(s, 3 H), 7.85 (s, 3 H), 8.82 (t, 3 H, J = 7 Hz); MS m/e 535.3044 (M^+ calcd for $C_{31}H_{41}N_3O_5$, 535.3036).

***N*-Acetylcelacinnine (8).** Celacinnine (20 mg) was dissolved in pyridine (2 mL) and acetic anhydride (0.5 mL) was added. The mixture was stirred at room temperature (24 h), $CHCl_3$ (25 mL) was added, and the solution was washed with H_2O (three 10-mL portions). The $CHCl_3$ fraction was dried (Na_2SO_4) and the solvent evaporated. Chromatography of the residue on alumina (10% MeOH/EtOAc) yielded *N*-acetylcelacinnine (**8**, 14 mg) as a white amorphous powder: IR 6.00, 6.10, 6.18, 6.33 μm; MS m/e 447.2476 (M^+ calcd for $C_{27}H_{33}N_3O_3$, 447.2514).

***N*-Methylcelacinnine (7).** Celacinnine (**1**, 18 mg) was dissolved in EtOH (1 mL) and methyl iodide (0.5 mL) was added. The mixture was heated at 65 °C for 20 h. After removal of solvent, chromatography of the residue on silica gel (10% MeOH/EtOAc) yielded *N*-methylcelacinnine (**7**, 13 mg): UV (MeOH) λ_{max} 224 (infl), 279 nm (ε 14 200, 22 100).

Hofmann Degradation of *N*-Methylcelacinnine. A solution of **7** (9 mg) and methyl iodide (1.5 mL) in acetone (1 mL) was heated at 65 °C for 24 h. After evaporation of the solvent, distilled water (1 mL) and silver oxide (10 mg, freshly prepared) were added to the residue and the mixture was stirred at room temperature for 20 h. The solution was filtered and the filtrate was concentrated to dryness. The residue was heated at 140 °C for 20 h and then separated by TLC on silica gel (10% MeOH/EtOAc) to yield the degradation product (**10**, 1 mg): MS m/e (rel intensity) 433 (3), 334 (27), 302 (13), 257 (33), 243 (98), 188 (85), 187 (100), 155 (10), 143 (12), 131 (100), 129 (21).

Synthesis of Degradation Product 10. Spermidine (5 g) was added to a suspension of barium hydroxide (6 g) in EtOH (200 mL), and cinnamoyl chloride (8.5 g) was added in small portions with stirring and cooling over 1 h. The mixture was then stirred at room temperature overnight. The solution was filtered and the filtrate was concentrated to dryness. Chromatography on alumina (Woelm, neutral, 200 g) using CH_2Cl_2 as eluent gave tricinnamoylspermidine (4.7 g), and elution with CH_2Cl_2/MeOH (1:1) gave a mixture of three products. Rechromatography of the mixture on alumina (15% MeOH/CH_2Cl_2) yielded *N,N'*-dicinnamoylspermidine (**11**, 248 mg): mp 127 °C; UV (MeOH) λ_{max} 223, 276 nm (ε 29 600, 41 000); IR (KBr) 2.90, 3.03, 6.06, 6.22, 6.45 μm; MS m/e (rel intensity) 405 (M^+, 5), 336 (7), 335 (6), 314 (5), 274 (9), 245 (13), 205 (36), 188 (30), 131 (100), 127 (29), 115 (4), 103 (98), 101 (4). Additionally, bands were obtained for maytenine (**12**, 2.3 g)[17] and for *N',N''*-dicinnamoylspermidine (**13**, 9 mg): mp 107 °C; UV (MeOH) λ_{max} 223, 278 nm (ε 27 300, 40 500); IR (KBr) 2.90, 3.08, 5.97, 6.15, 6.45; MS m/e (rel intensity) 405 (M^+, 4), 387 (4), 335 (8), 300 (8), 274 (10), 257 (10), 245 (14), 231 (10), 205 (36), 188 (34), 159 (56), 153 (16), 131 (100), 127 (26), 115 (6), 103 (98), 101 (5).

A solution of the dicinnamoylspermidine **11** (20 mg) and methyl iodide (0.6 mL) in EtOH (1 mL) was kept at room temperature for 3 days and then heated at 100 °C for 3 days. The product was chromatographed on alumina (15% MeOH/CH_2Cl_2) to yield **10** (6 mg), identical by MS with material from the Hofmann degradation of *N*-methylcelacinnine.

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Registry No.—**10**, 63301-68-8; **11**, 63301-69-9; **13**, 63301-70-2; **17**, 53938-10-6; spermidine, 124-20-9; cinnamoyl chloride, 17082-09-6.

References and Notes

(1) (a) Supported by grants from the National Cancer Institute, U.S. Public Health Service (CA 11718 and CA 125059), and the American Cancer Society (CI-102K). (b) Deceased October 19 1976. (c) School of Natural Resources, University of the South Pacific, Box 1168, Suva, Fiji.
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W-7783, a Unique Antifungal Antibiotic

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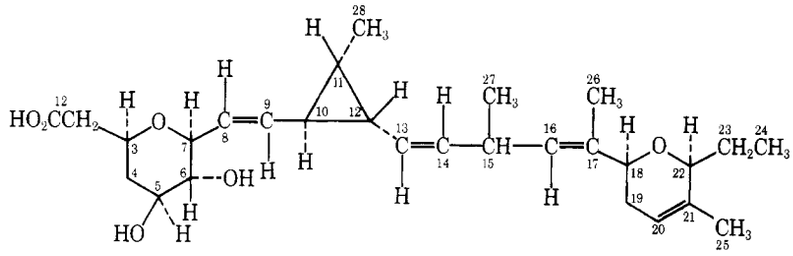
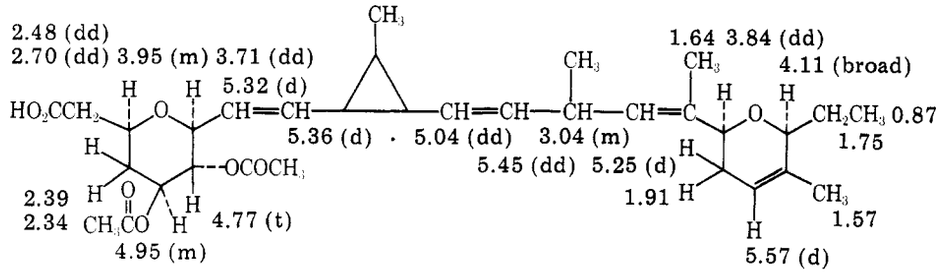
W-7783, $C_{28}H_{42}O_6$, an antifungal antibiotic with a unique structure, is produced by a myxobacteriale *Polyangium cellulosum* var. *fulvum*. The structure was deduced from chemical and spectral evidence including single-crystal x-ray analysis.

