(3 H). Treatment of **68** with an ethereal solution of diazomethane yielded the keto ester **69** which consisted, according to GLC, of two isomers in 1.6:1 ratio: IR ($CHCl_3$) 1735 (CO_2Me), 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.69 (s) and 3.60 (s) (3 H), 1.12 (d, J = 8 Hz) and 1.02 (d, J = 7 Hz) (3 H). Anal. Calcd $C_{13}H_{20}O_3$: C, 69.61; H, 8.89. Found: C, 69.66; H, 8.81.

Equilibrium of Keto Ester 69. A solution of the keto ester **69** (13 mg) in a 2 N methanolic solution of sodium methoxide (2 mL) was stirred overnight at room temperature under a nitrogen atmosphere. A saturated solution of sodium chloride (4 mL) was added, and the methanol was removed under reduced pressure. The mixture was acidified with 2 N hydrochloric acid and extracted with dichloromethane (5 × 10 mL). The extract was dried over anhydrous sodium sulfate, filtered, and concentrated to yield a dark residue which was in turn dissolved in ether and treated with an ethereal solution of diazomethane. The solvent was removed, and the residue was purified by preparative TLC to yield 7.4 mg of **69**. An NMR ($CDCl_3$) spectrum of the mixture included absorptions at δ 3.60, 3.62, 3.65, and 3.69, in the region of the carbomethoxyl group.

Acknowledgment. Eliezer Goldberg, Head, Scientific Editing Office of the Technion.

Registry No. **1**, 82026-08-2; **2**, 82026-09-3; **3**, 61589-86-4; **4**, 61563-72-2; **5**, 74056-07-8; **6**, 82026-10-6; **7**, 82026-11-7; **8**, 82026-12-8; **9**, 82026-13-9; **10**, 78877-14-2; **11**, 82026-14-0; **12**, 74056-08-9; **13**, 82026-15-1; **14**, 82026-16-2; **15**, 82026-17-3; **16**, 62547-87-9; **17**, 82026-18-4; **18**, 82026-19-5; **19**, 82026-20-8; **20**, 82026-21-9; **21**, 82026-22-0; **22**, 57234-60-3; **23**, 57234-61-4; **24**, 82026-23-1; **25**, 82026-24-2; **26**, 82026-25-3; **27**, 82026-26-4; **28**, 57234-62-5; **29**, 82026-27-5; **30**, 57234-68-1; **31**, 15070-50-5; **32**, 82026-28-6; **33**, 71280-40-5; **34**, 82026-29-7; **35**, 82026-30-0; **36**, 82043-89-8; **37**, 82026-31-1; **38**, 57133-56-9; **39**, 82026-32-2; **40**, 82026-33-3; **41**, 82026-34-4; **42**, 82026-35-5; **43**, 82026-36-6; **44**, 82026-37-7; **45**, 82026-38-8; **46**, 82026-39-9; **47**, 82043-90-1; **48**, 82026-40-2; **49**, 82026-41-3; **50**, 82026-42-4; **51**, 82078-85-1; **52**, 82026-43-5; **53**, 82079-43-4; **54**, 57234-65-8; **55**, 82026-44-6; **56**, 82026-45-7; **57**, 82026-46-8; **58**, 82078-86-2; **59**, 82026-47-9; **60**, 82026-48-0; **61**, 82026-49-1; **62**, 82026-50-4; **63**, 82026-51-5; **64**, 82026-52-6; **65**, 82026-53-7; **66a**, 82078-87-3; **66b**, 82078-88-4; **67a**, 82078-89-5; **67b**, 82078-90-8; **68a**, 82078-91-9; **68b**, 82078-92-0; **69a**, 82026-54-8; **69b**, 82078-93-1; **70**, 82026-55-9; acetaldehyde ethyl 3-bromopropyl acetal, 34399-67-2; 3-ethoxy-2-cyclohexen-1-one, 5323-87-5; acetaldehyde ethyl 4-bromobutyl acetal, 56904-94-0; 1,2-propadiene, 463-49-0; 1-acetyloxy-2-(5-hexyn-1-yl)cyclohexane, 82026-56-0; methyl vinyl ketone, 78-94-4; ethyl 2-oxocyclohexanecarboxylate, 1655-07-8; 1,12-diiodododecane, 24772-65-4; 2-(14-pentadecyn-1-yl)cyclohexanone, 82026-57-1; 3-methyl-1,2-butadiene, 598-25-4; 1,2-hexadiene, 592-44-9; 2-cyclohexenone, 930-68-7; 3-methyl-2-cyclohexenone, 1193-18-6.

