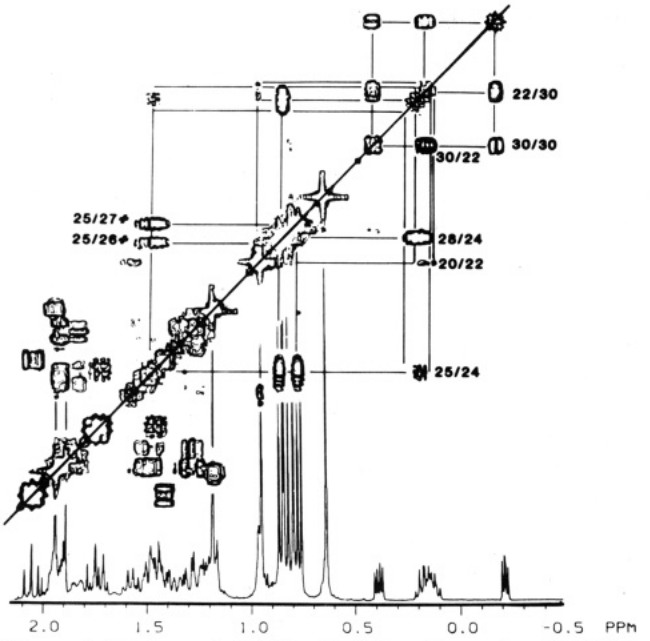

Figure 1. Contour plot (six level) of the autocorrelated (COSY) two-dimensional proton NMR spectrum (symmetrized[15]) of 1 in deuteriochloroform at 360 MHz. The final $S(F_2,F_1)$ matrix plotted consisted of 512 × 512 data points. Off-diagonal responses establishing proton spin-coupling connectivities are labeled with the protons involved, the downfield resonance listed first.

(20/22) to a multiplet resonating at δ 0.96 (H20), which was partially obscured by a methyl singlet resonance (Me-21).

The resonance of the non-cyclopropane proton at δ 0.17 can be seen to be coupled (Figure 1) to a methyl doublet (28/24) located at δ 0.85 (J = 6.9 Hz) and further to a complex multiplet (25/24) resonating at approximately δ 1.47. The latter multiplet can further be seen to be coupled to two methyl doublets, 25/26#[7] and 25/27# resonating at δ 0.83 and 0.76 (J = 7.0 Hz in each case). The proton spin-coupling network established through the COSY experiment thus identifies the anomalous high-field proton as H24, the eight-line pattern arising from nonequivalent couplings to the H25 methine and H28 methyl protons. The further couplings of the former resonance, also established by the COSY experiment, identify the 26- and 27-methyl doublets, thus completing the assignment of all of the proton resonances of this complex side chain.

Corroboration of the assignment of the resonance observed at δ 0.17 to H24 follows from consideration of the first-order character of this resonance and that at δ 0.13. The sole alternative proton that might account for the signal at δ 0.17 would be the 20-methine proton. In this case, we would expect the muliplet to be non-first-order due to strong coupling between the H20 and H22 resonances even at 360 MHz. The highly first-order character of these multiplets, however, and the coupling network established through the COSY experiment clearly precludes the assignment of the resonance at δ 0.17 to H20, thus confirming the assignment of this resonance as H24.

The dramatic shielding of H24 is undoubtedly caused by the steric demands of this very highly substituted side chain. The preferred conformations thus imposed are also reflected by the unusually large vicinal couplings displayed by the H22 (8.8 Hz) and H24 (8.7 Hz) protons on the side-chain backbone.

In summary, the utilization of two-dimensional autocorrelated ^{1}H NMR (COSY) spectra[4,5,8,9] or alternatively SECSY spectra,[10–13] promises to provide an extremely powerful tool for natural-products structure elucidation. Work is presently in progress in these laboratories to apply these techniques to other novel marine natural products, the results of which will be forthcoming.[14]

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Experimental Section

The COSY spectrum utilized in this study was obtained by using an initial $S(t_1,t_2)$ data matrix consisting of 1024 × 512 data points, the data acquired by using phase cycling of the second 90° pulse to provide the equivalent of quadrature detection in both time domains. Data presented in Figure 1 are shown as a six-level contour plot symmetrized after the second Fourier transformation.[15] All spectra were taken in deuteriochloroform on a sample prepared by dissolving 40 mg of 1 in approximately 0.5 mL of solvent. Spectra were taken at 361.053 MHz on a Nicolet WB-360 spectrometer. The proton reference spectrum plotted below the contour plot of the COSY data was obtained by using 32K data points.

