29690-15-1; **23j**, 96348-76-4; *o*-$C_6H_4(SH)_2$, 17534-15-5; 3,4-dibromothiophene, 3141-26-2; thiophene-3-thiol, 7774-73-4; thiophene-3,4-dithiol, 87207-45-2; 4-butylthiophene-3-thiol, 96348-77-5; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available: Atomic coordinates, thermal parameters, a complete listing of bond distances, bond angles and torsion angles for **3**, **7**, **12d**, **5b**, **15**, and S_8, and equipment and procedures for the synthesis of **9a** and **9b** and benzene-1,2-dithiol (41 pages). Ordering information is given on any current masthead page.

An Expeditious Synthesis of Resistomycin

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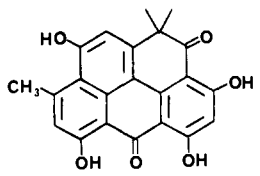
Contribution from the Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167. *Received January 8, 1985*

Abstract: A five-step synthesis of resistomycin (**1**) from emodin (**3**) is described. The key step is the one-pot conversion **6** + **7** → **8** (eq 1). Mechanistic details of this reaction are reported; its regiochemistry can be reversed by changing reaction conditions.

The benzo[*cd*]pyrene ring system is an uncommon one. A survey[1] of the literature reveals that chemists have accorded it scant attention, perhaps because Nature evinces a similar disinterest. In fact, of the thousands of known natural substances, only two embody its carbon framework: the antibiotic resistomycin (**1**)[2] and its apparent oxidation product resistoflavin (**2**).[3]

A number[4] of research groups have launched synthetic assults on resistomycin, but to date only one effort[4c]—which employed an intramolecular Diels–Alder reaction of an isobenzofuran as



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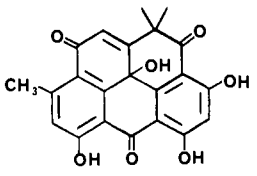
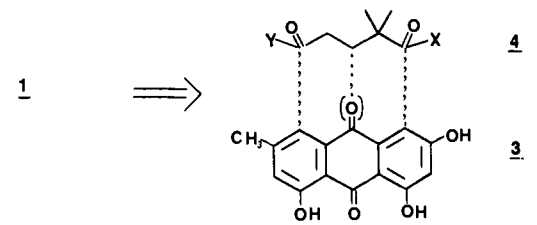


2

the key constructive step—has been capped by success. We now report an exceptionally brief synthesis based on an entirely different strategy.

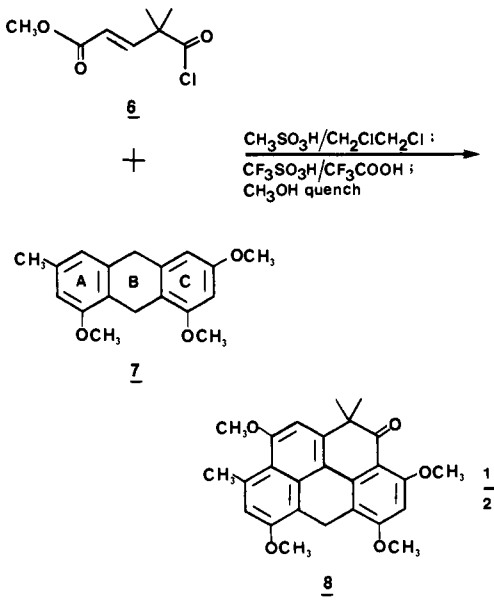
Our approach was prompted by the exact correspondence between the bottom three rings of resistomycin and the structure of emodin (**3**), a widely occurring anthraquinone which is an article of commerce and is also readily available by isolation[5] or synthesis.[6]

Recognition of the similarity between resistomycin (**1**) and emodin (**3**) suggested that if one were able to achieve in effect the three connections indicated by the dotted lines linking **3** and **4**, then an expeditious route to resistomycin would emerge. This expectation has now been realized. Indeed, construction of the pentacyclic skelton can be accomplished in a one-pot operation (eq 1). The consequence is the fabrication of resistomycin from emodin in five steps.