Regiospecific Synthesis of Sarkomycin and Some Analogues

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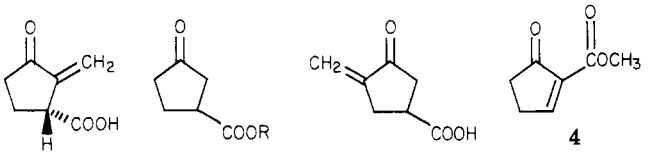
Received January 13, 1982

The first regiospecific total synthesis of the anticancer compound sarkomycin (1) is described. The starting material is 2-(carbomethoxy)cyclopent-2-enone (4), a useful precursor for cyclopentanoid natural products. The cyano derivative **5**, the amide derivative **6**, and the keto lactone **9** were also synthesized. The latter may be considered as a "cyclized" form of sarkomycin and was shown to open slowly to the natural product upon treatment with dilute acid.

Sarkomycin (1), a compound produced by a strain of the soil microorganism *Streptomyces erythrochromegenes*,[1] exhibits weak antibacterial activity and strong activity against the ascites type of tumor.[2] After its initial isolation and structure determination,[3] it attracted considerable attention[4] and was used in clinical trials in Japan[5] and the U.S.A.[6] In spite of initial reports of positive action, it was concluded that the compound is not active against solid tumors.[6]

The structure of sarkomycin (1) is deceptively simple, yet the early synthetic work was far from satisfactory. The initial report by Toki[7] of its synthesis via a Mannich condensation route from 3-carbethoxycyclopentanone (**2a**)



1 **2a**, R = Et; **b**, R = H **3** **4**

contrasted with the reported[8] synthesis of isosarkomycin (**3**) from 3-carboxycyclopentanone (**2b**) under similar Mannich conditions. In fact, Hill[9] has shown that Mannich condensation on either the acid or the ester gives a 2:1 mixture, respectively, of 5- to 2-substitution products. Thus, the originally reported[7,8] products were highly impure.[9] The early work[10,11] had also resulted in an incorrect

(1) Yamamoto, T.; Yamaoka, S. *J. Antibiot., Ser. A.* **1954**, *7*, 7. Umezawa, H.; Takeuchi, T.; Nitta, K. *Ibid.* **1953**, *6*, 101. Umezawa, H.; Yamamoto, T.; Takeuchi, T.; Yamaoka, S.; Nitta, K.; Okami, Y. *Ibid.* **1953**, *6*, 147.

(2) Umezawa, H.; Yamamoto, T.; Takeuchi, T.; Osato, T.; Okami, Y.; Yamaoka, S.; Okuda, T.; Nitta, K.; Yagishita, K.; Utahara, R.; Umezawa, S. *Antibiot. Chemother. (Washington, DC)* **1954**, *4*, 514.

(3) Hooper, I. R.; Cheney, L. C.; Cron, M. J.; ,Fardig, O. B.; Johnson, D. A.; Johnson, D. L.; Patermiti, F. M.; Schmitz, H.; Wheatley, W. B. *Antibiot. Chemother. (Washington, DC)* **1955**, *5*, 585.

(4) For reviews see: (a) Sung, S.-C. *Antibiotics (NY)* **1967**, *1*, 156. (b) Kondo, S. *J. Antibiot., Ser. B* **1963**, *16*, 210. (c) Umezawa, S.; Suami, T.; Kinoshita, M. *Keio Univ. Centenary Mem. Publ.* **1958**, 722. Goto, S.; Amano, H. *Chiryo* **1956**, *38*, 72.

(5) Ishiyama, S. *J. Antibiot. Ser. A* **1954**, *7*, 82.

(6) Magill, G. B.; Golbey, R. B.; Karnofsky, D. A.; Burchenal, J. H.; Stock, C. C.; Rhodes, C. P.; Crandall, C. E.; Yorukoglu, S. N.; Gellhorn, A. *Cancer Res.* **1956**, *16*, 960.

(7) Toki, K. *Bull. Chem. Soc. Jpn* **1957**, *30*, 450.

(8) Umezawa, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 267.

(9) Hill, R. H.; Foley, P. J.; Gardella, L. A. *J. Org. Chem.* **1967**, *32*, 2330.

0022-3263/82/1947-3306$01.25/0

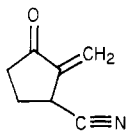
assignment of absolute stereochemistry for sarkomycin; the latter was shown unambiguously by Hill[9] to be *R*.