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Two Topologically Distinct Total Syntheses of (±)-Sarkomycin

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The labile cyclopentanone sarkomycin 1 has been the subject of several recent reports.[2] Although its structure appears deceptively simple, it is quite difficult to prepare or to manipulate because of the extreme reactivities of its functional groups. Since sarkomycin belongs to the class of antitumor antibiotics refered to as pentenomycins or methylenomycins[3] that is under current scrutiny for

(1) (a) Fellow of the Alfred P. Sloan Foundation, 1981–3. (b) Present address: G. D. Searle Co., Chicago, IL.
(2) Recent syntheses of sarkomycin: (a) Wexler, B. A.; Toder, B. H.; Minaskanian, G.; Smith, A. B., III. *J. Org. Chem.* **1982**, *47*, 3333. (b) Marx, J. N.; Minaskanian, G. *Ibid.* **1982**, *47*, 3306; *Tetrahedron Lett.* **1979**, 4175. (c) Boeckman, R. K., Jr.; Naegely, P. C. *J. Org. Chem.* **1980**, *45*, 752. (d) Kobayashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 4295. (e) Toki, K. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 450; *Ibid.* **1958**, *31*, 333. (f) Hewson, A. T.; MacPherson, D. T. *Tetrahedron Lett.* **1983**, *24*, 647.
(3) For a compilation of references relating to biological activity or clinical use of sarkomycin, see ref 2b.

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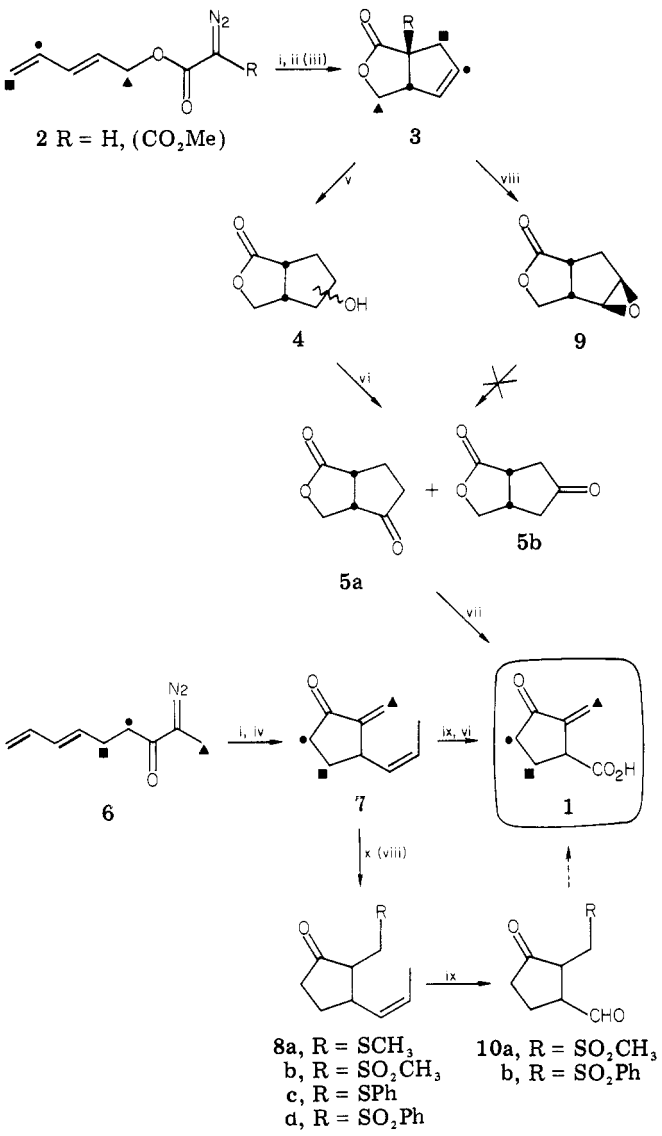
Scheme I[a]



[a] Reagents: i, $Cu(acac)_2$/benzene/Δ; ii, 580 °C/$PbCO_3$/Vycor; iii, LiI/DMF/Δ; iv, 450 °C/Pyrex; v, BH_3·THF/H_2O_2/NaOH; HCl; vi, CrO_3/H^+/acetone; vii, 3 N HCl/acetone/RT; viii, *m*-CPBA/CH_2Cl_2; ix, O_3/-78 °C/CH_2Cl_2/Me_2S; x, RSH/CH_3CN/diisopropylamine.

therapeutic purposes, it is understandable that sarkomycin should attract a great deal of attention from the synthetic point of view.

