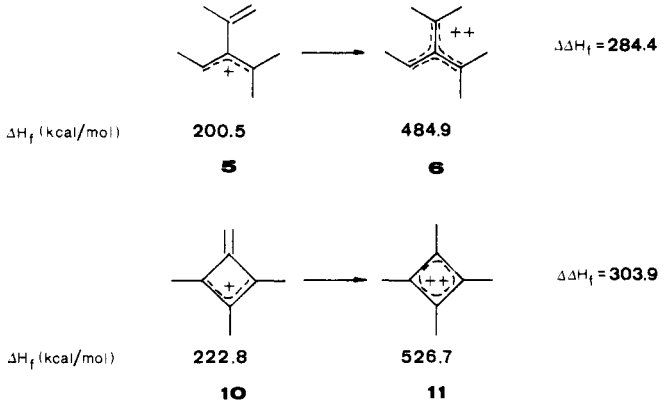
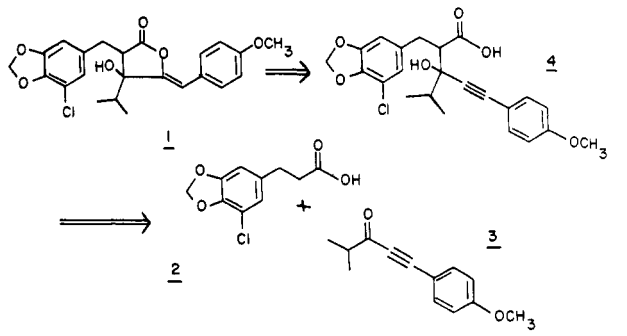


Scheme I



negate the electrostatic advantage of Y-conjugation, so that the Hückel resonance energy, which favors **11**, dominates.

Alternatively, our failure to observe **6** may be due to kinetic inhibition of protonation of **5**, which must be produced by a concerted elimination. In this context Olah[12] has noted that the 2,4-dimethylpenta-2,4-diyl dication has, at best, a transient existence. Our results suggest that **6** is not an intermediate in the elimination.

These observations indicate no special stabilization of trimethylenemethane dications in solution to be present. We are continuing to investigate such systems, which clearly behave differently from their dianionic counterparts.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

(12) Olah, G. A.; Grant, J. L.; Spear, R. J.; Bollinger, J. M.; Serianz, A.; Sipos, G. *J. Am. Chem. Soc.* **1976**, *98*, 2501.

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Total Synthesis and X-ray Structure Determination of Cyanobacterin[1]

Summary: Racemic cyanobacterin has been synthesized and subjected to X-ray diffraction analysis in order to establish unambiguously the structure.

Sir: Antibiotic activity was reported recently from the ether extract of a freshwater cyanobacterium, *Syctonema hofmanni*.[2] The active antibiotic, designated cyanobacterin, also inhibits the growth of numerous blue-green algae. This algicidal activity suggests that cyanobacterin may be an allelopathic substance that allows the *Scytonema* to compete favorably with more prolific algae. The structure of cyanobacterin, lacking stereochemistry, was reported as **1**.[2] This is the first chlorinated, fresh-water derived antibiotic and represents a new natural product skeleton. We report herein the first total synthesis and X-ray crystal structure determination of racemic cyanobacterin.

An expeditious route to cyanobacterin is given retrosynthetically in Scheme I. The key steps of our synthesis are depicted as addition of **2** to **3** and subsequent enol lactonization of **4**. The two starting materials in Scheme I, i.e., **2** and **3**, have not been prepared previously. Our preparation of both of these compounds is given in Scheme II.[3] This sequence of reactions allows for the preparation of both **2** and **3** on a multigram scale.

In Scheme III, the results of addition of lithium ester enolates **13a**, **13b**, or **13c** to ketone **3** are presented. These additions are carried out by adding **3** to a preformed enolate at −78 °C in THF, followed by warming to 0 °C.[8] Only the products of direct 1,2-addition of **13a**, **13b**, or **13c**, to **3** are observed.[9] The overall yields and isomer ratios for diastereomeric priority antireflective (PARF)[10] **14** and priority reflective (PREF)[10] products **15** are also given. The transition state pictured correctly predicts diastereoselection in favor of the PREF isomers, **15a** and **15c**, for the monoanion additions.

The diastereomeric esters **14a** and **15a**, from the reaction of **13a** with **3**, are readily separable by column chromatography. The less polar, minor isomer **14a** crystallized as long white needles, allowing for its unambiguous structure determination by X-ray crystallography.[11] It was not possible to hydrolyze the ethyl esters **14a** or **15a** without causing a retroaldol reaction or a dehydration. Consequently, it became advantageous to utilize the monoanion of trimethylsilyl ester **13c** because the trimethylsilyl ester hydrolyzes spontaneously upon workup. Both the yield and the diastereoselection of the reaction of **13c** with **3** are most favorable. Thus, the diastereomeric carboxylic acids **14b** and **15b** are obtained from reaction

(1) A preliminary account of this work, in which the first total synthesis of cyanobacterin was disclosed, was presented at the 186th National Meeting of the American Chemical Society, Washington, DC, Aug 1983, ORGN 293.