1 ⟹ **4** / **3**

Thus, successive exposure of a mixture of **6** and **7**—which are easily accessible as indicated in eqs 2 and 3—to CH_3SO_3H/CH_2ClCH_2Cl and then CF_3SO_3H/CF_3COOH followed by a



(1)

(1) Campbell, N.; Andrew, H. F. In "Rodd's Chemistry of Carbon Compounds", 2nd Ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1979; Vol. IIIH, pp 291–292. See also: Boffa, G. *Gazz. Chim. Ital.* **1973**, *103*, 1303–1305.

(2) Brockmann, H.; Schmidt-Kastner, G. *Naturwissenschaften* **1951**, *38*, 479–480. Brockmann, H.; Schmidt-Kastner, G. *Chem. Ber.* **1954**, *87*, 1460–1469. Brockmann, H.; Meyer, E.; Schrempp, K.; Reiners, F.; Reschke, T. *Chem. Ber.* **1969**, *102*, 1224–1246. Bailey, N. A.; Falshaw, C. P.; Ollis, W. D.; Watanabe, M.; Dhar, M. M.; Khan, A. W.; Vora, V. C. *Chem. Commun.* **1968**, 374–376. Rosenbrook, W., Jr. *J. Org. Chem.* **1967**, *32*, 2924–2925.

(3) Eckardt, K.; Fritzsche, H.; Tresselt, D. *Tetrahedron* **1970**, *26*, 5875–5883.

(4) (a) Kingston, J. F.; Weiler, L. *Can. J. Chem.* **1977**, *55*, 785–791. (b) James, K.; Raphael, R. A. *Tetrahedron Lett.* **1979**, 3895–3896. (c) Keay, B. A.; Rodrigo, R. *J. Am. Chem. Soc.* **1982**, *104*, 4725–4727.

(5) Kelly, T. R.; Chandrakumar, N. S.; Walters, N.; Blancaflor, J. *J. Org. Chem.* **1983**, *48*, 3573–3574.

(6) (a) Krohn, K. *Tetrahedron Lett.* **1980**, *21*, 3557–3560 and references therein. (b) For surveys of earlier literature, see: "Elsevier's Encyclopaedia of Organic Chemistry"; Josephy, E., Radt, F., Eds.; Elsevier: Amsterdam, 1946; Vol. 13, pp 590–593. And: Thomson, R. H. "Naturally Occurring Quinones", 2nd ed.; Academic Press: New York, 1971; pp 419–422.

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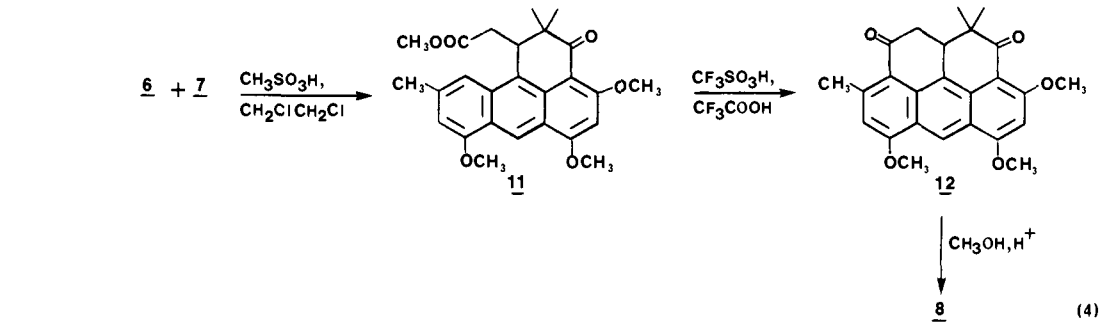