As part of our efforts in the area of *generalized* synthetic design for cyclopentanoid compounds, we investigated several independent routes to **1**. The cyclopentene annulation methodology, which represents a formal [4 + 1] intramolecular cycloaddition of a carbenoid to a conjugated diene, has recently been expanded to include diazo esters such as **2**.[4] Since lactones of the type **3** become accessible in good yields by this methodology, they can serve as synthons for multiply substituted cyclopentanoids as every position of the cyclopentane ring is functionally differentiated. We have converted lactone **3** to sarkomycin in good yield (Scheme I).

Our second approach to **1** exploited a secondary event of cyclopentene annulation performed previously in the carbocyclic series.[5] The enone **7** was obtained in high yield from diazo ketone **6** via a controlled pyrolysis of the corresponding *cis*-methylvinylcyclopropane.[6] This enone was converted to **1** via selective ozonolysis of the olefin.

The synthesis of lactone **3** has been described.[4] It is available in four steps from pentandienyl alcohol in perhaps 30% overall yield. We prepared the epoxide **9** (Scheme I), anticipating its conversion to **5** through either Lewis acid catalyzed rearrangement or via base-induced opening followed by hydrogenation and oxidation.[7] The latter process would impart greater control of regiochemistry on the formation of ketone **5**. Unfortunately, only fragmentation of **9** took place under a variety of experimental conditions. Attempts to produce alcohol **4** by oxymercuration have failed also. After much experimentation, the alcohols **4**, obtained by a carefully executed hydroboration sequence,[8] were purified as a mixture, and oxidized with Jones reagent to give ketones **5a** and **5b** in nearly quantitative yield and in a 70:30 ratio, respectively. The observed regioselectivity was both surprising and unexpected and would lead to speculations concerning any directing effect the lactone oxygen may have on the initial borane addition step. It may prove illustrative to use somewhat more electron-defficient borane $(B(OAc)_2H$, for example) to enhance the oxygen–boron interactions and to impart even greater selectivity on the formation of **5a**. The two ketones were easily separated by chromatography on silica, and cyclosarkomycin **5a**, a known precursor to the title compound, was converted to **1** by a published procedure.[2b] It should be emphasized that this separation becomes unneccessary in large-scale preparations of **1** since the unreacted **5a** is recycled during the hydrolysis step and since **5b** remains inert to the reaction conditions.

The selective ozonolysis of olefin **7** constituted the second synthetic approach to **1**.[9] Low-temperature addition of ozone-saturated CH_2Cl_2 solution[10] followed by reductive workup (either Zn/HOAc or Me_2S) gave an unstable aldehyde, which was immediately oxidized with Jones reagent to give **1**. The overall yield of **1** by this procedure was less then 10% due to the uncertain quantities of ozone used and due to the fact that we have initially isolated **1** as its methyl ester by treating with diazomethane the crude mixture obtained in the Jones oxidation. The tendency of enones such as **1** to form pyrazolines contributed to the loss of material. Although we have not optimized the yield, we feel that better results could be achieved by using a more controlled ozonization in the presence of an indicator[11] and by eliminating the esterification step. In the repetition of this work, there would be no need to prepare the methyl ester of **1**, which we used only as a criterion of identification.

A *controlled* alternative to the above oxidation, namely, the protection of the enone in **7** to yield **8**, was also attempted.[12] We prepared **8** and several of its derivatives

(4) Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.*, this issue.

(5) (a) Hudlicky, T.; Koszyk, F. J.; Dochwat, D. M.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 2911. (b) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. J.; Sheth, J. P. *Ibid.* **1980**, *45*, 5020.

(6) For a study of selectivity of vinylcyclopropane–cyclopentene vs. retro-ene rearrangement, see: Hudlicky, T.; Koszyk, F. J. *Tetrahedron Lett.* **1980**, *21*, 2487.

(7) The epoxide **9** was prepared from **3** in 60% yield (CH_2Cl_2 *m*-CPBA, room temperature, 4 h: IR (neat) 1760, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (m, 2 H), 2.9 (m, 2 H), 3.5 (br s, 2 H), 4.4 (m, 2 H).

(8) Procedure for this reaction was adapted from: Brown, H. C. "Organic Synthesis via Boranes"; Wiley: New York, 1975.

(9) We thank Prof. Albert I. Meyers (Colorado State University) for helpful suggestions concerning selective ozonolysis.

(10) Adapted from: Meyer, W. L.; Cameron, D. D.; Johnson, W. S. *J. Org. Chem.* **1962**, *27*, 1130.