(2) Mason, C. P.; Edwards, K. R.; Carlson, R. E.; Pignatello, J.; Gleason, F. K.; Wood, J. M. *Science (Washington, D.C.)* **1982**, *215*, 400.

(3) All new compounds reported herein were characterized by ^{1}H and ^{13}C NMR, IR, UV, and mass spectroscopy. Yields reported refer to distilled or chromatographically pure, isolated material.

(4) Weissenfels, M.; Schurig, H.; Huehsam, G.; *Z. Chem.* **1966**, *6*, 471.

(5) Bodendorf, K.; Mayer, R. *Chem. Ber.* **1965**, *98*, 3554.

(6) Hann, R. M.; Spencer, G. C. *J. Am. Chem. Soc.* **1927**, *49*, 535.

(7) Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett.* **1976**, 3361.

(8) Enolate **13a** is prepared by addition of a THF solution of **12** to a slight excess of LDA in THF at −78 °C. Enediolate **13b** is formed from the carboxylic acid **2** and a slight excess of 2 equiv of LDA analogously. Trimethyl silyl ester enolate **13c** is prepared by treatment of the corresponding trimethyl silyl ester, formed in situ from **3**, Me_3SiCl and LDA, with excess LDA. No significant dehydrohalogenation of **13a–c** is observed at −78 °C.

(9) We do not observe equilibration between 1,2-addition and 1,4-addition of the enolates **13a–c** to **3** at 0 °C as has been observed in the reaction of α-substituted ester enolates with cyclohexenone; cf. Schultz, A. G.; Lee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044.

(10) Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.

(11) Crystallographic parameters appear in the microfilm edition. Publication of complete crystallographic details is planned: P. G. Williard and T.-T. Jong, manuscript in preparation.

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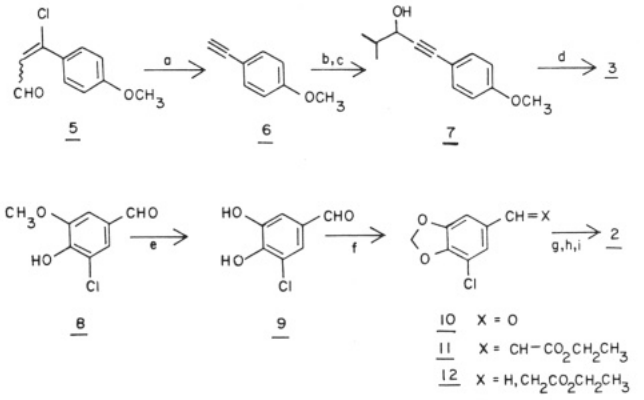
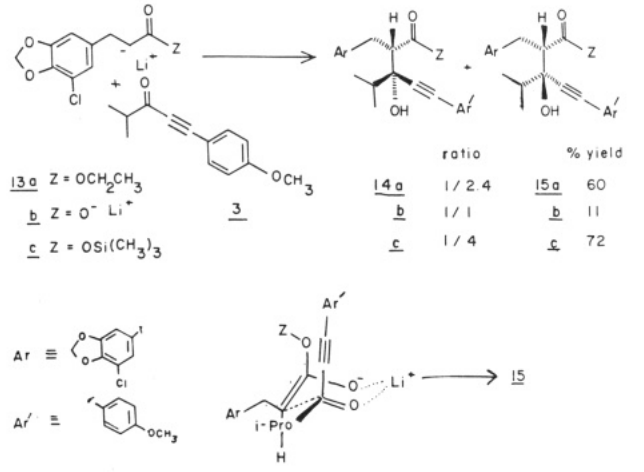
Scheme II[a]

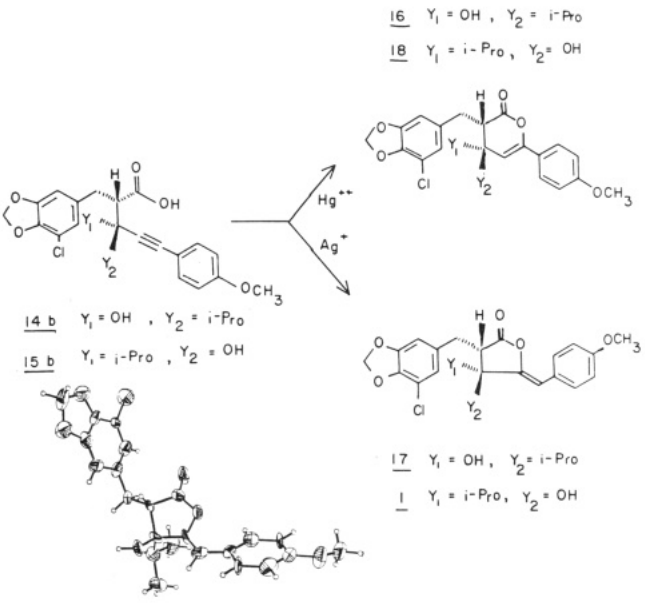


[a] (a) NaOH;[4,5] (b) *n*-BuLi, $(CH_3)_2CHCHO$; (c) H_3O^+; (d) MnO_2 or PCC; (e) 5-chlorovanillin,[6] BCl_3; (f) CH_2Br_2, NaF, DMF;[7] (g) $(CH_3CH_2O)_2POCH_2COOCH_2CH_3$, NaH, DME; (h) H_2, Pd/C; (i) NaOH.