The structure of W-7783 (5,6-dihydroxypolyangioic acid),[2] an antifungal antibiotic produced by growth under appropriate conditions from a soil inhabiting myxobacteriale *Polyangium cellulosum* var. *fulvum*,[3a] has been deduced from chemical and spectral data including single-crystal x-ray analysis. W-7783 shows in vitro[3a] and in vivo activity[3b] against a variety of pathogenic fungi including *Histoplasma capsulatum* and *Coccidioides immitis*. *Histoplasmois* and *coccidioidomycosis* are treated at the present time with the highly toxic agent amphotericin B requiring iv administration and prolonged hospitalization. W-7783 (**1**, see Scheme I) represents a completely novel type of antibiotic. It is an orally active

Scheme I

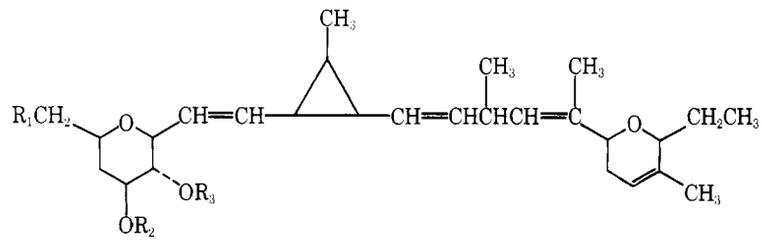


A L C



2

Scheme II



1. $R_1 = CO_2H$, $R_2 = R_3 = H$
2. $R_1 = CO_2H$, $R_2 = R_3 = COCH_3$
3. $R_1 = CO_2CH_3$, $R_2 = R_3 = H$
4. $R_1 = CO_2CH_3$, $R_2 = R_3 = COCH_3$
5. $R_1 = CH_2OH$, $R_2 = R_3 = H$
6. $R_1 = CH_2OCOCH_3$, $R_2 = R_3 = COCH_3$
7. $R_1 = CH_2OCOH$, $R_2 = R_3 = COH$
8. $R_1 = CH_2Br$, $R_2 = R_3 = COH$
9. $R_1 = CH_2Br$, $R_2 = R_3 = H$

antifungal agent, with a unique chemical structure, and is produced by a type of organism previously unexplored in the search for therapeutic agents.

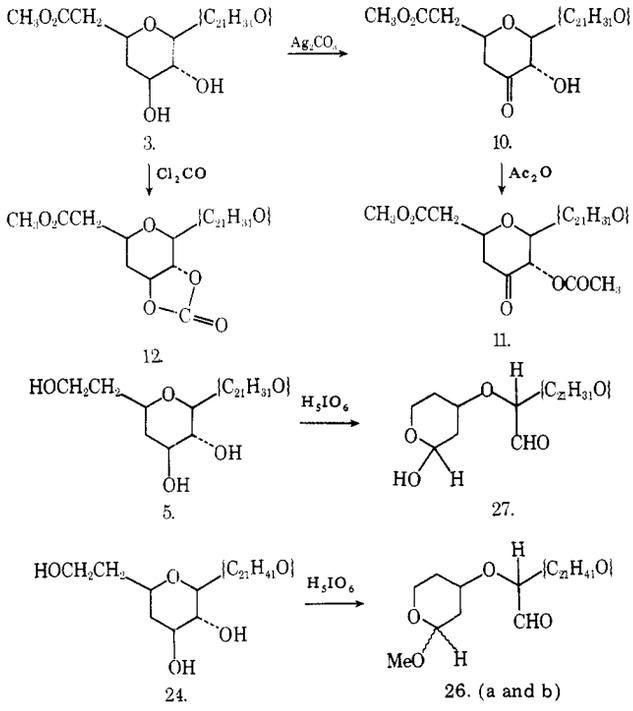
The molecular ion in the mass spectrum indicated a molecular formula $C_{28}H_{42}O_6$ (474). The infrared spectrum showed a carbonyl band at 1720 cm^{-1} and the ultraviolet spectrum indicated the molecule contained no conjugated functions. Acid **1** was converted to diacetate **2** and monomethyl ester **3** (Scheme II). The ester was converted to diacetate **4**, which showed no hydroxyl stretching in the infrared spectrum, indicating **1** is a dihydroxymonocarboxylic acid. Reduction of acid **1** or ester **3** with lithium aluminum hydride gave triol **5**, which was acetylated to give triacetate **6**. The ester was catalytically hydrogenated to give octahydro ester **19** indicating **1** contains four double bonds and thus three rings.

The ^{13}C NMR spectrum of **1** showed a carbonyl C (δ 175.1) and confirmed the presence of four double bonds (vinyl C resonances at δ 139.4, 136.0, 135.4, 129.9, 125.5, 124.1, and 121.3). The eighth vinyl C resonance was not clearly observed above the background. In the coupled spectrum these resonances were all doublets with the exception of the resonance at δ 135.4 (singlet). The presence of six carbons adjacent to oxygen (δ 80.7, 78.2, 78.1, 75.9, 72.3, and 71.7) was observed and all were doublets in the coupled spectrum. Two of these resonances represent the carbons attached to two secondary hydroxyl groups. Thus, the other four resonances must represent two ether linkages of the type >ĊHOĊH<. The spectrum also showed four methylene carbons (δ 40.3, 38.3, 30.2, and 25.6), four methine carbons (δ 35.0, 30.5, 29.0, and 21.6), and five methyl carbons (δ 21.2, 18.9, 13.0, 12.3, and 8.2).

