100 °C) to give analytically pure keto ester as a pale viscous oil: 0.80 g (69%); IR (film) 1730, 1682, 1445 cm^{-1}; NMR ($CDCl_3$) δ 8.01–7.76 (m, 2 H), 7.49–7.22 (m, 3 H), 4.20 (q, J = 7.5 Hz, 2 H), 2.89–2.58 (m, 1 H), 2.52–1.27 (m, 9 H), 1.10 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74. Found: C, 73.63; H, 7.80.

Ethyl 4-Phenyl-4-oxobutyrate (39). A 950-mg sample of adduct **13** was subjected to oxidation. Bulb-to-bulb distillation (0.25 mm, oven temperature 130 °C) [lit. bp 186 °C (24 mm),[31a] 120 °C (0.2 mm)[31b]] gave 380 mg of a pale orange oil (42%): IR (film) 1730, 1680 cm^{-1}; NMR ($CDCl_3$) δ 8.12–7.79 (m, 2 H), 7.55–7.30 (m, 3 H), 4.03 (q, J = 7.5 Hz, 2 H), 2.79 (br t, J = 8 Hz, 2 H), 2.52 (br t, J = 8 Hz, 2 H), 1.32 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.12; H, 6.85.

Ethyl 3-Benzoylbutyrate (40). A 1.66-g sample of adduct **14** was subjected to oxidation. Chromatography (B) and bulb-to-bulb distillation (0.02 mm, 100 °C) gave 1.14 g (72%) of a clear viscous oil: lit.[32] bp 108–116 °C (0.6 mm); IR (film) 1730, 1680, 1595, 1450 cm^{-1}; NMR ($CDCl_3$) δ 8.08–7.85 (m, 2 H), 7.59–7.32 (m, 3 H), 4.12 (q, J = 7.5 Hz, 2 H), 2.84 (d, J = 8 Hz, 2 H), 2.67 (t q, J = 7 Hz, 8 Hz, 1 H), 1.23 (d, J = 7 Hz, 3 H), 1.20 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 71.19; H, 7.55.

Ethyl 3,4-Diphenyl-4-oxobutyrate (41). An 840-mg sample of adduct **15** was subjected to oxidation. Chromatography (B) and bulb-to-bulb distillation (0.01 mm, 150 °C) gave 596 mg (74%) of a viscous oil: IR (film) 1730, 1680, 1601, 1453 cm^{-1}; NMR ($CDCl_3$) δ 8.16–7.92 (m, 2 H), 7.56–7.34 (m, 3 H), 7.26 (s, 5 H), 3.24 (t, J = 8 Hz, 1 H), 2.97 (d, J = 8 Hz, 2 H).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.76; H, 6.55.

Ethyl 7-Benzoyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (42). A 246-mg sample of adduct **19** was subjected to oxidation. The reaction mixture was quenched with 1 N sodium bisulfite and worked up as usual. Chromatography (B) gave 200 mg (84%) of **42**: IR (film) 1730, 1685, 1595 cm^{-1}; NMR ($CDCl_3$) δ 7.91–7.68 (m, 2 H), 7.59–7.23 (m, 3 H), 4.13 (q, J = 7 Hz, 2 H), 3.89 (br s), 3.85 (br s, 4 H), 3.08–2.72 (m, 1 H), 2.34–1.48 (m, 7 H), 1.19 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 67.78; H, 7.35.

Ethyl 2-(2-Methoxybenzoyl)cyclohexane-1-carboxylate (43). A 290-mg sample of adduct **21** was subjected to oxidation. Chromatography (B) and bulb-to-bulb distillation (0.03 mm, oven temperature 130 °C) gave 238 mg (85%) of **43** as a clear viscous oil: IR (film) 1730, 1682, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.59–6.72 (m, 4 H), 4.08 (q, J = 7 Hz, 2 H), 3.83 (s, 3 H), 3.03–2.68 (m, 1 H).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.17; H, 7.56.

Ethyl 2-[(Naphth-2-yl)carbonyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylate (44). A 709-mg sample of adduct **30** was subjected to oxidation. Preparative TLC (silica gel PF-254, eluted with chloroform) followed by bulb-to-bulb distillation (0.8 mm, 220 °C) gave 547 mg (60%) of an amber oil: IR (film) 1730, 1685, 1460 cm^{-1}; NMR ($CDCl_3$) δ 8.29–7.41 (m, 7 H), 4.38–3.92 (m, 2 H), 3.89 (br s, 4 H), 3.20–2.78 (m, 1 H), 2.74–1.48 (m, 8 H), 1.45–1.00 (m, 6 H).

Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.65; H, 6.95.

Acknowledgment. The authors gratefully acknowledge financial support for this work from the National Cancer Institute, Department of Health, Education, and Welfare (Grant No. CA16524), and the American Cancer Society (Institutional Grant No. ACS IN45P to Brown University). K.A.P acknowledges additional support in the form of an Alfred P. Sloan Foundation Fellowship. K.A.P. and J.L.K. are grateful for the continued support of Brown University.

Registry No. 6, 1617-22-7; **7**, 66617-28-5; **8**, 140-29-4; **9**, 66617-29-6; **10**, 140-88-5; **11**, 10544-63-5; **12**, 103-36-6; **13**, 19748-87-9; **14**, 66617-33-2; **15**, 31861-57-1; **16**, 80-62-6; **17**, 73481-50-2; **18**, 38334-82-6; **19**, 66617-34-3; **20**, 7035-03-2; **21**, 66617-35-4; **22**, 73481-51-3; **23**, 19924-43-7; **24**, 73453-62-0; **25**, 18086-24-3; **26**, 73481-52-4; **27**, 73453-53-9; **28**, 66617-31-0; **29**, 7498-57-9; **30**, 73481-53-5; **31**, 71056-95-6; **32**, 73481-54-6; **33**, 71742-31-9; **34**, 71771-25-0; **35**, 71611-77-3; **36**, 73481-55-7; **37**, 66617-32-1; **38**, 66617-36-5; **39**, 6270-17-3; **40**, 40394-84-1; **41**, 53647-50-0; **42**, 66617-37-6; **43**, 66617-38-7; **44**, 73481-56-8; ethyl 1-chlorocyclohexane-1-carboxylate, 71911-74-5; phenylacetonitrile, 140-29-4; *trans*-1-methoxy-3-[(trimethylsilyl)-oxy]butadiene, 54125-02-9; 2,5-dimethoxybenzaldehyde, 93-02-7.