Prior to our work, the only other synthetic work reported on sarkomycin was a ten-step synthetic sequence, which produced the semicarbazone of sarkomycin in very low overall yield.[12] Furthermore, attempts to hydrolyze the semicarbazone resulted only in polymerization.[13]

The present project was initiated to provide a regiospecific synthesis of this rather important natural product, to utilize our potentially valuable intermediate, 2-(carbomethoxy)cyclopent-2-enone (**4**), and to produce some simple and (hopefully) more stable analogues of sarkomycin for biological testing. A preliminary report of part of this work has appeared.[14] Shortly after our initial report appeared, Boeckman[15] reported a longer regiospecific synthesis, which gave the natural enantiomer. A Pd-mediated cyclization route has very recently given a new synthetic entry to sarkomycin,[16] and at least one more synthesis has been carried out.[17]

The α-methylene ketone and lactone functional groups are the active functionalities in a great number of compounds with anticancer properties. Sarkomycin appears to be the simplest naturally occurring molecule containing this functionality. Unfortunately, the compound is very reactive toward dimerization[18] and polymerization[19] and is not extremely stable toward storage. The methyl or ethyl ester of sarkomycin is evidently more stable toward storage and is reported to retain activity toward ascites tumors.[3]

One possible explanation for the reactivity of sarkomycin toward fluid tumors but inactivity toward solid tumors could be that the carboxylic acid group (or the overall polarity of the molecule) prevents penetration of the compound through the lipid barriers associated with solid tumors. Thus, we have prepared the cyano (**5**) and amide (**6**) compounds, as minimal-change analogues, for testing purposes.



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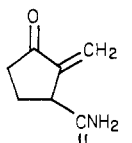
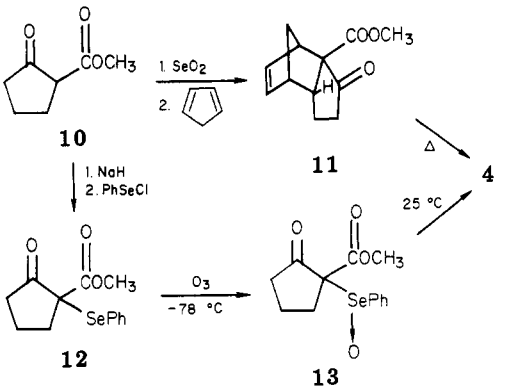


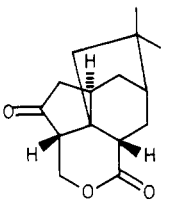
6

The tetracyclic terpene quadrone (**7**) has attracted much attention recently because of its anticancer properties.[20-22]

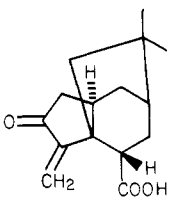
Scheme I



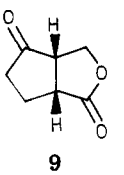
Its structure does not contain any functionality usually associated with such activity, and thus it has been suggested by Smith[21] and then Danishefsky[21] that it opens up in vivo to the α-methylene ketone **8**, which is the actual



7



8



9

anticancer agent. By analogy, it was hoped that the simple keto lactone **9**, which should be stable toward storage, might act as an in vivo precursor of sarkomycin. Such ideas have been investigated briefly in the current work.

Results

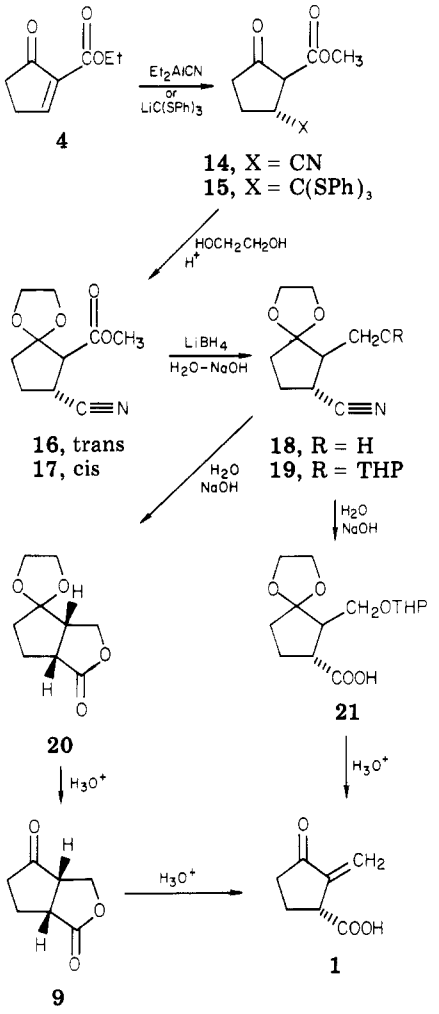
The starting material for our synthesis, 2-(carbomethoxy)cyclopent-2-enone (**4**), was initially prepared[23] (Scheme I) via SeO_2 oxidation of 2-(carbomethoxy)cyclopentanone (**10**). Trapping **4** with cyclopentadiene gave the Diels–Alder adducts **11** (1:1 endo/exo mixture). Purification of **11** and then pyrolysis gave pure **4**. Conditions to prepare **4** on a large scale were developed,[24] but the procedure was judged to be impractical.