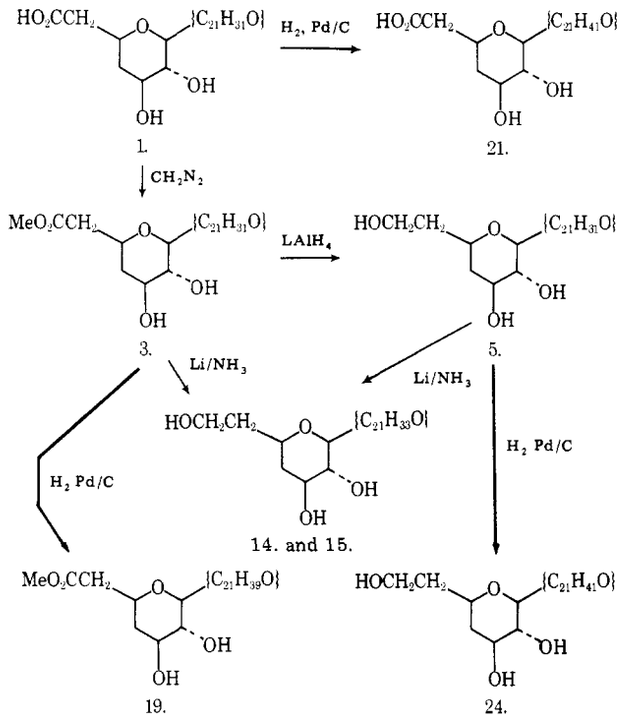
The ^1H NMR spectrum of diacetate **2** showed six vinyl protons (δ 5.57, 5.45, 5.36, 5.32, 5.25, and 5.04) and two vinyl methyl groups (δ 1.64 and 1.57), confirming the presence of four double bonds. Two protons (δ 4.95 and 4.77) on carbons next to acetoxy and the four protons (δ 4.11, 3.95, 3.84, and 3.71) of the two ether systems were observed. Other important features were a resonance at δ 3.04 characteristic of a proton on a bisallylic carbon and two quartets (δ 2.70 and 2.48) assigned to a methylene group next to the carboxylic acid function. The five methyl groups indicated by the ^{13}C NMR spectrum were also observed and assigned the following environments: two $CH_3C{=}C$ (δ 1.64 and 1.57), two CH_3CH (δ 1.01), and one CH_3CH_2 (δ 0.87).

The important mass spectral fragmentations of ester **3** are shown in Scheme V. Fragments at 171, 215, and 197 indicate a highly oxygenated fragment connected to a double bond ($C_8H_{13}O_5CH{=}CH{-}$). ^1H NMR decoupling experiments on diacetate **2** together with chemical evidence indicate this gragment has the structure (ring A) shown in Scheme I. Irradiation at δ 3.71 (C_7H) decouples δ 5.32 (d to s, C_8H) and δ 4.77 (t to d, C_6H). Irradiation at δ 3.95 (C_3H) decouples at C_2 2.48 (dd to d) and 2.70 (dd to d). Irradiation at δ 5.32 (C_8H) decouples at δ 3.71 (dd to d, C_7H). Irradiation at δ 4.95 (C_5H) collapses δ 2.34 (C_4H) and 2.39 (C_4H). The vicinal nature of the hydroxyl groups was deduced in several ways. Triol **5** was oxidized to aldehyde **27** with periodic acid (a reagent specific for vicinal diols). This oxidation was not reproducible with **5**

Scheme III



Scheme IV



and only small yields of **27** Were occasionally isolated. The reaction was reproducible with triol **24,** which was oxidized to isomeric acetals **26a** and **26b** under the same conditions. ^{1}H NMR and mass spectra indicate **26** has the structure shown in Scheme III.

Ester **3** formed cyclic carbonate **12,** with phosgene in pyridine showing a carbonyl band at 1820 cm^{-1} (five membered ring) in the IR. Ester **3** was oxidized with silver carbonate on Celite to ketone **10,** which was converted to acetate **11.** The ^{1}H NMR of **11** showed the following resonances not present in the NMR of **2,** at δ 2.54 (d, 1, J = 16 Hz) and at δ 2.65 (d, 1, J = 16 Hz) due to the C_4 hydrogens (now next to the newly generated carbonyl group) and at δ 5.00 (d, 1, J = 5 Hz) due to the C_6H which has moved downfield due to the presence of the adjacent carbonyl group and is no longer split by the hydrogen at C_5.

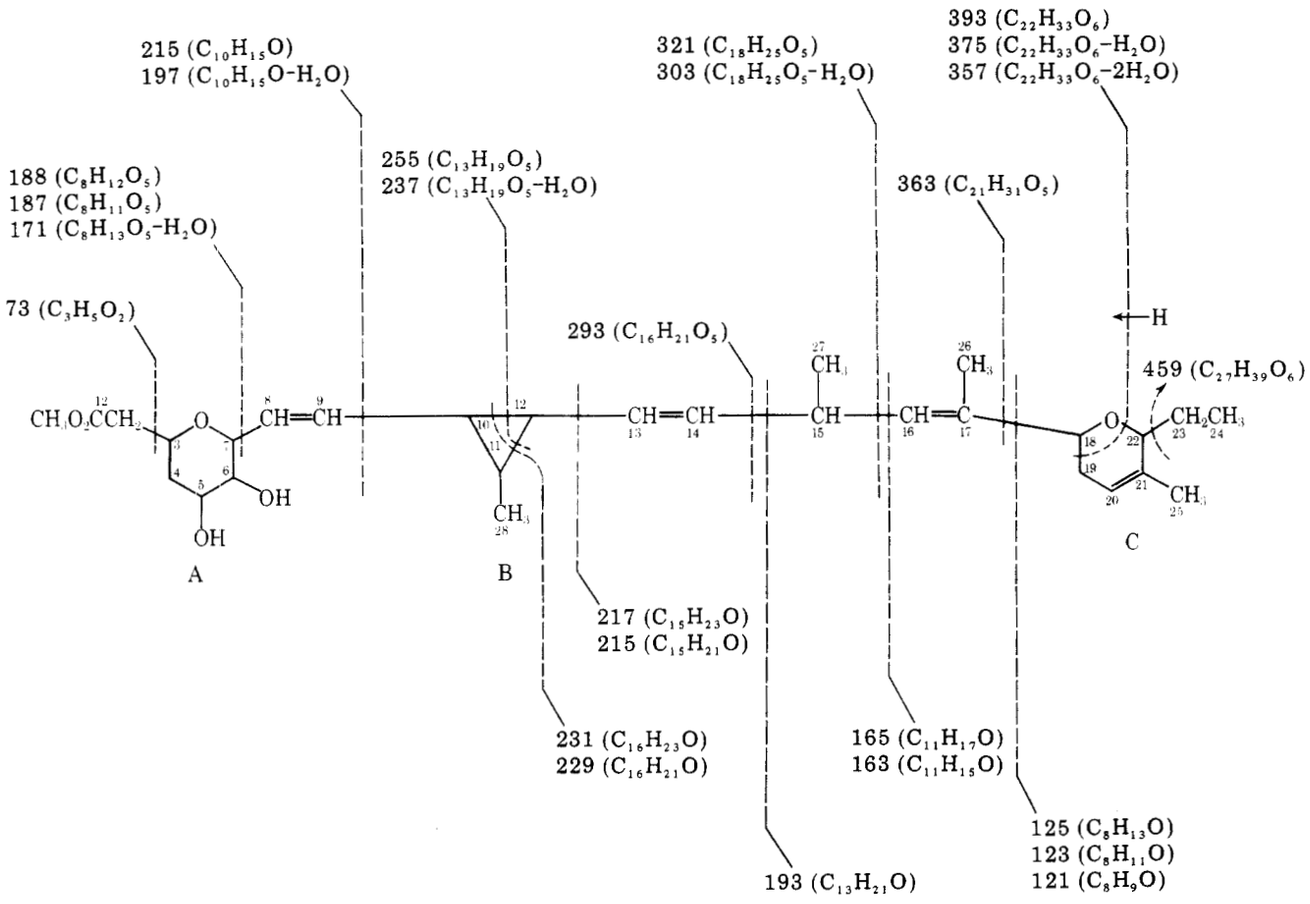
The mass spectrum also shows prominent fragments containing one oxygen at 125 ($C_8H_{13}O$), 165 (-CH=C(CH_3)-$C_8H_{13}O$) and 193 (-CH(Me)C=C(CH_3)$C_8H_{13}O$). Irradiation at δ 3.04 decouples at δ 5.45 (dd to d, C_{14}H) and 5.25 (d to s, C_{16}H) establishing the system CH=CHCH(Me)CH=C(Me)- in the molecule. The coupling constants and mass spectral fragments rule out the C_8-C_9 double bond from being part of this system and thus it constitutes the C_{13} to C_{17} portion as shown in **1.** This leaves a C_4H_6 moiety to link G_9 and C_{13}. The $C_8H_{13}O$ fragment must contain a CH-O-CH, a CH=CCH_3, an ethyl group, and a -CH_2-, for none of these groups could be fitted into the C_4H_6 fragment and make sense in light of the spectral evidence presented above. The $C_8H_{13}O$ fragment must contain a ring as well as the double bond, and the arrangement shown as ring C in **1** is the only one which fits the ^{1}H NMR evidence. Neither C_{18}H nor C_{22}H is coupled to C_{20}H and neither is a singlet. Irradiation at δ 1.91 decouples δ 3.84 (dd to d, C_{18}H) and 5.57 (d to s, C_{20}H). Irradiation at δ 4.11 (C_{22}H) simplifies the pattern at δ 1.75. The only carbons not now accounted for in the ^{13}C NMR spectrum are one methyl and three methines, and they must constitute the C_4H_6 fragment.