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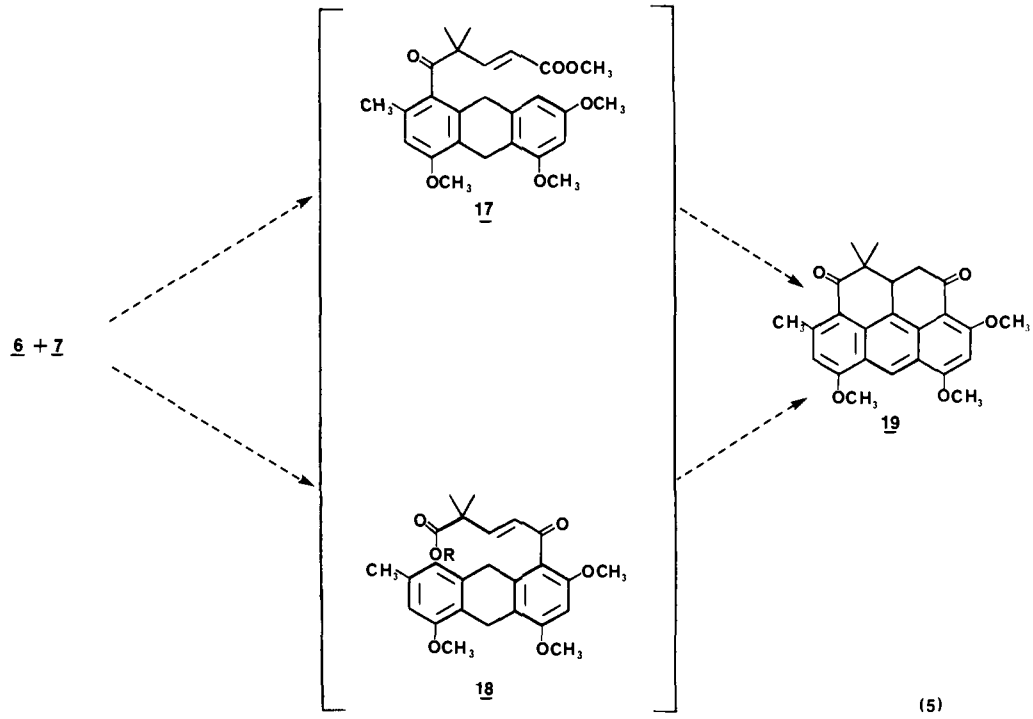

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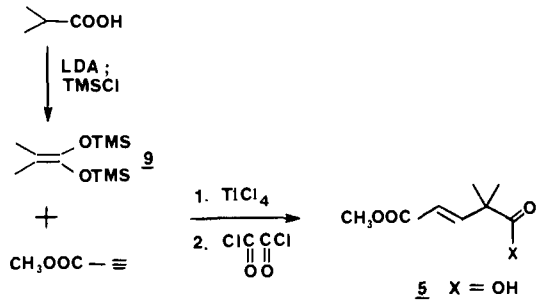

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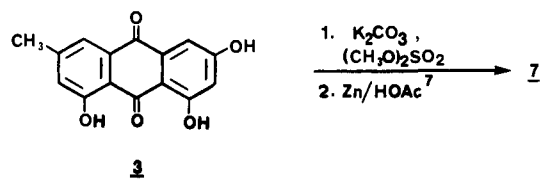
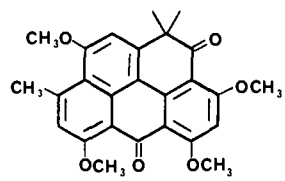


(3)

methanol quench gives **8**. Oxidation[8] (to **10**) and demethylation[4c,9] complete the synthesis.

The sequence of events attending the fusion of **6** and **7** into **8** has been examined in some detail. Isolation of intermediates **11** and **12** establishes that the transformation proceeds as indicated



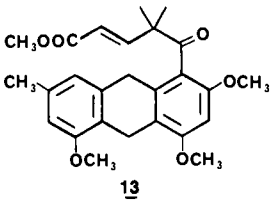
in eq 4.[10] Presumably[11] the chain of events commences with

(7) For the conversion of anthraquinone to anthracene with Zn/HOAc/pyridine, see: Traxler, J. T. *Synth. Commun.* **1977**, *7*, 161–166.

(8) (a) For the preparation of RuO_4, see: Nakata, H. *Tetrahedron* **1963**, *19*, 1959–1963. (b) Oxidation with K^+t-BuO^-/MoOPH [Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196] also gives **10**, but in poorer yield than RuO_4. Among other oxidants which were tried but failed are DDQ/H_2O [Lee, H.; Harvey, R. G. *J. Org. Chem.* **1983**, *48*, 749–751] $Na_2Cr_2O_7$/HOAc [Cook, J. W.; Ludwiczak, R. S.; Schoental, R. *J. Chem. Soc.* **1950**, 1112–1121], dilute HNO_3 [Scott, G. Brit. Patent 793 585, 1958; *Chem. Abstr.* **1959**, *53*, 322*h*], and CrO_3/HOAc (see ref 10b).