Reich[25] has reported the production of **4** (as a mixture of the methyl and ethyl esters) via oxidative elimination of the selenenyl derivative **12**. This recent method to introduce double bonds adjacent to carbonyl groups has become the method of choice in many cases but does present experimental difficulties in the present case. In our hands, repetition of Reich's conditions gave **4** contaminated with the starting material **10**. It was shown that the selenenyl compound **12**, when impure, easily decomposed to **10** and PhSeSePh, presumably by $PhSe^-$ attack on **12**.

By careful control of conditions,[14] we could obtain the selenenyl derivative **12** pure. However, use of H_2O_2 for the oxidation step[24] resulted in some spontaneous elimination of the selenenoxide **13**, the product **4** being partially destroyed by this reagent. However, oxidation of **12** with O_3 at −78 °C avoided the elimination reaction. Warming to

(10) Toki, K. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 333.
(11) Sato, Y.; Nishioka, S.; Yonemitsu, O.; Ban, Y. *Chem. Pharm. Bull.* **1963**, *11*, 829.
(12) Shemyakin, M. M.; Ravdel, G. A.; Chaman, Y. S.; Shvetsov, Y. B.; Vinogradova, E. I. *Chem. Ind. (London)* **1957**, 1320.
(13) Jankowski, K. *Tetrahedron Lett.* **1971**, 1733. This author has reported a synthesis of homosarkomycin, the cyclohexanone analogue of **1**. The work involves many steps, several of which produced mixtures of allylic rearrangement products.
(14) Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, 4175.
(15) Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752.
(16) Kobayushi, Y.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 4295.
(17) Footnote 4 in: Boschilli, D.; Smith, A. B., III. *Tetrahedron Lett.* **1981**, *22*, 3733.
(18) Maeda, K.; Kondo, S. *J. Antibiot., Ser. A* **1958**, *11*, 37.
(19) Hara, T.; Yamada, Y.; Akita, E. *J. Antibiot, Ser. A* **1957**, *10*, 70.
(20) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499. Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38.
(21) Footnote 16 in: Scarborough, R. M.; Jr.; Toder, H. H.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 3904. Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *Ibid.* **1981**, *103*, 4136.
(22) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *J. Am. Chem. Soc.* **1981**, *103*, 4647.
(23) Marx, J. N.; Cox, J. H.; Norman, L. R. *J. Org. Chem.* **1972**, *37*, 4489.
(24) For details, see the dissertation of G.M. Texas Tech University, 1979. Early work on this reaction was carried out by undergraduate students Brian Walker and Clint Melton.
(25) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

Scheme II

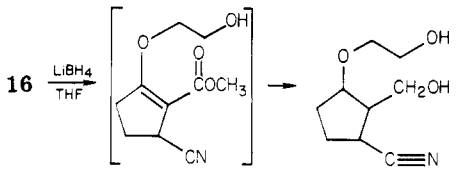


room temperature and filtration gave 2-(carbomethoxy)-cyclopentenone (**4**) of sufficient purity for further work.

2-(Carbomethoxy)cyclopentenone polymerizes instantly with many reagents. It has one of the most polarized double bonds known, as judged by the deshielded vinyl proton signal, which appears at δ 8.38 in the NMR spectrum. However, the compound does react with certain anhydrous nucleophilic reagents. For the current work, the reaction with Et_2AlCN gave the cyanide addition product **14** (Scheme II; 40% yield from **10**). Compound **14** exists in the keto form in the solid state, but as a 1:1 keto/enol mixture in $CHCl_3$ solution. Also, addition of $LiC(SPh)_3$[26] to **4** gave the compound **15**, which also has a masked carboxylic acid function. However, in our hands, the yield of this crystalline product was only ca. 10%; this approach was therefore not investigated further.

Ketalization of the keto cyano ester **14** proceeded well to give a crystalline 10:1 mixture of the trans/cis isomers **16** and **17**. The isomers, identified by the NMR signals for the C-2 and C-3 protons, were separated by careful chromatography on silica gel. The assignment of stereochemistry to the major isomer as trans follows from the method of formation. In practice, the mixture was used for further work.