In addition to the straightforward chemistry described above, certain anomalous reactions were observed. Thus, catalytic hydrogenation of ester **3** gave the expected octahydro ester **19,** but hydrogenation of acid **1** or triol **5** under the same conditions gave decahydro compounds **21** and **24.** All the reduced compounds gave the expected acetates, indicating that no C-O-C bonds had been reduced and thus the extra molecule of hydrogen was introduced by C-C bond breaking in a ring.

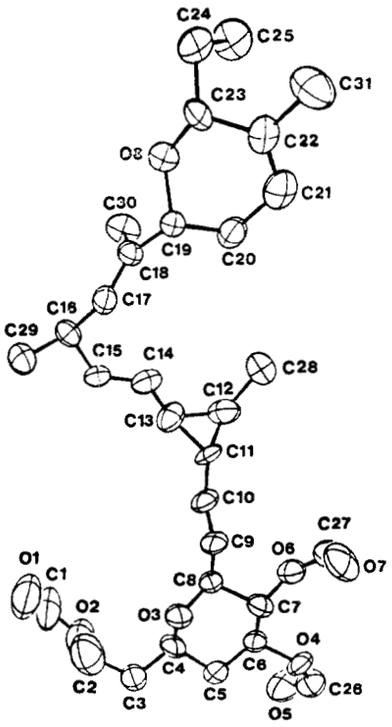
Reduction of ester **3** or triol **5** with lithium in liquid ammonia gave dihydrotriols **14** and **15**[4] and tetraol **13.** Initially, a triple bond to double bond transformation was suspected (acetylation indicates no extra hydroxyl groups are generated), but the ^{1}H NMR indicated six vinyl hydrogens (as in the unreduced compound). All the vinyl hydrogens had undergone shifts (all crowded around δ 5.41 to 5.18) except C_{20}H, further indicating it to be off in a ring by itself. The only type of C-C bonds broken by lithium in liquid ammonia are those in which the negative charges formed by bond breaking are stabilized by adjacent conjugation, and the bond broken is under strain.[5] Thus, the system -C=CC_{10}-C_{12}C=C- must be present in **1,** and the C_{10}-C_{12} bond must be part of a ring and be under strain. A possible arrangement for the C_4H_6 fragment is cyclopropane ring B, and this conveniently provides the double bond strained single bond-double bond system needed to explain the lithium in liquid ammonia reductions and anomalous catalytic hydrogenations. Attempts to obtain further evidence by cleaving the system with ozone gave a complex mixture from which no pure compounds were obtained.

To distinguish the proposed structure **1** from other alternatives that were considered, it was necessary to carry out an x-ray structure determination. In order to do the x-ray crystallography, a large number of derivatives were prepared, almost all of which were oils or gums. Triol **5** formed crystalline compounds with aryl isocyanates and they could be recrystallized to give analytically pure samples **28** and **29,** but no suitable crystals for x-ray analysis could be grown. The bromodiformate **8** was prepared from triol **5** with Ph_3PBr_2 and DMF.[6] This would have been the ideal compound for x-ray work. It could be recrystallized from ethanol by cooling and filtering the crystals, but attempts to obtain larger crystals by slow evaporation of the solvent resulted in hydrolysis to noncrystalline bromodiol **9.** The main product from the re-

Scheme V



Scheme VI



action of triol **5** with Ph_3PBr_2 and DMF was triformate **7**.

Unequivocal proof of the structure and stereochemistry of **1** was provided by single-crystal x-ray analysis[7] of polyangi-1,5,6-triol triformate (**7**) which crystallized from ethanol in the monoclinic system, space group $P2_1$, a = 15.671 (4), b = 5.309 (2), c = 19.995 (4) Å, β = 110.80° (2), z = 2. There were 2439 independent reflections measured on a Syntex $P\bar{1}$ diffractometer using graphite monochromated Cu-K_α radiation. The structure was solved by direct methods and refined by full-matrix least-squares to an R value of 0.087.