(9) (a) Curtis, R. F.; Hassall, C. H.; Parry, D. R. *J. Chem. Soc., Perkin Trans. I* **1972**, 240–244. (b) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249–280.

formation of **13** (reaction of **7** with isobutyric anhydride under Friedel–Crafts conditions gives **14**) which then either suffers (a) oxidation to **15** followed[11] by Friedel–Crafts cyclization (**15**, arrows) or (b) cyclization[12] by Michael-type addition of the acidic



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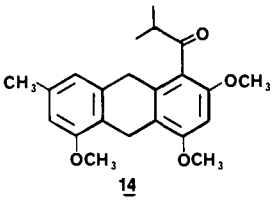

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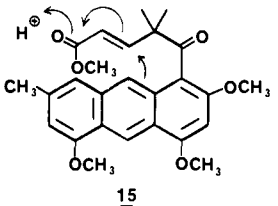

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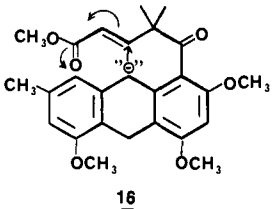

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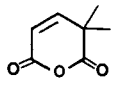
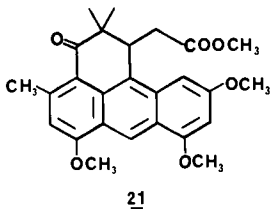
(note that this acidity is enhanced by the ortho keto group) benzhydryl carbon (see **16**) followed by oxidation. The nature of the oxidizing species has not been established, but it may be CH_3SO_3H (sulfuric acid is known[13] to function as an oxidizing agent on occasion).

The acidity of the reaction conditions for the first stage of the sequence (**6** + **7** → **11**) is crucial to the desired regiochemical outcome. Specifically, if the CH_2ClCH_2Cl is omitted and the initial reaction of **6** and **7** is conducted in P_2O_5/CH_3SO_3H[14] (conditions which were then known to convert **11** to **12**), then the product (before methanol quench) is **19**, which is in the opposite regiochemical series (compare **12**). In principle, this regiochemical reversal can be accounted for by invoking either of two different pathways, one proceeding via **17**, the other via **18** (eq 5). In the latter case, interchange of the two termini of **6** might occur through anhydride **20**. Characterization of the tetracyclic intermediate



20

(**21** or **22**) served to address the mechanistic question. The ^1H



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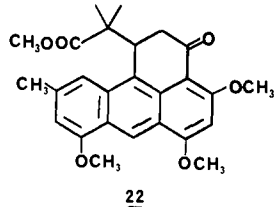
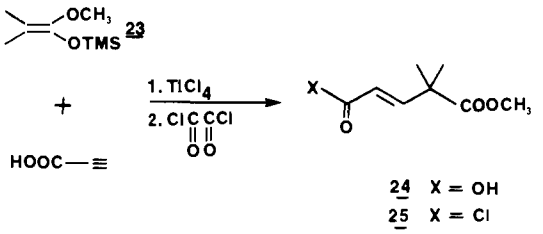


22

NMR spectrum of the intermediate supports[15] assignment of structure **21** rather than **22**. The chemical shifts of a number of resonances differ significantly from the corresponding resonances in **11**. Most notably, the aromatic methyl resonance appears 0.28 ppm downfield from the position in **11**; the position of the peak due to the aromatic methyl in **22** would be expected to be similar to that in **11**, while in **21** such a downfield shift is consistent with the anisotropic influence of the flanking carbonyl.[16] We submit that the change in pathway from eq 4 to eq 5 attending use of a more acidic reaction medium results from protonation of the more activated but more basic C ring (or a pendant methoxy) of **7**, and that electrophilic attack is thereby diverted to the A ring.[17]

Before the conditions which navigated the regiochemical Charybdis embodied in eq 5 were developed, we attempted to exploit its implications by replacing **6** with **25** (prepared as indicated in eq 6). Unfortunately, reaction of **7** with **25** not only

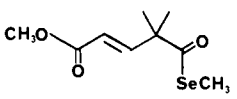


23

24 X = OH
25 X = Cl

(6)

gave a mixture of regiosomers but could not be induced to give **8** or **12** in one pot. Use of **26** in place of **6**, which was intended



26

to eliminate the need for a strongly acidic reaction medium,[19] also failed.