Several approaches were investigated either to reduce the ester or to hydrolyze the cyano group in **16** selectively. Reduction of the ester group proved to be the more productive approach. One reagent which has been used for this type of transformation successfully in other cases[30] is $LiBH_4$. This compound did indeed reduce the ester group, but the ketal group was also reductively destroyed, the major product being **23**. A possible mechanism for this reduction is a Lewis acid catalyzed elimination of the ketal to give **22**, followed by conjugate reduction and then ester reduction.



22 **23**

In order to reduce the Lewis acidity of the reagent, we added 5% aqueous NaOH to $LiBH_4$ in THF (2 mol of H_2O/mol of $LiBH_4$). The resulting solution was assumed to contain $LiB(OH)_2H_2$ as the major component, but no characterization of the actual reagent was attempted. This solution cleanly and reproducibly gave the desired keto cyano alcohol **18** in 78% isolated yield.

The ketal cyano alcohol **18** was converted into sarkomycin by two methods. Conversion of **18** into its tetrahydropyranyl ether derivative **19** and prolonged reflux (30 h) of this in 5% aqueous NaOH gave the corresponding protected acid **21**. This product was stirred overnight with 0.5 N HCl in 1:1 acetone/H_2O. Extraction of the reaction mixture with $CHCl_3$ and $NaHCO_3$, followed by reacidification, gave sarkomycin (**1**), essentially pure, in 20–25% yield. It was identified by its characteristic vinyl signals (δ 5.58 and 6.21, doublets, J = 2.5 Hz), as well as by its identity with the published IR spectrum and catalytic reduction to its crystalline dihydro derivative.

On the other hand, basic hydrolysis of the ketal cyano alcohol **18** was complete in less than 1 h at reflux with 1% NaOH, and the product was exclusively the ketal lactone **20**. The accelerated rate of hydrolysis of **18** as compared to **19** requires epimerization at C-3, followed by neighboring group participation, in the cyano hydrolysis step.

Treatment of the ketal lactone **20** with dilute HCl slowly removed the protecting group to give the crystalline keto lactone **9**. This compound very slowly underwent an eliminative opening in dilute aqueous acid to give sarkomycin. The rate of the reaction was very dependent upon acid concentration. At higher acid concentrations, the rate of polymerization of the sarkomycin competed with its rate of formation. The best conditions found were to stir the compound with 0.5 N HCl in 1:1 acetone/H_2O for 5–7 days at room temperature. Up to 50% of sarkomycin could be obtained by this procedure. The compound polymerizes after storage for several days in a freezer but can be kept for prolonged periods in the cold in $CHCl_3$ solution.

It is known that acid-catalyzed hydrolysis of sarkomycin methyl ester gives rather low yields. The keto lactone **4** thus appears to be a moderately efficient precursor for any chemical synthesis of sarkomycin, and, furthermore, it has

(26) Fruling, A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 1009. Manas, A.-R. B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 216.

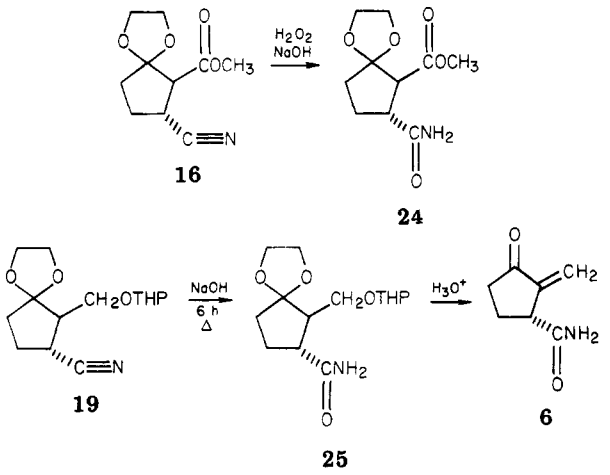
(27) Cook, M. J.; Forbes, J.; Khan, G. M. *J. Chem. Soc., Chem. Commun.* **1966**, 121.

(28) Oliveri-Mandala, E. *Gazz. Chim. Ital.* **1922**, *52*, 107; *Chem. Abstr.* **1922**, *16*, 2112.

(29) Sandler, R.; Karo, W. "*Organic Functional Group Preparations*"; Academic Press: New York, 1972; p 320. Tsai, L.; Miwa, T.; Newman, M. S. *J. Am. Chem. Soc.* **1957**, *79*, 2530. Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1965**, *30*, 2386.

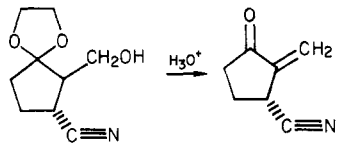
(30) Brown, H. C.; Ichikawa, K. *J. Am. Chem. Soc.* 1961, *83*, 4372. Brown, H. C. "Hydroboration"; W. A. Benjamin: New York, 1962; p 245.