The x-ray structure indicates that the double bonds at C_8–C_9, C_{13}–C_{14}, and $C_{16}C_{17}$ are all trans with respect to the chain. Ring A is in a chair conformation and the substituents at 3, 5, 6, and 7 are all equatorial. The substituents at 3, 5, and 7 are cis with respect to each other and trans to the 6 substituent. On the cyclopropane ring the methyl group is cis to the C_{12} substituent and trans to the C_{10} substituent. In ring C, the ethyl group and the C_{18} substituent are both equatorial and cis to each other. A computer drawing of the x-ray structure of triformate **7** is shown in Scheme VI.[8]

Experimental Section[9]

Melting points were measured with a Thomas-Hoover capillary melting-point apparatus without correction. ^{1}H NMR spectra were run in $CDCl_3$ on a Perkin-Elmer R-12B 60 MHz or Varian HR-220[10] spectrometer with Me_4Si used as internal standard. The ^{13}C NMR spectrum was run in $CDCl_3$ on a Varian XL-100 at 25.2 MHz in the pulsed fourier transform mode. Mass spectra[11] were obtained with an AE1 MS-902 instrument. TLC was performed on silica gel plates (Quantum) using iodine vapors for visualization.

Isolation of W-7783 (1). The crude acid was extracted from the fermentation medium with ethyl acetate and purified by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5). The pure acid (homogeneous by TLC0 was obtained as a gum, which could be ground to give an off-white amorphous powder: IR (film) 3600–3200 (br, OH), 2800–2400 (OH), 1720 cm^{-1} (CO); ^{13}C NMR δ 175.1 (s, c=O), 139.4 (d, H–C=), 136.0 (d, H–C=), 135.4 (s, C=), 129.9 (d, H–C=), 125.5 (d, H–C=), 124.1 (d, H–C=), 121.3 (d, H–C=), 80.7 (d, H–C–O), 78.2 (d, H–C–O), 78.1 (d, H–C–O), 75.9 (d, H–C–O), 72.3 (d, H–C–O), 71.7, (d, H–C–O), 40.3 (t, CH_2), 38.3 (t, CH_2), 35.0 (d, CH), 30.5 (d, CH), 30.2 (t, CH_2), 29.0 (d, CH), 25.6 (t, CH_2), 21.6 (d, CH), 21.2 (q, CH_3), 18.9 (q, CH_3), 13.0 (q, CH_3), 12.3 (q, CH_3), 8.2 (q, CH_3); mass spectrum m/e (rel intensity) 474 (20), 456

(13), 445 (30), 379 (18), 279 (20), 193 (100). Found M^+ 474.3009; $C_{28}H_{42}O_6$ requires 474.2981.

Anal. Calcd for $C_{28}H_{42}O_6 H_2O$: C, 68.26; H, 9.00. Found: C, 68.07; H, 8.78.

Methyl 5,6-Dihydroxypolyangioate (3). Excess diazomethane in ether was added to W-7783 (100 mg) in ethanol (10 mL). The solution was allowed to stand at room temperature for 15 min. A few drops of acetic acid were added and the solvents were removed at reduced pressure to give a yellow oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (90 mg): IR (film 3600–3200 (br, OH), 1730 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 488 (6), 470 (2), 460 (11), 459 (47), 393 (14), 375 (10), 363 (7), 357 (6), 321 (10), 305 (3), 303 (6), 294 (7), 293 (12), 279 (7), 277 (9), 255 (17), 237 (27), 231 (8), 229 (9), 217 (8), 215 (10), 215 (3), 211 (48), 197 (16), 193 (69), 188 (10), 171 (52), 165 (64), 163 (44), 159 (100), 152 (79), 139 (45), 135 (48), 129 (90), 127 (74), 125 (83), 124 (26), 123 (81), 122 (32), 121 (30), 120 (19), 119 (8), 73 (17). Found: M^+ 488.3240; $C_{29}H_{44}O_6$ requires 488.3238.

5,6-Dihydroxypolyangioic acid, Diacetate 2. Acetic anhydride (1 mL) was added to a solution of W-7783 (100 mg) in pyridine (2 mL). The reaction mixture was allowed to stand at room temperature overnight. A few drops of water were added and the solvents were removed at reduced pressure to give a brown oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (homogeneous by TLC) (84 mg, 71%): IR (film) 1745 (CO), 1720 cm^{-1} (CO); ^1H NMR δ 5.57 (d br, 1, $C_{20}H$), 5.45 (dd, 1, J = 15.5 and 6.2 Hz, $C_{14}H$), 5.36 (d, 1, C_9H), 5.32 (d, 1, C_8H), 5.25 (d, 1, J = 9.2 Hz, $C_{16}H$), 5.04 (dd, 1, J = 15.5 and 8.2 Hz, $C_{13}H$), 4.95 (m, 1, C_5H), 4.77 (t, 1, J = 9.5 and 9.5 Hz, C_6H), 4.11 (br, $C_{22}H$), 3.95 (m, 1, C_3H), 3.84 (dd, 1, J = 2.2 and 10.5 HZ, $C_{18}H$), 3.71 (dd, 1, J = 5.7 and 9.5 Hz, C_7H), 3.04 (m, 1, $C_{15}H$), 2.70 (dd, 1, J = 5.5 and 16.0 HZ, C_2H), 2.48 (dd, 1, J = 5.5 and 16.0 Hz), 2.39 (m, 1, C_4H), 2.34 (m, 1, C_4H), 2.00 (s, 3, CH_3CO), 1.98 (s, 3, CH_3CO), 1.64 (s, 3, CH_3C=), 1.57 (s, 3, CH_3C=), 1.01 (m, 6, 27-CH_3 and 28-CH_3), 0.87 (t, 3, 24-CH_3); mass spectrum *m/e* (rel intensity) 558 (10), 529 (32), 463 (14), 345 (7), 245 (32), 193 (100), 165 (57), 125 (70). Found: $M^+ - 29$, 529.2939; $C_{30}H_{41}O_8$ requires 529.2801.

Methyl 5,6-Dihydroxypolyangioate, Diacetate 4. Prepared from methyl 5,6-dihydroxypolyangioate (100 mg) by the general method described for the preparation of acetate 2. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (80 mg): IR (film) 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 572 (23), 543 (53), 477 (29), 259 (35), 193 (100).

Polyangi-1,5,6-triol 5. Lithium aluminum hydride (100 mg) was added to a solution of W-7783 (100 mg) in THF (20 mL). The reaction mixture was refluxed with stirring under nitrogen for 3 h. The mixture was cooled in an ice bath, and a few drops of water were added, followed by magnesium sulfate (50 mg). The inorganic solids were filtered off and thoroughly washed with ethyl acetate. The filtrate and washings were evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5) to give a colorless oil (75 mg, 77%) (homogeneous by TLC): IR (film) 3400–3200 cm^{-1} (br, OH); mass spectrum *m/e* (rel intensity) 460 (6), 442 (5), 431 (52), 365 (6), 347 (26), 329 (10), 195 (75), 193 (100), 167 (100), 165 (100), 152 (100), 125 (100), 123 (100). Found: 123 (100). Found: M^+ 460.3223; $C_{28}H_{44})_5$ requires 460.3189.