(31) (a) E. D. Bergmann, S. Yaroslavsky, and H. Weiler-Feilchenfeld, *J. Am. Chem. Soc.*, **81**, 2775 (1959); (b) K. Butler and G. P. Ellis, *J. Chem. Soc.*, 4426 (1956).

(32) F. J. McEvoy and G. R. Allen, *J. Org. Chem.*, **38**, 4044 (1973).

Approaches to Anthracyclines. 2. Regiospecific Annelative Quinone Synthesis[1a]

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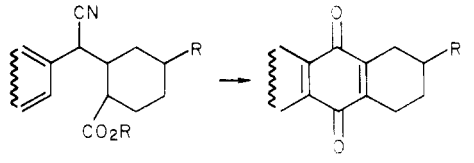
Received January 23, 1980

Linear polycyclic quinone systems may be assembled by an efficient regiospecific annelation procedure in which the key step is oxidative decyanation of a cyanocyclohexenone system to the quinone moiety.

The conjugate addition of arylacetonitriles to cyclohexene esters[2] rapidly and efficiently assembles the structural components of potential polycyclic systems. We hoped to convert the Michael adducts obtained in this reaction to quinones by a sequence involving cyclization and oxidation steps (eq 1).



(1)

We have shown[2b] that the conditions of oxidative decyanation lead to mixtures when applied to Michael ad-

(1) (a) Abstracted from the doctoral dissertation of James L. Kallmerten, Brown University, October, 1979. (b) Camille and Henry Dreyfus Teacher-Scholar award recipient.

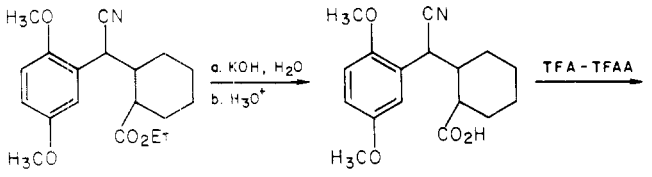
(2) (a) K. A. Parker and J. L. Kallmerten, *Tetrahedron Lett.*, 4557 (1977). (b) This work is described in detail in K. A. Parker and J. Kallmerten, *J. Org. Chem.*, previous paper in this issue.

0022-3263/80/1945-2620$01.00/0

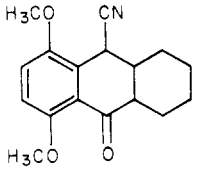
ducts in which the aromatic substituent is electron rich. Therefore, we chose to study the possibility of converting these Michael adducts to quinones by a route in which ring closure precedes oxidative decyanation. Herein we report the successful execution of this strategy, a novel annelative route to linear quinone systems of defined regiochemistry.

Results and Discussion

The readily available Michael adduct 1[2b] was chosen as a model substrate for the desired sequence. Ester 1 was converted to the corresponding carboxylic acid 2 by eth-



1 2



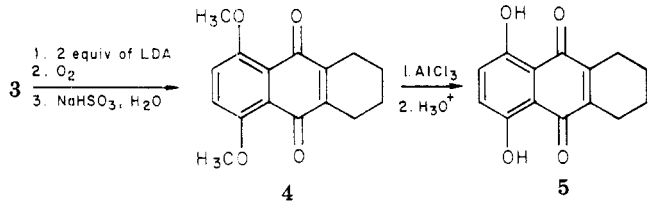
3

anolic potassium hydroxide; cyclization of the acid 2 to the tricyclic ketone 3 proceeded smoothly in trifluoroacetic acid–trifluoroacetic anhydride. Keto nitrile 3 shows the anticipated infrared absorptions at 2240 and 1680 cm^{-1}; the NMR spectrum suggests that 3 is a mixture of diastereomers.

An attempt to convert keto nitrile 3 to quinone 4 by treatment with alkaline hydroperoxide, conditions which effect the oxidative decyanation of 9-cyano-10-anthrols to anthraquinones,[3a-c] resulted only in recovery of starting material.

Application of Watt's oxidative decyanation sequence[3d] (1 equiv of lithium diisopropylamide, oxygen gas, sodium bisulfite and sodium hydroxide washes) resulted in recovery of a mixture of starting material and a new compound. Chromatography led to isolation of 41% of cyano ketone 3 and 41% of material which proved to be the desired quinone 4 (for evidence of structure, see below). Inverse addition of base resulted in a similar ratio of recovered starting material and product.

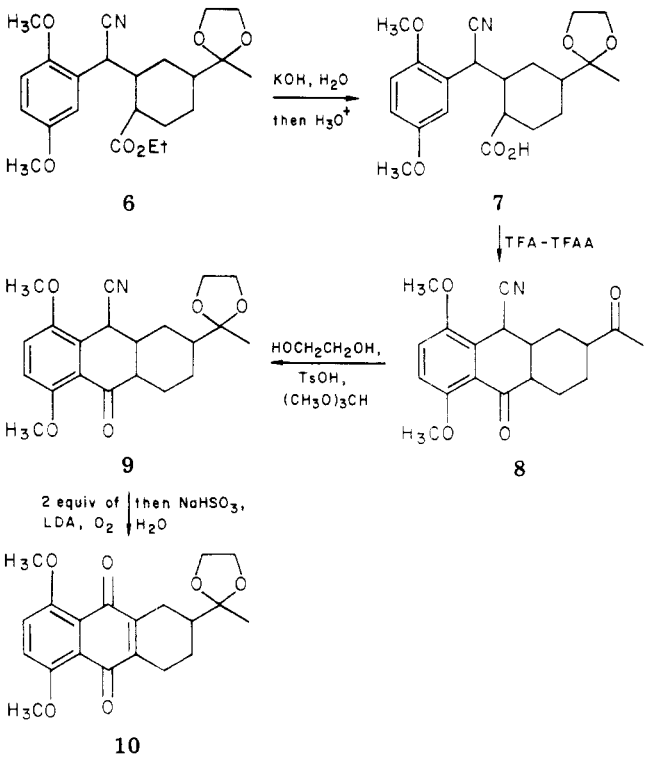
In order to effect complete conversion of cyano ketone to quinone, we utilized 2 equiv of base. Addition of an HMPA–THF solution of keto nitrile 3 to 2 equiv of lithium diisopropylamide in tetrahydrofuran gave a deep violet solution. This color faded upon treatment of the reaction mixture with oxygen gas. Reductive workup with sodium bisulfite followed by chromatography afforded an 83% yield of quinone 4,[4] as bright orange solid. The NMR



