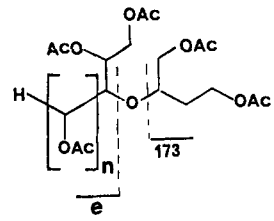
11 $R^1 = CH_2OAc$; $R^2 = CHOAcCH_2CH(OCOCD_2CHOAcCHCH_3CH{=}CHCHOAcCH_2CH_2CH_2OAc)CHOAcCHDOAc$

12 $R^1 = CH_2OAc$; $R^2 = CHOAcCH_2CHOAcCH(OCOCD_2CHOAcCHCH_3CH{=}CHCHOAcCH_2CH_2CH_2OAc)CHDOAc$



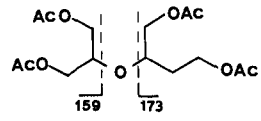
d

13 n = 1 d = 159
14 n = 2 d = 231
15 n = 3 d = 303



e

16 n = 1 e = 231
17 n = 2 e = 303
18 n = 3 e = 375
19 n = 4



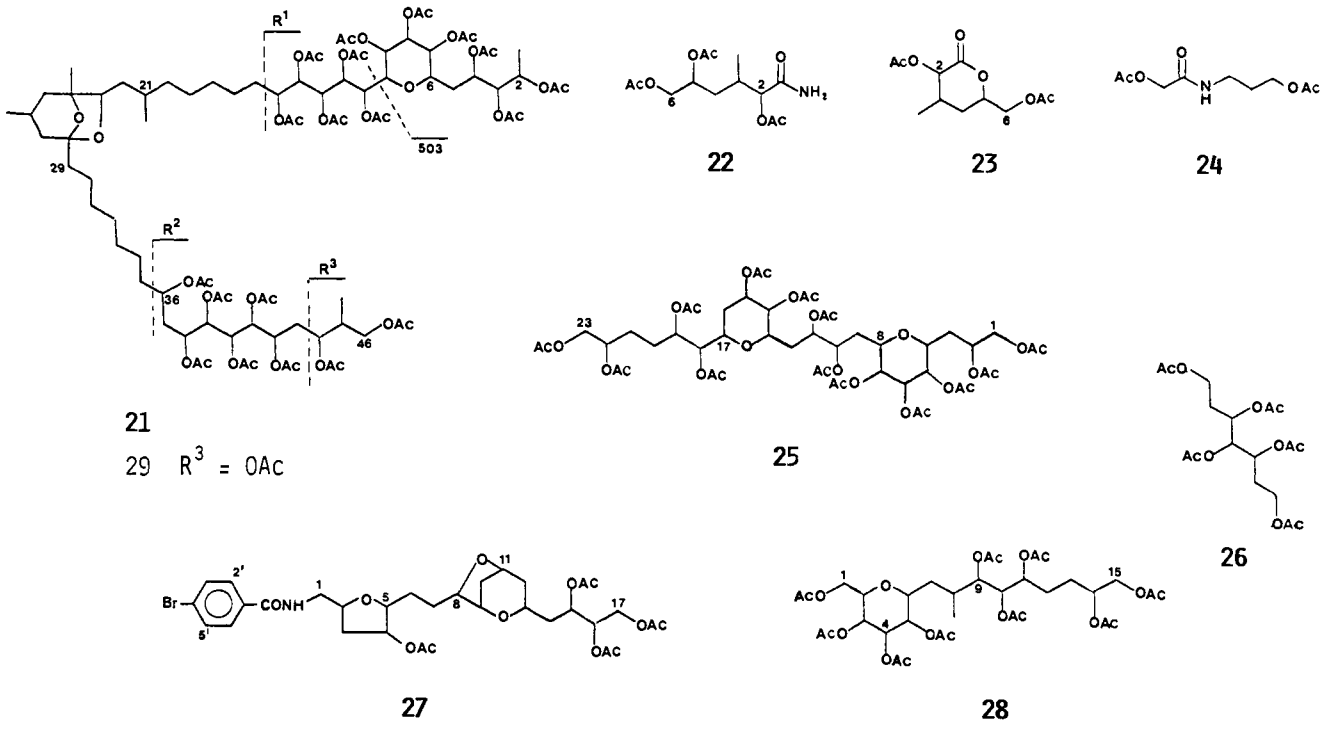
20

products (**2**–**28**) are formed from periodate oxidation and ozonolysis of the *P. toxica* toxin. The ^{13}C NMR spectrum of the *P. toxica* toxin in D_2O at 25 °C,[1b] however, does not show hemiketal carbon signals, whereas the ^{13}C NMR spectrum of **1A** in D_2O at 25 °C shows a signal at δ 100.2 for the C-55 ketal carbon which disappears when the sample is heated to 55 °C. At this temperature the ketal system in **1A** apparently opens up and a mixture[7] of **1B** and **1C** is formed. The C-54 and C-56 protons in **1B** and **1C** now rapidly exchange with deuterium, causing the C-55 carbons of **1B** and **1C** to have much longer relaxation times. As a result the ^{13}C NMR signals are not readily observed.