Polyangi-1,5,6-triol, Triacetate 6. Acetic anhydride (1 mL) was added to a solution of **5** (30 mg) in pyridine (2 mL). The reaction mixture was allowed to stand at room temperature overnight. A few drops of methanol were added and the solvents were removed at reduced pressure to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate– cyclohexane (4:1) to give a colorless oil (homogeneous by TLC) (30 mg, 79%): IR (film) 1740 cm^{-1} (CO); ^1H NMR δ 5.58 (d br, 1, $C_{20}H$), 5.46 (dd, 1, $C_{14}H$), 5.37 (d, 1, C_9H), 5.35 (d, 1, C_8H), 5.25 (d, 1, $C_{16}H$), 5.06 (dd, 1, $C_{13}H$), 4.97 (m, 1, C_5H), 4.77 (t, 1, C_6H), 4.13 (m, 3, $C_{22}H + C_1$, 2 H), 3.86 (dd, 1, $C_{18}H$), 3.68 (dd, 1, C_7H), 3.62 (m, 1, C_3H), 3.07 (m, 1, $C_{15}H$), 2.16 (m, 1, C_4H), 2.10 (m, 1, C_4H), 2.04 (s, 3, CH_3CO), 2.03 (s, 3, CH_3CO), 1.99 (s, 3, CH_3CO), 1.64 (s, 3, CH_3C=), 1.59 (s, 3, CH_3C=), 1.05 (m, 6, 27-CH_3 and 28-CH_3), 0.89 (t, 3, 24-CH_3); mass spectrum *m/e* (rel intensity) 586 (10), 557 (50), 491 (20), 431 (6), 371 (20), 193 (100).

Methyl 5,6-Dihydroxypolyangioate, 5,6-Cyclic Carbonate (12). A solution of 12% phosgene in benzene (2 mL) was added to methyl 5,6-dihydroxypolyangioate (40 mg) in pyridine (2 mL). The resulting mixture was allowed to stand at room temperature overnight. The reaction mixture was cooled, diluted with ice-cold water, and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give a brown oil. The oil was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:2) to give a colorless oil (29 mg, 69%) (homogeneous by TLC): IR (film) 1820 (CO), 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 514 (7), 485 (20), 419 (13), 193 (100), 165 (80), 125 (50). Found: M^+ 514.2902; $C_{30}H_{42}O_7$ requires 514.2930.

Methyl 6-Hydroxy-5-oxopolyangioate (10). Silver carbonate on celite (2.0 g) was added to a solution of methyl 5,6-dihydroxypolyangioate (200 mg) in toluene (100 mL). The reaction mixture was refluxed under nitrogen with vigorous stirring. Further portions of silver carbonate on celite were added (total amount added 5.0 g) until TLC indicated an absence of starting material in the reaction mixture. The inorganic solids were filtered off and washed with ethyl acetate. The filtrate and washings were evaporated under reduced pressure to give a brown oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a yellow oil (95 mg, 48%) (homogeneous by TLC): IR (film) 3600–3300 (br, OH), 1740 (CO), 1720 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 486 (20), 468 (22), 457 (21), 391 (42), 373 (20), 275 (35), 193 (60), 165 (100).

Methyl 5-Oxo-6-hydroxypolyangioate Acetate (11). Acetic anhydride (1 mL) was added to a solution of methyl 6-hydroxy-5-oxopolyangioate (40 mg) in pyridine (3 mL). The solution was allowed to stand at room temperature overnight. The reaction mixture was cooled, diluted with methanol, and evaporated at reduced pressure to give a yellow oil. The product was purified by preparative TLC with chloroform as the solvent system to give a yellow oil (31 mg) (homogeneous by TLC): IR (film) 1740 (CO), 1720 cm^{-1} (CO); ^1H NMR δ 5.57 (d br, 1, $C_{20}H$), 5.48 (dd, 1, $C_{14}H$), 5.42 (d, 1, C_9H), 5.40 (d, 1, C_8H), 5.26 (d, 1, $C_{16}H$), 5.08 (dd, 1, $C_{13}H$), 4.99 (d, 1, J = 10 Hz, C_6H), 4.11 (m, 2, $C_{22}H$ and C_3H), 4.00 (dd, 1, C_7H), 3.85 (dd, 1, $C_{18}H$), 3.70 (s, 3, OMe), 3.05 (m, 1, $C_{15}H$), 2.77 (dd, 1, C_2H), 2.65 (d, 1, J = 15 Hz, C_4H), 2.57 (dd, 1, C_2H), 2.54 (d, 1, J = 15 Hz, C_4H), 2.15 (s, 3, CH_3CO), 1.64 (s, 3, CH_3C=), 1.59 (s, 3, CH_3C=), 1.06 (m, 6, 27-CH_3 and 28-CH_3), 0.89 (t, 3, 24-CH_3).

Reduction of Methyl 5,6-Dihydroxypolyangioate with Lithium/Liquid Ammonia. Lithium (enough to maintain a blue color for 30 min) was added to a solution of methyl 5,6-dihydroxypolyangioate (160 mg) in anhydrous liquid ammonia (35 mL) and absolute ethanol (3 mL). The solution was stirred for 30 min. The ammonia was allowed to evaporate and the residue was diluted with water. The resulting aqueous solution was extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. The oil was fractionated by preparative TLC (ethyl acetate) into three compounds. **Tetraol (13)** (12 mg), a colorless oil (most polar): IR (film) 3600–3200 cm^{-1} (br, OH). **Dihydropolyangi-1,5,6-triol (14)** (20 mg), a colorless oil: IR (film) 3600–3200 cm^{-1} (br, OH); mass spectrum *m/e* (rel intensity) 462 (25), 444 (9), 433 (28), 367 (37), 349 (36), 331 (22), 313 (14), 195 (20), 193 (100), 167 (60), 165 (86), 125 (60), 123 (85). **Isodihydropolyangi-1,5,6-triol (15)** (44 mg), a colorless oil: IR (film) 3600–3200 cm^{-1} (br OH); mass spectrum *m/e* (rel intensity) 462 (26), 444 (11), 433 (44), 367 (66), 349 (55), 331 (22), 313 (13), 195 (70), 193 (85), 167 (81), 165 (100), 125 (80), 123 (80).