Scheme III



the advantage of being completely stable to storage.

With the successful regiospecific synthesis of sarkomycin complete, attention was turned to produce some derivatives of sarkomycin. In fact, treatment of the cyano ketal alcohol **18** with 1 N HCl in acetone gave the cyano ana-



logue of sarkomycin (**5**) directly. No attempt was made to maximize conditions. The compound was isolated in 45–50% yield as an oil. It is somewhat more stable toward storage than sarkomycin.

In order to prepare the amide analogue of sarkomycin (**6**), two approaches were investigated (Scheme III). In the first, selective hydrolysis of the cyano group of compound **16** with activated MnO_2[27] was not successful, but hydrolysis with H_2O_2 in NaOH[28] worked well to give the crystalline ketal amide ester **24**. Attempts to hydrolyze the amide to a carboxylic acid by using deamination techniques[29] were unsuccessful, since the ketal group was unstable under all conditions investigated. Since this route to sarkomycin did not appear to be as promising as the route of Scheme II, work to reduce the ester in **24** was not investigated.

In the second approach, hydrolysis of the ketal cyano THP ether **19** for 6 h in refluxing 5% aqueous NaOH gave, as the major product, the corresponding amide **25**. This crystalline product, when treated with HCl in aqueous acetone, gave the amide derivative of sarkomycin (**6**) in 57% yield. This compound is more water soluble and appears to be more unstable toward storage than the cyano analogue **5**.

Discussion

Compounds **5** and **6** were submitted to the National Cancer Institute for screening. However, the samples had decomposed before they could be tested, and thus they would seem to show little promise, at least in the pure form, as useful antitumor agents.

The keto lactone **9**, which can be considered as a "cyclized" form of sarkomycin, was also screened in the NCI program. It was hoped that the acid-catalyzed opening to sarkomycin we had demonstrated might possibly have its counterpart in an in vivo opening to generate sarkomycin. The previously mentioned postulates on the keto lactone quadrone (**7**) seemed to lend a reasonable analogy.

However, preliminary tests at NCI on the keto lactone **9** were negative. Though many causes could be considered for this result, one possibility is that quadrone is not really a good model for our compound. Quadrone contains a six-membered lactone ring, whereas our compound has a five-membered one. The required ring opening is the reverse of a 5-endo-trig cyclization reaction, which according to Baldwin's rules[31] is disfavored, whereas the 6-endo-trig case for quadrone is favored.

Indeed, Smith[32] has found substantial difficulty in carrying out concerted eliminative openings on similar β-keto γ-lactones. The acid-catalyzed opening we have observed for **9** is presumably not concerted and thus need not be germane to these principles.

Experimental Section

General Procedures. Melting points were taken in open capillaries on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian XL-100 spectrometer; coupling constants are given in hertz. IR spectra were recorded as thin films or in $CHCl_3$ solution on a Perkin-Elmer 457 spectrometer. Column chromatography was performed on Sargent-Welch silica gel (60–200 mesh). Columns were packed in the less polar solvent and eluted with increasing gradients of the more polar solvent. Extractions were performed with the indicated solvent, neutralized as required, and dried over anhydrous $MgSO_4$. Elemental analyses were carried out by Chemalytics, Inc., Tempe, AZ.

2-(Carbomethoxy)-3-cyanocyclopentanone (14). To a benzene solution (250 mL) of 17.5 g of 2-(carbomethoxy)cyclopent-2-enone (**4**), prepared as described previously,[14] was added by syringe 150 mL of 1.69 M Et_2AlCN (Alfa) at 0 °C. The solution was stirred overnight at 25 °C, cooled to 5 °C, quenched with ice, acidified, and extracted with $CHCl_3$. The product was extracted into 10% NaOH to reverse some cyanohydrin formation. Reacidification and $CHCl_3$ extraction gave a dark orange oil which crystallized after standing at room temperature for a few days. Two recrystallizations of the product from ether and petroleum ether gave 16 g (38% based on the sodium salt of 2-(carbomethoxy)cyclopentanone) of **14**: mp 47–48 °C; IR (film) 2225, 1770, 1735, 1670, 1625 cm^{-1} (keto and enol form); IR (KBr) 1770, 1735 cm^{-1} (keto form); NMR δ 3.86, 3.88 (1:1 ratio, 3 H total), 3.5–3.7 (1.5 H total), 2.1–3.0 (4 H, m), 10.3 (0.5 H, br s). Anal. Calcd for $C_8H_9NO_3$: C, 57.46; H, 5.42. Found: C, 57.55; H, 5.62.