(11) Veysoglu, T.; Mitscher, L. A.; Swazye, J. K. *Synthesis* **1980**, 807. This procedure appeared after completion of our studies on the oxidation of **7**.

of various oxidation levels and carried these through to the aldehyde **10** via epoxidation/hydrolysis/$NaIO_4$-cleavage or via ozonolysis.

Although this approach avoided polymerization of the enone moiety, it was abandoned as a possible source of **1** in view of its many steps and of our successful and facile functionalization of lactone **3**.

In conclusion, we feel that the two approaches presented above are, in principle, adaptable to the preparation of not only other methylenomycins but also of various prostanoid compounds. The unsubstituted periphery of sarkomycin can be functionalized in either of the precursors **2** or **6** (see Scheme I) since carbons 2 and 3 of sarkomycin occupy different functional positions in **2** and **6** (see the symbolic representation of these in Scheme I). Thus a greater choice of precursory functionalities becomes available for the construction of compounds such as **1** in the context of a single method of general synthetic design.

Experimental Section

Melting and boiling points are uncorrected. ^1H NMR spectra were determined at 90 MHz (Varian EM-390), 200 MHz (JEOL-FX 200), and 300 MHz (Nicolet 300 spectrometer). ^{13}C NMR spectra were recorded at 20 MHz (Varian CFT-20), 15 MHz (JEOL-FX60Q), and 50 MHz (JEOL-FX 200 spectrometers). Chemical shifts are reported in parts per million relative to internal tetramethylsilane or chloroform-*d*. Infrared spectra were obtained on Perkin-Elmer 257, Pye-Unicam 3-300, and Beckman IR 20A-X spectrophotometers. Mass spectra were recorded on a DuPont 20-491 instrument, Varian MAT-112 instruments (low resolution), or on a double-focusing DuPont 21-110C instrument (high resolution and exact mass data).

Gas chromatography was performed on a Varian 3700 instrument (F.I.D., 5% OV-101 on Chromosorb, 50 cm, 30 mL/min N_2).

All solvents were distilled from usual drying agents (Et_2O/$LiAlH_4$; THF, benzene, toluene, DME/K, and benzophenone). All nonhydrolytic reactions were performed under an inert atmosphere and in previously flame-dried glassware.

Chromatography was performed with J.T. Baker Alumina, Macherey Nagle Co, with Silica gel 60 or silica PF 254 by EM reagents (TLC). Flash chromatography utilized Kieselgel 60 (230–400 mesh) by EM reagents.

Purity of all compounds was ascertained by GC, TLC, and carbon 13 and high-field proton spectra with emphasis on the latter.

3a,5,6,6a-Tetrahydro-3*H*-cyclopenta[*c*]furan-1,4-dione (5a) and Its Regioisomer (5b). Lactone **3**[4] (87 mg, 0.0007 mol) in 1.5 mL of dry THF was cooled to 0 °C under argon and treated dropwise with 0.4 mL of a 0.92 M solution (1.6 equiv) of a borane–THF complex. The cooling bath was removed after the addition (2 min), and the mixture was stirred at room temperature for 2 h, whereupon excess BH_3 was decomposed by the addition of 0.04 mL of H_2O. The reaction mixture was cooled in ice, 0.12 mL of 3 M NaOH solution was added followed by 0.1 mL of 30% H_2O_2, and the entire mixture was then heated at 50 °C for 1 h. The reaction mixture was cooled, acidified with 0.2 mL of 3 M HCl, and stirred at room temperature for $^1/_2$ h, when it was partitioned between brine and ethyl ether and extracted. The organic layers were combined, dried, and evaporated to give an oil, which was chromatographed (1 g of silica, hexane:Et_2O (1:1)) to give 40 mg (40%) of a mixture of alcohols **4**: IR (neat) 3400, 1780 cm^{-1}; mass spectrum (Chem. Ionization mode), *m/e* (relative intensity)) 143 ($M^+ + 1$) (B), 124 (15), 85 (60), 81 (70), 71 (B).

A mixture of alcohols **4** (51 mg, 0.000 35 mol) was dissolved in 1 mL of acetone and cooled to 0 °C. Standard Jones reagent was added dropwise until the solution remained reddish brown. Stirring was continued for additional 30 min, 2-propanol was added to quench excess reagent, and the solution was filtered through a plug of silica to remove inorgnaic materials. Evaporation yielded 46.8 mg (93%) of ketones **5**, shown by GC (50 cm OV-101, on Chromosorb W, FID., 150 °C → 200 °C (5° min^{-1}), 30 mL/min of N_2) to consist of 70% **5a** and 30% **5b**. Careful chromatography (silica, hexane → Et_2O, gradient elution) afforded 22 mg (44%) of **5a**[2b] and 8 mg (16%) of **5b**.