Tetraol, Tetraacetate 16. Tetraol (**13**) was acetylated under the conditions described above to give tetraacetate **16** (colorless oil): IR (film) 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 632 (7), 630 (15), 603 (27), 543 (7), 537 (40), 477 (88), 417 (16), 375 (20), 357 (20), 315 (20), 297 (40), 195 (65), 193 (80), 167 (74), 165 (100), 125 (65), 123 (65).

Dihydropolyangi-1,5,6-triol, Triacetate 17. Triol **14** was acetylated under the conditions described above to give **17** (colorless oil0: IR (film) 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 588 (19), 559 (25), 493 (69), 479 (14), 433 (18), 419 (12), 391 (14), 373 (26), 359 (6), 313 (18), 259 (33), 195 (69), 193 (100), 167 (60), 165 (73), 125 (80), 123 (60).

Isodihydropolyangi-1,5,6-triol, Triacetate 18. Triol **15** was acetylated under the conditions described above to give **18** (colorless oil): IR (film) 1740 cm^{-1} (CO); ^1H NMR δ 5.58 (d br, 1, $C_{20}H$), 5.41–5.18 (m, 5, vinyl), 4.96 (m, 1, C_5H), 4.79 (t, 1, C_6H), 4.17 (t, 2, C_1H), 4.11 (br, $C_{22}H$), 3.85 (m, 1, $C_{18}H$), 3.55 (m, 1, C_3H), 3.33 (m, 1, C_7H), 3.02 (m, 1, $C_{15}H$), 2.05 (s, 3, CH_3CO), 2.04 (s, 3, CH_3CO), 2.01 (s, 3, CH_3CO), 1.65 (d, 3, 26-CH_3), 1.58 (s, 3, 25-CH_3), 27-CH_3 and 28-CH_3 signals are complex, indicating a mixture of isomers; mass spectrum *m/e* (rel intensity) 588 (26), 559 (18), 493 (100), 433 (25), 419 (14), 391 (17), 373 (13). Found: M^+ 588.3706; $C_{34}H_{52}O_8$ requires 588.3696.

Methyl Octahydro-5,6-dihydroxypolyangioate (19). A solution of methyl 5,6-dihydroxypolyangioate (150 mg) in absolute ethanol (20 mL) was hydrogenated over 10% palladium on carbon at atmospheric pressure for 3 h. The catalyst was filtered off and washed with

ethanol. The filtrate and washings were evaporated to give a colorless oil. The oil was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (72 mg, 47%) (homogeneous by TLC): IR (film) 3600–3300 (br, OH), 1740 cm^{-1} (CO); mass spectrum spectrum *m/e* (rel intensity) 498 (0.5), 496 (4.5), 494 (1.8), 167 (37), 154 (100), 127 (14), 109 (11). Found: M^+ 496.3792; $C_{29}H_{52}O_6$ requires 496.3764.

Methyl Octahydro-5,6-dihydroxypolyangioate, 5,6-Diacetate 20. Acetic anhydride (1 mL) was added to a solution of methyl octahydro-5,6-dihydroxypolyangioate (15 mg) in pyridine (2 mL). The reaction mixture was allowed to stand at room temperature overnight. Methanol was added and the solvents were removed at reduced pressure to give a colorless oil. The product was purified by preparative TLC to give a colorless oil (14 mg, 80%) (homogeneous by TLC): IR 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 582 (5), 580 (20), 578 (7), 520 (15), 460 (15), 367 (12), 337 (17), 214 (45), 197 (35), 167 (100), 154 (100), 127 (50), 109 (45).

Decahydropolyangin (21). A solution of W-7783 (50 mg) in absolute ethanol (20 mL) was hydrogenated over 10% palladium on charcoal for 4 h. The catalyst was filtered off and washed with ethanol. The filtrate and washings were evaporated to give a colorless oil. The oil was purified by preparative TLC with the solvent system ethyl acetate–2-porpanol–water (85:10:5) to give a colorless oil (20 mg, 39%) (homogeneous by TLC): IR (film) 3600–3200, 2800–2400 (br OH), 1715 cm^{-1} (CO).

Methyl Decahydro-5,6-dihydroxypolyangioate (22). Acid **21** was methylated with diazomethane to give methyl ester **22:** IR (film) 3600–3200 (br, OH), 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 498 (4), 373(2), 339 (7), 167 (9), 154 (63), 127 (100), 109 (34).

Methyl Decahydro-5,6-dihydroxypolyangioate, Diacetate 23. Ester **22** was acetylated by the method described above to give diacetate **23:** IR (film) 1745 (CO), 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 582 (8), 522 (4), 506 (1), 367 (5), 223 (5), 201 (4), 167 (8), 154 (36), 127 (100), 109 (36). Found: M^+ 582.4130; $C_{33}H_{58}O_8$ requires 582.4131.

Decahydropolyangi-1,5,6-triol (24). A solution of polyangi-1,5,6-triol (47 mg) in absolute ethanol (20 mL) was hydrogenated over 10% palladium on charcoal for 3 h. The catalyst was filtered off and washed with ethanol. The filtrate and washings were evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5) to give a colorless oil (40 mg): IR (film) 3600–3200 cm^{-1} (br OH); mass spectrum *m/e* (rel intensity) 470 (4), 339 (7), 315 (4), 297 (6), 154 (15), 127 (100), 109 (60).

Decahydropolyangi-1,5,6-triol, Triacetate 25. Triol **24** was acetylated by the method described above to give triacetate **25:** IR (film) 1745 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 596 (6), 536 (5), 520 (2), 476 (3), 462 (4), 441 (4), 381 (4), 237 (4), 215 (4), 199 (18), 167 (7), 154 (25), 127 (100), 109 (42). Found: M^+ 596.4355; $C_{34}H_{60}O_8$ requires 596.4288.

Oxidation of Decahydropolyangi-1,5,6-triol with Periodic Acid. A solution of periodic acid (60 mg) in water (1 mL) was added to **24** (80 mg) in methanol (5 mL). The reaction mixture was allowed to stand at room temperature for 20 h, concentrated at reduced pressure, diluted with water, and extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. The oil was fractionated by preparative TLC (chloroform) into two pure components. **26a** (20 mg) (colorless oil): IR (film) 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 482 (5), 453 (20), 450 (12), 432 (5), 421 (30), 309 (20), 154 (100), 127 (100). **26b** (14 mg) (colorless oil): IR (film) 1735 cm^{-1} (CO); ^1H NMR δ 9.5 (d, 1, CHO), 3.2 (s, 3, OMe); mass spectrum *m/e* (rel intensity) 482 (5), 464 (5), 453 (14), 432 (24), 421 (32), 154 (100), 127 (100).