4 5

spectrum exhibits singlets at δ 7.25 and 3.94; the infrared

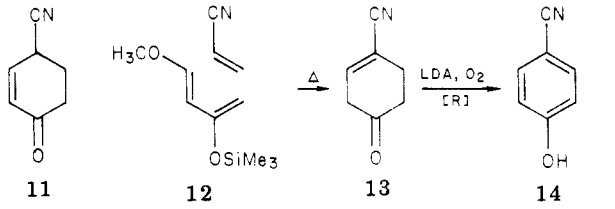
Scheme I



spectrum has an absorption at 1674 cm^{-1} but no nitrile band at 2240 cm^{-1}. Demethylation of 4 with aluminum chloride in nitrobenzene[5] gave the known tetrahydroquinizarin 5[5] in 67% yield.

As an extension of this model study, ester 6[2] was hydrolyzed to the acid 7 (Scheme I), which was cyclized by trifluoroacetic acid–trifluoroacetic anhydride to give diketo nitrile 8 in 56% yield (from 6). Ketalization of 8 followed by treatment with 2 equiv of lithium diisopropylamide and oxygen gas afforded, after reductive workup and chromatography, a 70% yield of quinone 10.

Having established the viability of this three-step annelative quinone synthesis, we proceeded to test its generality and to demonstrate its regiospecificity. The simplest substrate containing the requisite functionality for the oxidation reaction would be 4-cyano-2-cyclohexenone (11). Diels–Alder reaction of diene 12 and acrylonitrile,



11 12 13 14

followed by hydrolysis, yielded the isomeric cyano ketone 13.[6] Because both 11 and 13 might be expected to give the same enolate, nitrile 13 was deemed an acceptable substrate for oxidation. Treatment of cyano ketone 13 with 2 equiv of lithium diisopropylamide and oxygen followed by bisulfite and sodium hydroxide washes gave a 43% yield of *p*-cyanophenol (14). Some starting material was recovered but benzoquinone could not be detected in

(3) (a) J. S. Davies, V. H. Davies, and C. H. Hassal, *J. Chem. Soc. C*, 1873 (1969); (b) C. H. Hassal and B. A. Morgan, *J. Chem. Soc. D*, 1345 (1970); (c) G. M. Holmwood and J. C. Roberts, *J. Chem. Soc. C*, 3899 (1971); (d) D. S. Watt and S. J. Selikson, *J. Org. Chem.*, **40**, 267 (1975).

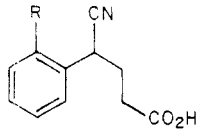
(4) K. Zahn and H. Koch, *Chem. Ber.*, **71**, 172 (1938).

(5) E. Hardegger, E. Widmer, K. Steiner, and A. Pfiffner, *Helv. Chim. Acta*, **47**, 2027, 2031 (1964).

(6) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974). Likewise condensation of methyl vinyl ketone and diene 12 followed by hydrolysis of the adduct is reported to give 4-acetyl-2-cyclohexenone.

the crude product mixture.[7] Quinone formation by oxidative decyanation (the third step of our quinone annelation) must require, then, a fixed carbon–carbon double bond contained in an aromatic ring α to the ketone.

The general application of the annelation–oxidation sequence to the synthesis of quinones hinges on the availability of the key cyano ketone substrates. Despite our early success in obtaining these intermediates, the method is not without certain limitations. The cyano acids **15** and **16** were recovered unchanged from trifluoroacetic



15, R = H
16, R = OCH_3

acid–trifluoroacetic anhydride. Attempts to effect closure by using strong mineral acids (H_2SO_4, anhydrous HF) led to hydrolysis of the cyano group;[8] conversion of **15** to the corresponding acid chloride and treatment with aluminum chloride or stannic chloride in benzene afforded ketone **17**, the product of solvent acylation. The reluctance of γ-arylbutyrates with ortho–para-directing substituents in the meta position to undergo cyclization has been noted;[9] the observation that the cyclohexane analogue **2** is readily cyclized no doubt reflects activation of the ring toward electrophilic attack by the second methoxy group as well as a decreased entropic barrier to ring closure for this compound.

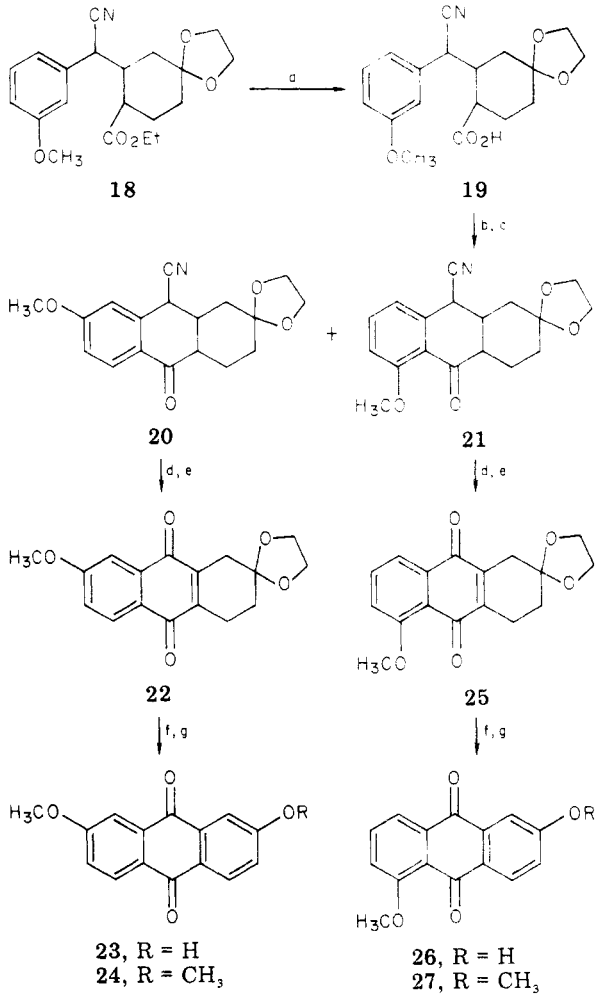
That regiochemical integrity is maintained during the annelative quinone synthesis was conclusively demonstrated by the synthesis of anthraquinones of defined regiochemistry. Hydrolysis of cyano ester **18** gave the acid **19**, which was treated with trifluoroacetic acid–trifluoroacetic anhydride (Scheme II). Reketalization of the crude cyclization product afforded a 1:1 mixture of isomeric cyano ketals which were readily separated by preparative thin-layer chromatography. On the basis of the aromatic patterns of the proton NMR spectra, structure **20** was assigned to the faster moving component and structure **21** to the slower component; these assignments were ultimately confirmed by conversion to the corresponding quinones. The appearance of significant amounts of ketone **21**, the product of ortho closure, is noteworthy.