Experimental Section

Melting points were determined in Pyrex capillaries and are uncorrected. NMR spectra were recorded on either a Hitachi Perkin-Elmer Model R-24 or a Varian FT-80A spectrometer; chemical shifts are reported in parts per million (ppm) downfield from internal Me_4Si. Routine mass spectra were obtained by using a Hitachi Perkin-Elmer RMS-4

(10) (a) For the use of CF_3SO_3H as a catalyst in Friedel–Crafts reactions, see: Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 299–300; **1972**, *11*, 300–301. And: Effenberger, F. *Ibid.* **1980**, *19*, 151–171. (b) For a reaction analogous to the conversion of **12** to **8**, see the conversion of 1,2-dihydro-3*H*-benz[*de*]anthracene-3-one to 3-ethoxy-7*H*-benz[*de*]-anthracene: Cameron, D. W.; Kingston, D. G. I.; Schütz, P. E. *J. Chem. Soc. C* **1967**, 2113–2118.

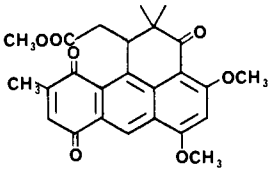
(11) Haddon, R. C.; *Aust. J. Chem.* **1982**, *35*, 1733–1738. Williams, H. J.; Harlow, R. L. *J. Chem. Soc., Perkin Trans. I* **1975**, 1537–1539.

(12) For exceptional reactivity of the methylene protons of 9,10-dihydroanthracene in a Friedel–Crafts acylation, see: Cook, J. W.; Robinson, A. M.; Roe, E. M. F. *J. Chem. Soc.* **1939**, 266–268.

(13) Chinn, L. J. "Selection of Oxidants in Synthesis", Marcel Dekker: New York, 1971; p 130.

(14) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071–4073.

(15) Further confirmation of the structure of **21** was achieved by oxidative demethylation of **11** and **21** to **29** and **30**, respectively, with pyridinium chlorochromate (see Experimental Section) and comparison of the effect of oxidation on the chemical shifts of the aromatic methyl protons in the ^1H



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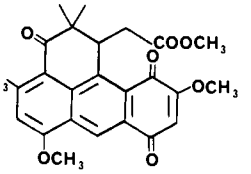


30

NMR. In **29**, the aromatic methyl protons are shifted upfield by 0.31 ppm when compared with **11**; in contrast, the aromatic methyl proton resonance in **30**, the oxidation product of **21**, does not show any significant shift (vs. **21**) which indicates that the environment of the aromatic methyl group has not been appreciably altered by the oxidation.

(16) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed.; Pergamon Press: Oxford, 1969; pp 204–207.

(17) For a similar reversal of regiochemical outcome in the presence of excess acid in a Friedel–Crafts reaction, see: Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056–3062.

(18) (a) Kuo, Y. N.; Chen., F.; Ainsworth, C.; Bloomfield, J. J. *Chem. Commun.* **1971**, 136–137. (b) Ainsworth, C.; Kuo, Y. N. *J. Organometal. Chem.* **1972**, *46*, 73–87.

(19) (a) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860–862. (b) Coates, G. E. *J. Chem. Soc.* **1953**, 2839.

spectrometer; high-resolution mass spectra were obtained at the NIH-supported Regional Mass Spectrometry facility at the Massachusetts Institute of Technology. IR spectra were recorded on a Perkin-Elmer Model 421 spectrometer. E.M. Reagents silica gel 60 F-254 plates (0.2 mm) were used for analytical TLC. For preparative TLC, Analtech silica gel G or GF plates were employed. Flash column chromatography was conducted according to the method of Still et al.[20] with silica gel 60 (particle size 0.040–0.063 mm, EM Reagents). Column chromatography was also conducted with neutral alumina (Brockmann Activity I, 80–200 mesh) under a positive pressure of nitrogen.