Scheme III



Scheme IV



of **3** with either **13b** or **13c**.[12] The acids **14b** and **15b** are also easily separable chromatographically. The PREF isomer **15b** is required for synthesis of cyanobacterin (**1**) (vide infra). The overall yield of **15b**, formed from **13c** and **3**, after chromatographic separation from **14b**, is 57%.[3]

It is reported that Hg^{2+}-catalyzed cyclization of γ,Δ-acetylenic carboxylic acids greatly favors butyrolactones over valerolactones.[13] However, only a trace of either **1** or **17** (Scheme IV) was observed in the Hg^{2+}-catalyzed cyclization of **14b** or **15b**. The Hg^{2+}-catalyzed reactions of these compounds provide nearly exclusively endocyclic valerolactones **16** and **18**.[3] The enol valerolactones are identified by their characteristic IR absorbances at 1760 and 1670 cm^{-1}.[14] *However, cyclization of* ***15b*** *with 0.1 N silver nitrate in methanol provides the exocyclic γ-methylene-γ-butyrolactone* ***1*** *in over 90% yield.*[15] Only a trace (<5%) of valerolactone **18** is produced in the Ag^+-catalyzed cyclization. A similar cyclization of **14b** to **17** is observed.[3,16] Dehydration is not a significant problem in the Ag^+-catalyzed reactions. Synthetic cyanobacterin (**1**) (mp 146–147.5 °C) is identical in all respects except optical rotation with the the natural product.[17] The results of X-ray diffraction analysis of synthetic **1** are depicted in Scheme IV as a thermal ellipsoid plot.[11]

In conclusion, we would like to emphasize both the "simple diastereoselectivity"[18] observed upon addition of anions **13** to **3** and also the cyclospecificity of Ag^+- and Hg^{2+}-catalyzed enol lactonization of **14b** and **15b**. Both γ-ylidene-γ-butyrolactones and pyranone rings are incorporated into a number of physiologically active natural products. Thus, we anticipate that the synthetic strategy outlined may be directly applicable to the preparation of other medicinally important compounds.[19]

Acknowledgment. The ^{13}C NMR spectra and X-ray crystal structures were recorded at Brown University on a Bruker WM-250 spectrometer and a Nicolet R3m/E crystallographic system, respectively. These instruments were purchased in part with grants from the NSF (Grant CHE-8206423) and from the Montedison Group of Milan. J.P.P. acknowledges support from the NIH via Grant AM-18101.

Supplementary Material Available: Full crystallographic parameters including unit cell parameters, atomic coordinates, thermal parameters, bond lengths and angles, and standard deviations for compound **14a** and **1** and IR, NMR, and UV spectra of **1** (15 pages). Ordering information is given on any current masthead page.

(12) We did not pursue the addition of **13b** to **3** because of the low yield and lack of diastereoselectivity. Little diastereoselection has been reported for reactions of most metal enediolate dianions; cf. Evans, D. A.; Nelson, J. V. Taber, T. R. *Top. Stereochem.* **1982**, *13*, 28.

(13) Yamamoto, M. *J. Chem. Soc., Chem. Commun.* **1978**, 649. Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560. Yamamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 582.

(14) Nakanishi, K.; Soloman, P. H. In "IR Absorption Spectroscopy", 2nd ed.; Holden-Day: San Francisco, 1977; p 40.

(15) The final lactonization step to give a five-membered lactone using Ag^+ as catalyst was first discovered by the group at Brown.

(16) Silver(I) carboxylates are implicated in the cyclization of propargylidene malonic acids to mixtures of butenolides and α-pyrones; cf. Belil, G.; Castella, J.; Castells, J.; Mestres, R.; Pascual, J.; Serratosa, F. *An. R. Soc. Esp. Fis. Quim., Ser. B* **1961**, 57B, 617. Belil, C.; Pascual, J.; Serratosa, F. *Tetrahedron* **1964**, *20*, 2701. Castaner, J.; Pascual, J. *J. Chem. Soc.* **1958**, 3962.

(17) See supplementary material for IR, NMR, and UV spectral data of **1**.

(18) Heathcock, C.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

(19) For examples, see: *Chem. Abstr. 9th Collect. Index*, **1972–76**, *76–85*, 33246cs–33247cs.

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