Treatment of **20** with 2 equiv of lithium diisopropylamide and oxygen gas, followed by reductive workup, afforded a single, bright yellow product, identified as quinone **22** by the NMR spectrum; the aromatic region shows δ 8.00 (d, J = 8.0 Hz, 1 H), 7.48 (d, J = 2.6 Hz, 1 H), 7.07 (dd, J = 8.0, 2.6 Hz, 1 H).

Deketalization of **22** in the presence of oxygen gave the hydroxyanthraquinone **23** directly; methylation of **23** afforded the known 2,7-dimethoxyanthraquinone (**24**).[10]

In similar fashion cyano ketal **21** was transformed into quinone **25**. The aromatic region of the NMR spectrum of this compound was identical with that of 2-allyl-5-methoxynaphthoquinone.[11] Deketalization and air oxidation afforded anthraquinone **26**, which was methylated to give 1,6-dimethoxyanthraquinone (**27**), identical with authentic material prepared by methylation of the Diels–Alder adduct of diene **12** and juglone.[12]

Scheme II[a]



18 **19** **20** **21** **22** **25**

23, R = H
24, R = CH_3

26, R = H
27, R = CH_3

[a] (a) KOB, H_2O, then H_3O^+; (b) TFA–TFAA; (c) $HOCH_2CH_2OH$, TsOH; (d) 2 equiv of LDA; (e) O_2, then $NaHSO_3$, H_2O; (f) O_2, H_3O^+; (g) CH_3I, K_2CO_3.

Summary

The successful oxidative decyanation of 4-cyano-1-tetralones represents a fundamentally new approach to the synthesis of quinones. This reaction completes a three-step annelation procedure in which the quinone nucleus is assembled efficiently and with total control of regiochemistry. Application of this scheme to the regiospecific synthesis of a daunomycinone intermediate will be reported elsewhere.

Experimental Section

Instrumentation and Materials. Infrared spectra were determined on a Perkin-Elmer 257 grating infrared spectrophotometer. Ultraviolet and visible spectra were obtained on a Perkin-Elmer 552 spectrophotometer. Nuclear magnetic resonance spectra were measured on a Varian Associates A-60A spectrometer. Fourier transform ^1H spectra were determined on a Bruker WP-60. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses

(7) By a similar transformation, ethyl 2-methyl-4-hydroxybenzoate was obtained in 40% yield when Hagemann's ester [3-methyl-4-(carboethoxy)-2-cyclohexenone] was treated with 2 equiv of lithium diisopropylamide, oxygen, bisulfite, and base.

(8) See D. E. Green, A. R. Martin, and A. I. White, *J. Pharm. Sci.*, **59**, 526 (1970), and references therein.

(9) W. S. Johnson, *Org. React.*, **2**, 114–7 (1946).

(10) (a) R. Melby, R. Crawford, D. McGreer, and R. B. Sandin, *J. Am. Chem. Soc.*, **78**, 3816 (1956); (b) A. Etienne, J. C. Lepeley, and R. Heymes, *Bull. Chim. Soc. Fr.*, 835 (1949).

(11) W. Eisenbuth and H. Schmid, *Helv. Chim. Acta*, **41**, 2021 (1958).

(12) R. K. Boeckman, T. M. Dolak, and K. O. Cules, *J. Am. Chem. Soc.*, **100**, 7098 (1978).

were performed by Schwarzkopf Microanalytical Laboratory and Galbraith Laboratories.

Column chromatography was carried out by using Baker silica gel 60, 60–200 mesh. Individual fractions were collected by using a Gilson FC-100 microfractionator. Preparative thin-layer chromatography (TLC) was carried out on 20 × 20 cm plates, prepared with Merck silica gel PF-254.

Except where noted, reactions were carried out under nitrogen and argon atmospheres. Dry tetrahydrofuran (THF) was distilled from lithium aluminum hydride. Dry benzene was distilled from calcium hydride. Hexamethylphosphoramide (HMPA) was distilled from sodium metal.

2-[Cyano(2,5-dimethoxyphenyl)methyl]cyclohexene-1-carboxylic Acid (2). A solution of 1.02 g (3 mmol) of cyano ester 1 in 10 mL of ethanol was treated with 5 mL of 1 N NaOH, and the mixture was stirred at reflux for 12 h. The reaction was cooled and concentrated. The residual aqueous solution was diluted with 40 mL of H_2O and washed with 40 mL of ether. The aqueous phase was acidified with dilute HCl and extracted with two 50-mL portions of ether. The combined organic layers were washed with H_2O and saturated brine and dried over $MgSO_4$. Concentration afforded the cyano acid 2 (624 mg, 60%) as a pale oil which solidified on standing. This material was of sufficient purity for use in the subsequent cyclization procedure. An analytical sample was obtained by recrystallization from ether–pentane to give white prisms: mp 172–173.5 °C; IR ($CHCl_3$) 3400–2500 (br), 2240, 1705 cm^{-1}; NMR ($CDCl_3$) δ 11.30 (br s, 1 H), 7.80–6.73 (m, 3 H), 4.81–4.48 (m, 1 H), 4.06 (s, 3 H), 3.94 (s, 3 H), 3.31–3.12 (m, 1 H), 2.75–1.40 (m, 9 H).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.39; H, 7.25; N, 4.46.