Oxidation of Polyangi-1,5,6-triol with Periodic Acid. A solution of periodic acid (40 mg) in water (1 mL) was added to **5** (10 mg) in methanol (2 mL). The reaction mixture was stirred for 1 h at room temperature and worked up as described above to give **27** (2 mg) as a colorless oil: IR (film) 3600–3200 (br, OH), 1730 cm^- (CO); mass spectrum *m/e* (rel intensity) 458 (16), 440 (40), 429 (16), 422 (86), 411 (18), 404 (26), 393 (18), 375 (8), 363 (12), 357 (14), 345 (26), 327 (24), 297 (20), 263 (20), 229 (66), 193 (100).

Polyangi-1,5,6-triol, Triphenylcarbamate 28. A solution of polyang-1,5,6-triol (40 mg) and phenyl isocyanate (60 mg) in toluene (5 mL) was refluxed under nitrogen for 2 h. The solvent was removed under reduced pressure to give an oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:2) to give a crystalline solid. Recrystallization from ethyl acetate gave white crystals (39 mg, 55%): mp 178–181 °C; IR (Nujol) 3300 (NH), 1705 cm^{-1} (CO).

Anal. Calcd for $C_{49}H_{59}N_3O_8$: C, 71.95; H, 7.27; N, 5.14. Found: C, 71.71; H, 7.34; N, 5.36.

Polyangi-1,5,6-triol, Tri-4-bromophenylcarbamate (29). A solution of polyangi-1,5,6-triol (200 mg) and 4-bromophenyl isocyanate (350 mg) in toluene (50 ML) was refluxed under nitrogen for 4 h. The reaction was worked up as described above to give a white powder. Recrystallization from ethyl acetate gave white crystals (95 mg, 21%): mp 184–190 °C; IR (nujol) 3300 (NH), 1705 cm^{-1} (CO).

Anal. Calcd for $C_{49}H_{56}Br_3N_3O_8$: C, 55.80; H, 5.35; N, 3.98; Br, 22.73. Found: C, 55.67; H, 5.57; N, 3.69; Br, 22.54.

Polyangi-1,5,6-triol, Triformate 7, and 1-Bromopolyangi-5,6-diol, Diformate 8. Bromine (0.16 g, 0.001 mol) was added to a solution of triphenylphosphine (0.262 g, 0.001 mol) in DMF (2.5 mL) at 0 °C under nitrogen. A solution of polyangi-1,5,6-triol (115 mg, 0.00025 mol) in DMF (1 mL) was added to the above triphenylphosphine dibromide solution at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and stored in a freezer for 4 days. The reaction mixture was poured into a brine and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give a white solid. The product mixture was separated into four fractions by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:10). (1) **Triphenylphosphine oxide** (most polar). (2) **Polyangi-1,5,6-triol, triformate (7).** A colorless oil (73 mg, 54%), which crystallized on standing. Recrystallization from ethanol gave white crystals: mp 94–95 °C; IR (Nujol) 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 544 (56), 515 (100), 449 (64), 419 (25), 357 (36), 259 (45), 193 (100), 165 (50), 152 (90), 125 (80). Found: M^+ 544.3089; $C_{31}H_{44}O_8$ requires 544.3036. (3) **1-Bromopolyangi-5,6-diol, Diformate 8.** A colorless oil (38 mg, 26%), which crystallized on standing. Recrystallization from methanol gave white crystals: mp 80–83 °C; IR (Nujol) 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 580 (20), 578 (20), 541 (50), 539 (50), 485 (25), 483 (25), 193 (100), 165 (50), 152 (100), 125 (100), 123 (100). (4) **Triphenylphosphine** (least polar). **1-Bromopolyangi-5,6-diol (9).** A solution of 1-bromopolyangi-5,6-diol diformate (12 mg) in ethanol (3 mL) was allowed to stand at room temperature overnight. The ethanol was removed at reduced pressure to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:1) to give diol **9** (a colorless oil homogeneous by TLC) (5 mg, 46%): IR (film) 3600–3200 cm^{-1} (br, OH); mass spectrum *m/e* (rel intensity) 524 (100), 522 (100), 506 (50), 504 (50), 495 (50), 493 (50), 429 (25), 472 (25). Found: M^+ 522.2450; $C_{28}H_{43}Br^{79}O_4$ requires 522.2351.

Registry No.—**1,** 58857-02-6; **2,** 63511-83-1; **3,** 62711-77-7; **4,** 63511-84-2; **5,** 63511-77-3; **6,** 63511-79-5; **7,** 63511-85-3; **8,** 63511-86-4; **9,** 63511-87-5; **10,** 63511-88-6; **11,** 63511-89-7; **12,** 63511-90-0; **14–15,** 63511-78-4; **17–18,** 63511-80-8; **27,** 63533-50-6; **28,** 63511-91-1; **29,** 63511-82-0; phenylisocyanate, 103-71-9; 4-bromophenyl isocyanate, 2493-02-0.

References and Notes

(1) (a) Uniroyal, Inc., Middlebury, Conn. 06749; (b) ICI North America, Wilmington, Delaware.
(2) The trivial chemical name 5,6-dihydroxypolyangioic acid is suggested for this system. This facilitates the naming of derivatives and epimers. Ambruticin is the suggested USANC name.
(3) (a) S. M. Ringel et al., *J. Antibiot.* **30,** 371 (1977); (b) H. B. Levine and S. M. Ringel, Proceedings of the Third International Coccidioldomycosis Symposium, June 1977.
(4) The exact nature of these compounds is under investigation.
(5) For an example of reductive ring opening with Na in liquid NH_3, see P. G. Gassman and X. Creary, *Chem. Commun.* 1214 (1972).
(6) R. K. Boeckman, Jr., and B. Ganem, *Tetrahedron Lett.,* 913 (1974).
(7) X-ray analysis performed by Molecular Structure Corp., College Station, Texas 77840.
(8) In this drawing the carbons and oxygens are numbered consecutively from the first formate and not systematically as in the previous figures and discussion.
(9) Many of the compounds described were gums or oils, which slowly decomposed at room temperature. The homogeneity of each compound was checked by TLC in at least two solvent systems. Molecular formulas were determined by high-resolution mass spectroscopy where possible. In cases where high resolution was not possible, the molecular composition of the low-resolution molecular ion was obvious from either the composition of the starting material or from a subsequent transformation product.
(10) 22-MHz ^1H NMR spectra were performed by Morgan-Schaffer Corp., Montreal, Canada.
(11) A high-resolution mass spectrum of methyl 5,6-dihydroxypolyangioate (**3**) with a computer printout of molecular compositions of fragment ions was performed at Battelle Institute, Columbus, Ohio 43201.