5a: IR ($CHCl_3$) 1770, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2–2.6 (m, 4 H), 3.1 (m, 1 H), 3.4 (m, 1 H) 4.5 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (t), 36.6 (t), 41.5 (d), 47.7 (d), 68.8 (t), 178.4 (s), 217.0 (s).

5b: IR ($CHCl_3$) 1735, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (d, 1 H, J = 7 Hz), 2.8 (m, 3 H), 3.3 (m, 2 H), 4.2 (dd, J = 6, 1 Hz), 4.56 (dd, J = 7, 4 Hz).

Sarkomycin (1). A. From Cyclosarkomycin 5a.[2b] Keto lactone **5a** (22 mg, 0.000 15 mol) was stirred in a mixture of acetone and 3 M HCl (1.5 mL, 1:1) at room temperature for 8 h. The reaction mixture was extracted with $CHCl_3$ (5 × 1 mL). The chloroform extract was concentrated to ~2 mL and extracted with cold 5% $NaHCO_3$ (3 × 0.5 mL). Acidification of the aqueous layer (3 N HCl) and extraction with $CHCl_3$ (5 × 1 mL) gave, after drying and evaporation, 4 mg (25%) of **1**: IR ($CHCl_3$) 3500–2900, 1730–1700, 1640, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (m, 2 H), 2.3 (m, 2 H), 2.6 (m, 1 H), 5.69 (s, 1 H), 6.23 (s, 1 H). The unreacted **5a** was recovered from the neutral extract.

B. From Olefin 7. Exocyclic olefin **7**[5a,6] (200 mg, 0.0014 mol) was dissolved in 5 mL of CH_2Cl_2 and cooled to −78 °C. To this solution was added 0.1 mL (1.5 equiv) of a saturated solution of ozone in CH_2Cl_3.[10] The reaction was stirred for 30 min, degassed with nitrogen, and poured into 10 mL of Me_2S (or 5 mL of HOAc containing 1 g of Zn dust). The resulting mixture was stirred for 20 min at 0 °C, evaporated, dissolved in acetone, and titrated with standard Jones reagent. Workup of this mixture as in the case of **5** gave oil, which was treated with ethereal diazomethane. From the resulting complex mixture, 25 mg (11%) of the methyl ester of sarkomycin was isolated by preparative TLC (CH_2Cl_2). Its NMR spectrum and R_f-value (0.7) were identical with those of an authentic sample: ^1H NMR ($CDCl_3$) δ 2.1–2.6 (m, 5 H), 3.75 (s, 3 H), 5.6 (d, 1 H, J = 4 Hz), 6.2 (d, 1 H, J = 4 Hz). No attempt was made to optimize the yields of the above sequence. The low yield of the ester is in part due to the pyrazoline formaiton at the site of the enone moiety. The yield would probably be greatly improved by utilizing the more selective ozonization procedure[11] and by purifying sarkomycin by base extraction rather than by the conversion to its methyl ester.

Acknowledgment. We are indebted to the National Science Foundation (Grant CHE-8102944) for the financial support of this work. We also thank Prof. Robert Boeckman and Dr. Paul Naegely of Wayne State University for providing us with a sample and NMR and IR spectra of sarkomycin methyl ester.

Registry No. (±)-**1**, 72581-31-8; (±)-**3** (R = H), 84899-17-2; **4** 4-OH, 86900-33-6; **4** 5-OH, 86853-72-7; (±)-**5a**, 86853-73-8; (±)-**5b**, 86853-74-9; (±)-**7**, 86900-34-7; (±)-**9**, 86853-75-0.

(12) The protected enones **8** were prepared from **7** in nearly quantitative yields by stirring **7** in CH_3CN saturated with CH_3SH and containing 10 mol % of diisopropylamine followed by evaporation of solvent (**8a**) or by stirring **7** with 1 equiv of thiophenol in CH_3CN at room temperature (**8c**). Oxidation of either **8a** or **8c** with 2 equiv of *m*-CPBA led to **8b** and **8d**, respectively. The use of 3 equiv of *m*-CPBA gave good yields of the corresponding epoxides. Ozonolysis of either **8a** or **8c** or $NaIO_4$ cleavage of the diols obtained by acid hydrolysis of the epoxides gave aldehydes **10a** or **10b**, respectively (^1H NMR ($CDCl_3$) 9.1 (d, 1 H, J = 6 Hz).

Chiral Ether Glycerides from a Marine Sponge

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Though sponges provide the most primitive example of a marine invertebrate, they have exhibited much fascinating natural products chemistry to date.[1] Many expo-

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