1,4-Dimethoxy-9-cyano-10-oxo-5,6,7,8,8a,9,10,10a-octahydroanthracene (3). Cyano acid 2 (2.40 g, 7.9 mmol) was dissolved in 20 mL of 1:1 trifluoroacetic acid–trifluoroacetic anhydride, and the solution was stirred at room temperature for 3 h and at reflux for 0.5 h. Then the reaction mixture was cooled and quenched by cautious addition of 150 mL of ice-cold saturated $NaHCO_3$. The resulting aqueous suspension was extracted with two 75-mL portions of methylene chloride. The combined organic layers were washed with 100-mL portions of saturated $NaHCO_3$, H_2O, and saturated brine and dried over $MgSO_4$. Concentration gave 1.97 g (87%) of a tan solid. Recrystallization from ethanol gave tiny white crystals: mp 118–120 °C; IR (KBr) 2240, 1680, 1585 cm^{-1}; NMR ($CDCl_3$) δ 7.09–6.95 (m, 2 H), 4.35–4.20 (m, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 2.70–1.63 (m, 10 H).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.58; H, 6.59; N, 4.89.

1,4-Dimethoxy-5,6,7,8-tetrahydro-9,10-anthracenedione (4). A solution of keto nitrile 3 (104 mg, 0.36 mmol) in 4 mL of 10:1 (v/v) THF–HMPA was added dropwise to a solution of lithium diisopropylamide (0.72 mmol) in 8 mL of THF at −78 °C. The resulting deep purple solution was stirred for 1 h at −78 °C, and then dry oxygen gas was bubbled vigorously through the mixture for 1 h. The reaction mixture was stirred an additional 0.5 h at −78 °C and warmed to 0 °C over a 0.5-h period, during which the deep purple solution became pale orange. The reaction was quenched by rapid addition of 1 mL of 1 M aqueous $NaHSO_3$, and the resulting mixture was extracted with 50 mL of methylene chloride. This solution was washed with 50-mL portions of 0.5 M NaOH, H_2O, and saturated brine and dried over Na_2SO_4. Concentration afforded a red-brown solid. Preparative thin-layer chromatography of this material (eluted with $CHCl_3$) gave 84 mg (83%) of a bright orange solid: mp 150–152 °C (lit.[4] mp 153 °C); IR ($CHCl_3$) 1674 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (s, 2 H), 3.94 (s, 6 H), 2.53 (m, 4 H), 1.70 (m, 4 H); UV–vis ($CHCl_3$) 267 nm (log ϵ 4.33), 432 (3.87).

1,4-Dihydroxy-5,6,7,8-tetrahydro-9,10-anthracenedione (5). Quinone 4 (101 mg, 0.37 mmol) was dissolved in 15 mL of nitrobenzene, and the solution was cooled in an ice bath. The reaction mixture was stirred vigorously while 2.80 g of aluminum chloride was added portionwise. The resulting purple solution was allowed to warm to room temperature, stirred for 2 h, and poured into 200 g of ice and 10 mL of concentrated HCl. The resulting mixture was stirred to freeze out the nitrobenzene; the ice-cold mixture was filtered, and the deep red aqueous solution was heated on a steam bath for 2 h. A red precipitate formed and was collected by suction filtration and washed with H_2O. Recrystallization from ether gave 60 mg (67%) of long red needles, mp 155–156 °C (lit.[5] mp 159 °C). The NMR and ultraviolet–visible spectra are in agreement with values reported for this compound.[5]

2-[Cyano(2,5-dimethoxyphenyl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylic Acid (7). A solution of ester 6[2] (3.43 g, 8.2 mmol) in 30 mL of 95% ethanol was treated with 600 mg of potassium hydroxide in 10 mL of H_2O, and the mixture was stirred at reflux for 20 h. The reaction mixture was cooled, diluted with 100 mL of H_2O, and washed with ether. The aqueous layer was acidified with 1 N HCl and extracted with two 50-mL portions of ether; the combined organic solution was then extracted with two 50-mL portions of saturated sodium bicarbonate. The aqueous phases were combined, carefully acidified with dilute HCl, and quickly extracted with two 50-mL portions of ether. Finally, the combined organic layers were washed with 50-mL portions of H_2O and saturated brine, dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation to give 2.55 g (81%) of an off-white solid. The extractive workup described above provided material of sufficient purity for use in the cyclization described below. An analytical sample was obtained by recrystallization from ether to give a white solid: mp 190–191 °C; IR ($CHCl_3$) 3300–2800, 2240, 1705, 1495 cm^{-1}; NMR ($CDCl_3$) δ 10.98 (s, 1 H), 6.99 (br s, 1 H), 6.85–6.73 (m, 2 H), 4.62–4.50 (m, 1 H), 3.87 (br s, 4 H), 3.76 (s, 6 H), 2.71–1.33 (m, 9 H), 1.20 (br s, 3 H).

Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.63; H, 6.82; N, 3.31.

1,4-Dimethoxy-6-acetyl-10-cyano-9-oxo-5,6,7,8,8a,9,10,10a-octahydroanthracene (8). Cyano acid 7 (0.75 g, 1.95 mmol) was dissolved in 10 mL of 1:1 (v/v) trifluoroacetic acid–trifluoroacetic anhydride, and the reaction mixture was stirred at reflux under nitrogen for 3 h. The reaction was quenched by careful addition to 100 mL of cold saturated aqueous sodium bicarbonate; the resulting mixture was then extracted with three 60-mL portions of methylene chloride. The combined organic solution was washed with 100 mL of saturated bicarbonate, H_2O, and saturated brine and dried over $MgSO_4$. Concentration afforded a viscous red-brown oil, which was subjected to preparative TLC (eluted with chloroform, three developments) and recrystallized from ethyl acetate–hexane (2:1 v/v) to give 420 mg (70%) of tiny white crystals: mp 191–193 °C; IR ($CHCl_3$) 2240, 1710, 1685, 1595 cm^{-1}; NMR ($CDCl_3$) δ 7.27–6.82 (m, 2 H), 4.28–4.08 (m, 1 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 2.61–1.76 (m, 9 H), 2.21 (s, 3 H).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47. Found: C, 69.65; H, 6.54.