Ethylene Ketal of 2-(Carbomethoxy)-3-cyanocyclopentanone (16 and 17). A mixture of 15.25 g (91 mmol) of **14**, 250 mL of benzene, and about 30 mg of *p*-toluenesulfonic acid was treated with 34 g of ethylene glycol and refluxed for 8 h into a Dean–Stark trap and then for 4 h into a large Soxhlet extractor filled with anhydrous $MgSO_4$. Extraction with $CHCl_3$ and washing with 10% NaOH and then water gave 16.4 g (82%) of crude **16** plus **17**. Column chromatography on silica gel gave crystals (mp 40–40.5 °C) on elution with 15% ether in petroleum ether. These were a 10:1 mixture of the trans (**16**) and cis (**17**) isomers: IR 2225 and 1740 cm^{-1}; NMR δ 1.7–2.5 (4 H, m), 3.14–3.62 (2 H, m), 3.78 (3 H, s), 3.85–4.2 (4 H, m). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20. Found: C, 56.55; H, 6.28.

Careful rechromatography with the same solvent gave the major isomer **16** as a slightly impure oil. Further elution gave **17** as crystals [mp 73–74 °C (ether)] with spectral data similar to those for the mixture except the NMR signals are at δ 3.04–3.18 for the C-2 and C-3 H's in **17** and at δ 3.25–3.62 for **16**. Also, the ethylene ketal H's are a singlet at δ 3.98 in **17** and a multiplet for **16**.

Ethylene Ketal of 2-(Hydroxymethylene)-3-cyanocyclopentanone (18). To a solution of 0.52 g (2.4 mmol) of the crystalline mixture of **16** and **17** in 5 mL of dry THF under N_2 was added 0.2 mL of 5% NaOH solution and then 10 mL of an 0.8 M solution of $LiBH_4$ in THF. The solution was stirred at 25

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°C for 24 h, H_2O was added dropwise, and the mixture was extracted with $CHCl_3$ to give 0.33 g (78%) of a yellow oil, which could not be obtained crystalline. Short-path distillation [bath temperature 80–90 °C (0.25 mmHg)] gave **18**, presumably containing 10% of the cis isomer: IR 3500 (br), 2220 cm^{-1}; NMR δ 1.6–2.7 (5 H, m), 3.06 (1 H, m), 3.80 (1 H, d, J = 4), 3.84 (1 H, d, J = 4), 3.98 (4 H, s).

2-Methylene-3-cyanocyclopentanone (5). To 0.88 g (4.80 mmol) of **18** was added 20 mL of a 1:1 mixture of 1 N HCl and acetone, and the solution was stirred for 12 h at room temperature and then extracted with $CHCl_3$. The resulting 0.47 g of crude oil (81%) was a mixture of **18** and **5**. Molecular distillation of the crude product was carried out during 2 h at 0.25 mmHg and a 80–90 °C bath temperature, which gave **5** essentially pure: IR 2220, 1750, 1645 cm^{-1}; NMR δ 1.8–2.8 (5 H, m), 5.78 (1 H, d, J = 2.5), 6.28 (1 H, d, J = 2.5). The compound is stable during at least several months of storage in $CHCl_3$ at 0 °C.

Ketal Lactone 20. To a solution of 0.50 g (2.7 mmol) of **18** in 5 mL of 95% ethyl alcohol was added 5 mL of 5% NaOH solution, and the mixture was allowed to reflux for 1 h. After cooling, the basic solution was washed several times with $CHCl_3$ and then carefully acidified with 5% HCl. Extraction with $CHCl_3$ resulted in 0.32 g (64%) of ketal lactone **20**. After several recrystallizations (ether/petroleum ether), **20** had the following: 67–67.5 °C; IR 1765 cm^{-1}; NMR δ 1.46–2.34 (4 H, m), 2.7–3.26 (2 H, m), 3.96 (4 H, s), 4.32 (1 H, dd, J = 8, 10), 4.46 (1 H, dd, J = 4, 10). Anal. Calcd for $C_9H_{12}O_4$: C, 58.68; H, 6.56. Found: C, 58.76; H, 6.24.

Keto Lactone 9. A solution of 0.23 g (1.25 mmol) of **20** was stirred with a 1:1 mixture of acetone and 3 N HCl for 6 h at 25 °C. $CHCl_3$ extraction and crystallization ($CHCl_3$–ether) gave 0.16 g (91%) of **9**: mp 45–46 °C; IR 1780, 1750 cm^{-1}; NMR δ 1.96–2.74 (4 H, m), 2.84–3.22 and 3.28–3.56 (2 H, m), 4.44 (1 H, d, J = 5.5), 4.45 (1 H, d, J = 4). The crude product showed small amounts of sarkomycin (**1**) by NMR. Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.86; H, 5.75.