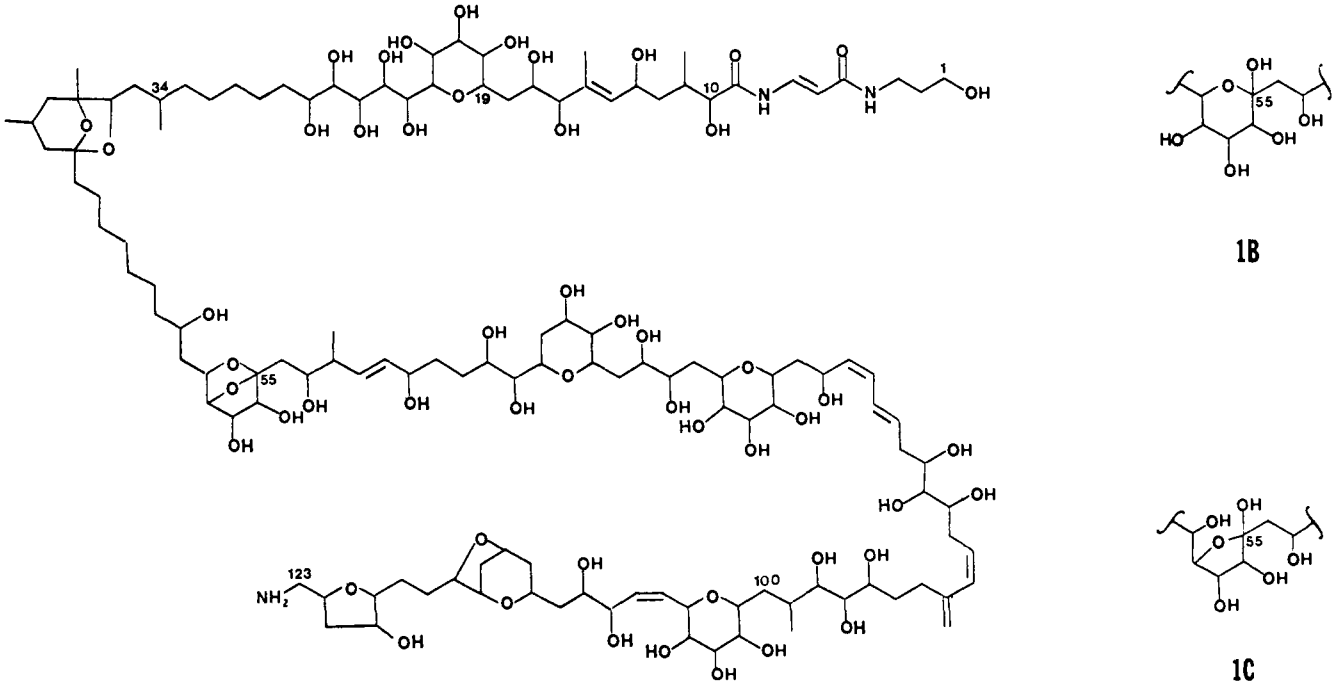
The molecular formulas are $C_{129}H_{221}N_3O_{54}$ (M_r 2659) for palytoxin from the Tahitian *Palythoa* and $C_{129}H_{223}N_3O_{54}$ (M_r 2677) for the two palytoxins from *P. toxica*. Our findings are consistent with the molecular weights reported by ^{252}Cf-plasma desorption mass spectrometry[8] for the two components in palytoxin from Okinawan *P. tuberculosa*. Interestingly we find that palytoxin from Hawaiian *P. tuberculosa* is a mixture of **1A**–**C**.[9] The two components in palytoxin from Okinawan *P. tuberculosa*, however, may be the related C-54 ketal and hemiketal.

Acknowledgment. This research was supported by Grant CA 12623-08, awarded by the National Cancer Institute, Department of Health, Education, and Welfare and Grant CHE79-25416 from the National Science Foundation. The preliminary work on palyoic acid was carried out by Dr. Frank X. Woolard. NMR studies at 360 MHz were carried out at the Stanford Magnetic Resonance Laboratory under the auspices of NSF Grant GP-23633 and NIH Grant RR00711. The 600-MHz NMR studies at Carnegie Mellon University were supported by NIH Grant RR00292. We thank Dr. J. Ford and Professors A. A. Bothner-By and J. Datok for their assistance. We also thank Dr. K. Straub at the University of California Bio-organic, Biomedical Mass Spectrometry Resource (A. L. Burlingame, Director), supported by NIH Grant

Scheme III



Scheme IV



[a] 1A is the proposed structure of palytoxin from a Tahitian *Palythoa* sp. The two palytoxins from Hawaiian *P. toxica* are the related C-55 hemiketals (partial structures 1B and 1C).

RR00719, for determining the GC–MS and the field desorption and high-resolution EI mass spectra. The CI and FD mass spectra of palyoic acid and its Me ester were determined at the University of Utah MS facility (J. A. McCloskey, Director).

Supplementary Material Available: Mass and ^{1}H NMR spectral data for compounds **2–23** and **25–29** and ^{13}C NMR spectral data for compound **2** (7 pages). Ordering information is given on any current masthead page.