1,4-Dimethoxy-6-(2-methyl-1,3-dioxolan-2-yl)-5,6,7,8-tetrahydro-9,10-anthracenedione (10). Keto nitrile 8 (194 mg, 0.55 mmol) was combined with ethylene glycol (37 mg, 0.6 mmol), *p*-toluenesulfonic acid (10 mg), and triethyl orthoformate (125 mg) in 2 mL of anhydrous benzene, and the mixture was stirred at room temperature for 48 h. The reaction mixture was dissolved in 30 mL of methylene chloride, and the resulting solution was washed with 30-mL portions of saturated aqueous sodium bicarbonate, H_2O, and saturated brine. The organic phase was dried over Na_2SO_4 and concentrated to give 195 mg (95%) of the ketal 9 as a gold-brown foam: IR (KBr) 2240, 1680, 1590 cm^{-1}.

To a stirred solution of lithium diisopropylamide (1.1 mmol) in 10 mL of THF at −78 °C was added ketal 9 (190 mg, 0.5 mmol) in 4 mL of 10:1 (v/v) THF–HMPA. The resulting deep purple solution was stirred for 1 h and then dry oxygen gas was bubbled through the reaction mixture for 1 h while the temperature was maintained at −78 °C. After the mixture was stirred an additional 0.5 h, it was slowly warmed to 0 °C; during this time the deep violet solution became orange-red. The reaction mixture was quenched with 2 mL of 1 N aqueous $NaHSO_3$. Then 50 mL of methylene chloride was added, and the organic solution was washed with 50-mL portions of H_2O and saturated brine and dried over Na_2SO_4. Concentration afforded a viscous orange oil. Preparative TLC (eluted with $CHCl_3$, three developments) gave 174 mg (95%) of a bright yellow solid. Recrystallization from ethyl acetate–hexane (1:1 v/v) gave analytically pure material: mp 181–183 °C; IR ($CHCl_3$) 1670 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (s, 2 H), 3.95 (br s, 10 H), 2.9–1.98 (m, 7 H), 1.35 (s, 3 H); UV–vis ($CHCl_3$) 266 nm (log ϵ 4.29), 430 (3.78).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.19; H, 6.47.

4-Cyanophenol (14). 1-Methoxy-3-[(trimethylsilyl)oxy]butadiene (**12**,[6] 18.60 g, 0.11 mmol) and acrylonitrile (6.11 g, 0.11 mmol) were combined in 50 mL of anhydrous benzene, and the reaction mixture was stirred at reflux for 22 h. The reaction mixture was cooled, and the volatiles were removed by rotary evaporation. The residual dark-brown oil was stirred into 100 mL of 1 N HCl in aqueous THF. After being stirred 1 h at room temperature, the orange-red reaction mixture was diluted with 100 mL of ether, washed with 100-mL portions of H_2O and saturated brine, and dried over $MgSO_4$. Concentration and chromatography of the resulting dark oil (Baker silica gel 60, 60–200 mesh, eluted with 15:1 benzene–ether) afforded the 9.70 g (72%) of nitrile **13** as a pale orange, low-melting solid: IR (film) 2220, 1715, 1640 cm^{-1}; NMR ($CDCl_3$) δ 6.88–6.64 (m, 1 H), 3.15–2.92 (m, 2 H), 2.78–2.32 (m, 4 H).

To a solution of lithium diisopropylamide (6.5 mmol) in 10 mL of THF was added keto nitrile **13** (351 mg, 2.9 mmol) in 5 mL of 4:1 (v/v) THF–HMPA. The resulting dark blue solution was stirred at −78 °C for 1 h. Dry oxygen gas was bubbled through the reaction mixture for 1 h, during which the solution became bright orange. The reaction mixture was warmed to 0 °C, quenched by rapid addition of 6 mL of 1 M $NaHSO_3$, and acidified (pH 5) with dilute HCl. The mixture was poured into 75 mL of methylene chloride. The organic phase was washed with water, dried over $MgSO_4$, and concentrated to give a viscous brown oil. Preparative TLC of this material (buffered silica gel PF-254, eluted with 20:1 ethyl acetate–methanol) afforded a pale orange oil which was triturated with cold ether to give a light yellow solid (146 mg, 43%). This material was identical in all respects with an authentic sample obtained from Aldrich Chemical Co.

2-Methoxy-7,7-(ethylenedioxy)-9-cyano-10-oxo-5,6,7,8,8a,9,10,10a-octahydroanthracene (20) and 1-Methoxy-6,6-(ethylenedioxy)-9-oxo-10-cyano-5,6,7,8,8a,9,10,10a-octahydroanthracene (21). A solution of cyano ester **18**[26] (915 mg, 2.5 mmol) in 15 mL of 95% ethanol was treated with 200 mg of potassium hydroxide in 5 mL of H_2O, and the mixture was stirred at reflux for 16 h. The reaction mixture was diluted with 60 mL of H_2O, and the resulting solution was washed with 60 mL of ether. The aqueous phase was acidified with dilute HCl and rapidly extracted with two 40-mL portions of ether. The combined organic solution was extracted with two 40-mL portions of saturated $NaHCO_3$. The aqueous layers were combined and carefully acidified with dilute HCl and then extracted with two 50-mL portions of ether. The organic layers were combined, washed with H_2O and saturated brine, dried over $MgSO_4$, and filtered. Concentration gave 484 mg (58%) of the acid **19** as a beige solid: mp 144–146 °C; IR ($CHCl_3$) 3400–2700 (br), 2240, 1700 cm^{-1}; NMR ($CDCl_3$) δ 11.16 (s, 1 H), 7.34–6.78 (m, 4 H), 4.56–4.34 (m, 1 H), 3.74 (br s, 7 H), 2.85–1.82 (m, 8 H).