Sarkomycin (1). (a) From Keto Lactone 9. A solution of 0.16 g of **9** in 10 mL of 1:1 acetone/1.5 N HCl was stirred 5 days at 25 °C and then extracted well with $CHCl_3$. Extraction with cold 5% $NaHCO_3$ and reacidification removed starting material and polymer and gave **1** essentially pure: yield 0.07 g (43%); IR 1730–1720, 1640 cm^{-1} (entire spectrum matches the published one);[8,11] NMR δ 2.2–2.7 (5 H, m), 5.68 (1 H, d, J = 2.5), 6.21 (1 H, d, J = 2.5).

Another run, using 1:1 acetone/3 N HCl for 8 h at 25 °C, gave 35% of sarkomycin and most of the remainder as starting material.

(b) From Protected Hydroxy Acid 21. A solution of 0.38 g of **21** in 10 mL of 0.5 N HCl after being stirred 10 h at 25 °C gave 0.06 g (33%) of crude sarkomycin, after purification by $NaHCO_3$ extraction as above.

Ethylene Ketal of 2-[(Tetrahydropyranyloxy)methyl]-3-cyanocyclopentanone (19). To a magnetically stirred solution of 0.81 g (4.42 mmol) of **18** and 0.05 g of *p*-toluenesulfonic acid in 10 mL of anhydrous methylene chloride at 25 °C was added 10 mL of 2,3-dihydropyran. After 1 h, $CHCl_3$ extraction gave 2.18 g of a mixture of **19**, contaminated with self-condensation products from the 2,3-dihydropyran.

Ethylene Ketal of 2-[(Tetrahydropyranyloxy)methyl]-3-(aminocarbonyl)cyclopentanone (25). To the total crude sample of **19** was added a solution of 1:1 EtOH/1.3 N NaOH. After a 6-h reflux, acidification and $CHCl_3$ extraction gave a yellow oil, which upon being dissolved in ether deposited **25**: mp 144–145 °C (ether); 0.24 g (60% from **18**); IR 3550, 3300, 1680, 1600 cm^{-1}; NMR δ 1.3–2.94 (12 H, m), 3.2–3.72 (4 H, m), 3.92 (4 H, s), 4.66 (1 H, br s), 5.76 and 6.68 (1 H each, br s). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12. Found: C, 58.93; H, 8.19.

Ethylene Ketal of 3-Carboxy-2-[(tetrahydropyranyloxy)methyl]cyclopentanone (21). A mixture of 0.58 g (2.0 mmol) of **25** and 10 mL of a 1:1 EtOH/2.5 N NaOH was refluxed for 24 h. Acidification and $CHCl_3$ extraction gave 0.51 g (87%) of **21**, mp 69–72 °C (ether/petroleum ether).

Alternatively, similar hydrolysis of crude **19** for 30 h gave **21** in comparable yield: IR 3000 (vbr), 1730, 1705 cm^{-1}; NMR δ 1.36–2.28 (10 H, m), 2.42–3.0 (2 H, m), 3.24–3.86 (4 H, m), 3.92 (4 H, s) 4.68 (1 H, br s), 9.85 (1 H, s). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.72; H, 7.74. Found: C, 58.28; H, 7.68.

Ethylene Ketal of 2-(Carbomethoxy)-3-(aminocarbonyl)-cyclopentanone (24). To a solution of 0.77 g (3.6 mmol) of **16** in 5 mL of THF at 25 °C was added 5 mL of 30% H_2O_2, and then 3 mL of 10% Na_2CO_3 was added dropwise. After 1 h, $CHCl_3$ extraction gave a yellow oil which deposited crystals from ether: 0.27 g (32%); mp 114–115 °C; IR 3520, 3420, 1735, 1690, 1600 cm^{-1}; NMR δ 1.8–2.2 (4 H, br s), 3.2–3.5 (2 H, br s), 3.75 (3 H, s), 3.9–4.1 (4 H, m), 6.0–6.7 (2 H, br s). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.59. Found: C, 52.52; H, 6.50.

2-Methylene-3-(aminocarbonyl)cyclopentanone (6). A solution of 0.10 g (0.35 mmol) of **25** was stirred for 12 h with a 1:1 acetone/0.5 N HCl. Several extractions with $CHCl_3$ gave 0.03 g (57%) of **6**: IR 3350 (br), 1730, 1670, 1640, 1620 cm^{-1}; NMR δ 1.8–2.8 (5 H, m), 5.58 (1 H, d, J = 2.5), 6.24 (1 H, d, J = 2.5). The sample was contaminated with some of the corresponding alcohol (signals at δ 3.2–4.2).

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