Cyano acid **19** (1.30 g, 3.9 mmol) was dissolved in 10 mL of 1:1 (v/v) trifluoroacetic acid–trifluoroacetic anhydride, and the mixture was stirred at reflux for 5 h. The reaction mixture was cooled and quenched by slow addition to 100 mL of ice-cold saturated $NaHCO_3$. The aqueous mixture was extracted with two 50-mL portions of methylene chloride. The combined organic solution was washed with saturated $NaHCO_3$, H_2O, and saturated brine and dried over $MgSO_4$. Concentration afforded a viscous orange oil which was combined with 202 mg of ethylene glycol and 30 mg of *p*-toluenesulfonic acid in 30 mL of anhydrous benzene. The resulting solution was stirred at reflux with azeotropic removal of H_2O (Dean–Stark trap) for 24 h. The reaction mixture was cooled and partioned between methylene chloride and 10% aqueous $NaHCO_3$. The organic phase was washed with H_2O and dried over $MgSO_4$. Concentration afforded a mixture of the crude ketals **20** and **21** which were separated by preparative thin-layer chromatography (eluted with $CHCl_3$, three developments). The faster moving isomer (**20**) was recrystallized from 3:1 ethyl acetate–hexane to give 427 mg (35%) of a white solid: mp 186.5–189 °C; IR ($CHCl_3$) 2240, 1685, 1605 cm^{-1}; NMR ($CDCl_3$) δ 8.06 (d, J = 5 Hz, 1 H), 7.10 (d, J = 1 Hz, 1 H), 6.94 (dd, J = 5, 1 Hz, 1 H), 3.99 (s, 3 H), 3.91 (s, 4 H), 2.95–1.55 (m, 8 H).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.82; H, 6.18; N, 4.18.

The slower moving isomer (**21**) was recrystallized from 2:1 benzene–hexane to give 411 mg (34%) of a white solid: mp 118–123 °C; IR ($CHCl_3$) 2240, 1685, 1605 cm^{-1}; NMR ($CDCl_3$) δ 8.22–7.89 (m, 1 H), 7.40–6.83 (m, 2 H), 4.55–4.09 (m, 1 H), 3.96 (s, 3 H), 3.88 (s, 4 H), 2.83–1.56 (m, 8 H).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 70.21; H, 5.81; N, 4.47.

2-Methoxy-7,7-(ethylenedioxy)-5,6,7,8-tetrahydro-9,10-anthracenedione (22). To a stirred solution of lithium diisopropylamide (0.6 mmol) in 8 mL of THF at −78 °C was added 78 mg (0.25 mmol) of keto nitrile **20** in 3 mL of 10:1 (v/v) THF–HMPA. The resulting deep red solution was stirred for 1 h at −78 °C, and then dry oxygen gas was bubbled vigorously through the reaction mixture for 1 h. The mixture was stirred an additional 0.5 h at −78 °C, warmed to 0 °C, and quenched by addition of 1 mL of 1 M $NaHSO_3$. The bright orange solution was poured into 30 mL of methylene chloride. The resulting solution was washed with H_2O and saturated brine and dried over $MgSO_4$. Concentration afforded an orange-brown oil, which was subjected to preparative thin-layer chromatography (eluted with $CHCl_3$, two developments) to give 36 mg (48%) of the bright yellow solid. Recrystallization from methanol gave yellow-orange prisms: mp 141–142 °C; IR ($CHCl_3$) 1670, 1635, 1605 cm^{-1}; NMR ($CDCl_3$) δ 8.00 (d, J = 8 Hz, 1 H), 7.48 (d, J = 2.6 Hz, 1 H), 7.07 (dd, J = 8, 2.6 Hz, 1 H), 4.04 (s, 3 H), 3.93 (s, 4 H), 2.96–2.71 (m, 4 H), 2.07–1.77 (m, 2 H); UV–vis ($CHCl_3$) 267 nm (log ϵ 4.42), 333 (3.34), 366 (3.26).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.67; H, 5.30.

1-Methoxy-6,6-(ethylenedioxy)-5,6,7,8-tetrahydro-9,10-anthracenedione (25). The procedure described above for synthesis of the 2-methoxyquinone **22** was used to convert 62 mg (0.20 mmol) of keto nitrile **21** into 41 mg (54%) of quinone **25**. Preparative TLC (eluted with $CHCl_3$) and recrystallization from methanol gave an analytically pure yellow-orange solid: mp 138–139 °C; IR ($CHCl_3$) 1670, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.80–7.19 (m, 3 H), 4.03 (s, 3 H), 3.98 (s, 4 H), 3.02–2.69 (m, 4 H), 2.03–1.73 (m, 2 H); UV–vis ($CHCl_3$) 265 nm (log ϵ 4.31), 324 (3.56).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.62; H, 5.39.

2,7-Dimethoxy-9,10-anthracenedione (24). Quinone **22** (60 mg, 0.2 mmol) was dissolved in 10 mL of acetone. After the addition of 10 drops of 1 N HCl, the mixture was stirred at reflux under an air atmosphere for 18 h. The reaction mixture was cooled and concentrated. The residue was dissolved in methylene chloride, and this solution was washed with H_2O and dried over $MgSO_4$. Concentration gave 46 mg (95%) of anthraquinone **23** as a brown solid: IR (KBr) 3400, 1670, 1640 cm^{-1}; NMR (acetone-d_6) δ 8.28–8.20 (m, 2 H), 7.73–7.55 (m, 2 H), 7.49–7.21 (m, 2 H), 4.05 (s, 3 H).

Anthraquinone **23** (11.5 mg, 0.045 mmol) was combined with 28 mg of potassium carbonate and 34 mg of methyl iodide in 6 mL of dry acetone, and the resulting mixture was stirred at reflux for 14 h. The reaction mixture was cooled and concentrated. The remaining brown solid was dissolved in 30 mL of methylene chloride, and the resulting solution was washed with H_2O, dried over $MgSO_4$, and filtered. Concentration afforded the dimethoxyanthraquinone **24** (11 mg, 91%) as a pale yellow solid: mp 211–212 °C (lit. mp 213 °C,[10a] 210 °C[10b]); IR (KBr) 1670, 1650, 1590 cm^{-1}; NMR (Me_2SO-d_6) δ 8.10 (d, J = 5.6 Hz, 2 H), 7.63 (d, J = 2.5 Hz, 2 H), 7.45 (dd, J = 5.6, 2.5 Hz, 2 H), 3.98 (s, 6 H).

1,6-Dimethoxy-9,10-anthracenedione (27). Quinone **25** (52 mg, 0.17 mmol) was dissolved in 15 mL of acetone and 0.5 mL of 1 N HCl, and the mixture was stirred at reflux under an air atmosphere for 16 h. The reaction mixture was cooled and concentrated. The remaining brown solid was dissolved in 20 mL of methylene chloride, and this solution was washed with H_2O and dried over Na_2SO_4. Concentration gave the crude hydroxyanthraquinone **26** as a brown solid.

The crude quinone **26** was combined with 40 mg of potassium carbonate and 31 mg of methyl iodide in 10 mL of dry acetone, and the mixture was stirred at reflux for 18 h. The reaction mixture was cooled, filtered through glass wool, and concentrated. The residual brown solid was dissolved in 30 mL of methylene chloride; this solution was washed with H_2O and dried over Na_2SO_4. Concentration gave the dimethoxyanthraquinone **27** (11.5

mg, 25% from **25**) as a yellow-orange solid: mp 138–140 °C; IR ($CHCl_3$) 1670, 1595 cm^{-1}; NMR ($CDCl_3$) δ 8.32–7.53 (m, 4 H), 7.43–7.13 (m, 2 H), 4.04 (s, 3 H), 3.96 (s, 3 H).

Acknowledgment. The authors gratefully acknowledge financial support for this work from the National Cancer Institute, Department of Health, Education, and Welfare (Grant No. CA16524), and the American Cancer Society (Institutional Grant No. ACS IN45P to Brown University). K.A.P acknowledges additional support in the form of an Alfred P. Sloan Foundation Fellowship. K.A.P and J.L.K are grateful for the continued support of Brown University, and we would like to thank Paul Barbara and Elizabeth Tallman for assistance during the course of this work.

Registry No. 1, 73453-53-9; 2, 73453-54-0; 3, 73453-55-1; 4, 73453-56-2; 5, 21418-08-6; 6, 66617-31-0; 7, 73453-57-3; 8, 73453-58-4; 9, 73453-59-5; 10, 73453-60-8; 12, 54125-02-9; 13, 73453-61-9; 14, 767-00-0; 18, 73453-62-0; 19, 73453-63-1; 20, 73453-64-2; 21, 73453-65-3; 22, 73453-66-4; 23, 73453-67-5; 24, 73453-68-6; 25, 73453-69-7; 26, 73453-70-0; 27, 73453-71-1; acrylonitrile, 75-05-8.

Syntheses of the Fungal Metabolites (±)-Gliovictin and (±)-Hyalodendrin

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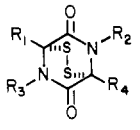
Received February 21, 1980

The syntheses of (±)-gliovictin (**9**) and (±)-hyalodendrin (**20**) are described. Factors which control the stereochemistry of alkylation or sulfenylation of piperazinedione-derived enolates are discussed. An improved technique for introducing a mercapto group by enolate sulfenylation is presented.

The epidithiapiperazinedione moiety **1** is common to the



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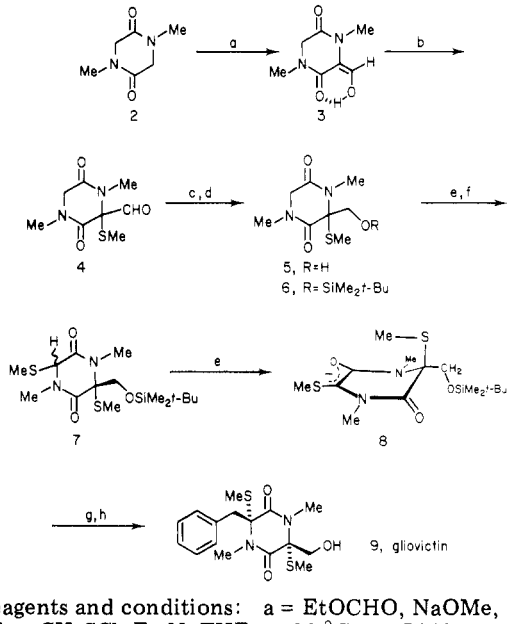
class of fungal metabolites which includes the gliotoxins, sporidesmins, aranotins, verticillins, hyalodendrins, melinacidins, and others.[1a-d] This unique ring system is responsible for the potent antiviral, antifungal, antibiotic, antitumor, and cytotoxic properties which the class displays.

The most successful strategies for the synthesis of epidithiapiperazinediones involve introduction of sulfur into a preformed 2,5-piperazinedione ring. Both nucleophilic and electrophilic sources of sulfur have been utilized.[1a-d] Any approach to epidithiapiperazinediones must address the problem of stereochemistry; both sulfur atoms must be oriented on the same face of the 2,5-piperazinedione ring. Recently, we communicated[2] a stereoselective synthesis of (±)-gliovictin (**9**, Scheme I). Herein, we detail our syntheses of (±)-gliovictin (**9**) and (±)-hyalodendrin (**20**, Scheme III) and discuss factors which control stereochemistry during the assembly of these and other related systems.

Results

Synthesis of (±)-Gliovictin. As outlined in Scheme I, monoformylation of 1,4-dimethyl-2,5-piperazinedione (**2**, sarcosine anhydride) with ethyl formate and sodium methoxide provides enolic aldehyde **3** in 96% yield. Enol **3** can be sulfenylated cleanly at low temperature with a variety of sulfenyl chlorides in the presence of base,[3] typically triethylamine. For example, addition of a slight excess of methylsulfenyl chloride[4] to **3** and 1.0 equiv of triethylamine in tetrahydrofuran at −100 °C provides, after filtration of insoluble $Et_3N{\cdot}HCl$, analytically pure, crystalline (methylthio)carboxaldehyde **4**, in nearly quantitative yield. The high yield and purity of the sulfenylation reactions obviates the need for purification of the derived α-mercapto aldehydes which deformylate upon contact with silica gel or dilute aqueous acid.

Scheme I[a]



[a] Reagents and conditions: a = EtOCHO, NaOMe, THF; b = CH_3SCl, Et_3N, THF, −100 °C; c = LiAl-(t-BuO)$_3$H, THF; d = t-$BuMe_2SiCl$, imidazole, DMF; e = LDA, THF, −78 °C; f = MeSSMe, THF, −78 °C; g = benzyl bromide; h = HCl, MeOH, H_2O.

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(3) Somewhat surprisingly, **3** was found to be unreactive toward sulfenyl chlorides (Ph_3CSSCl, CH_3SCl) in the absence of base.

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