Reactions sensitive to air or moisture were conducted in oven- or flame-dried glassware under an atmosphere of dry nitrogen or argon. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl; CH_2Cl_2 from CaH_2. Petroleum ether refers to the fraction boiling from 30 to 50 °C. Elemental analyses were performed by Galbraith Laboratories, Inc., and Robertson Laboratory, Inc.

1,3,8-Trimethoxy-6-methylanthracene-9,10-dione (Emodin Trimethyl Ether, 27). To a mechanically stirred solution of 8.0 g (29 mmol) of emodin[5] (**3**) in 1200 mL of acetone was added 120 g of anhydrous K_2CO_3 followed by 80 mL of dimethyl sulfate. The mixture was heated at reflux for 24 h, concentrated (at atmospheric pressure) to a volume of ca. 600 mL, and diluted with 500 mL of H_2O. A yellow solid (5.0 g, **27**) separated which was collected by filtration. Removal of most of the acetone from the filtrate at aspirator pressure caused an additional 3.8 g of **27** to separate, and this was collected by filtration. The crude **27** (total yield: 8.8 g, 28 mmol, 95%) was sufficiently pure for use in the next reaction. A sample recrystallized from 95% ethanol melted at 225–226 °C (lit.[6b] mp 225 °C): ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s), 3.90 (9 H, br s), 6.71 (1 H, br s), 7.04 (1 H, s), 7.25 (1 H, br s), 7.54 (1 H, s).

9,10-Dihydro-1,3,8-trimethoxy-6-methylanthracene (7). To a mechanically stirred solution of 2.0 g (6.4 mmol) of emodin trimethyl ether (**27**) in 315 mL of glacial acetic acid was added 8 g of zinc dust. The mixture was heated at reflux for 4 h and then allowed to cool to room temperature and filtered. The filtrate was concentrated, and the residue was dissolved in 200 mL of ethyl acetate. The organic layer was washed with 5% sodium bicarbonate solution (3 × 50 mL) and water, dried (Na_2SO_4), and passed through a short column of neutral alumina (30 g). The eluate was concentrated to give 1.73 g (6.09 mmol, 95%) of **7**. An analytical sample, mp 95–97 °C, was obtained as pale yellow crystals by recrystallization from petroleum ether/ethyl acetate: ^1H NMR ($CDCl_3$) δ 2.32 (3 H, s), 3.78 (3 H, s), 3.82 (6 H, s), 3.91 (2 H, s), 4.01 (2 H, s), 6.35 (2 H, br s), 6.55 (1 H, s), 6.67 (1 H, s).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.05; H, 7.09. Found: C, 76.33; H, 6.95.

Methyl 5-Chloro-4,4-dimethyl-5-oxopent-2-enoate (6). To a 1-L three-necked flask equipped with a mechanical stirrer and a dropping funnel was added 150 mL of freshly distilled CH_2Cl_2 followed by 14.2 mL (0.13 mol) of $TiCl_4$. The reaction mixture was cooled to −78 °C under an argon atmosphere and a solution of 10.8 g (0.13 mol) of methyl propiolate in 75 mL of CH_2Cl_2 was added dropwise over a period of 2 h. After the addition was over, the reaction mixture was stirred at −78 °C for an additional 20 min and a solution of 30.0 g (0.130 mmol) of ketene acetal **9**[18b] in 100 mL of CH_2Cl_2 was then added dropwise over a period of 1.5 h. After stirring for an additional 15 min at −78 °C, the reaction mixture was quenched at −78 °C with 100 mL of 5% aqueous K_2CO_3 solution, and the mixture was allowed to stand at room temperature for 18 h. The organic layer was separated, washed with water (2 × 200 mL), dried ($MgSO_4$), and evaporated to give 17.3 g of crude half acid **5** which was used in the next step without further purification.

To a solution of 17.3 g of the crude half acid **5** in 20 mL of CH_2Cl_2 was added a solution of 9.6 mL (0.11 mol) of oxalyl chloride in 10 mL of CH_2Cl_2 dropwise over a period of 0.5 h at 0 °C. The mixture was heated at reflux, the progress of the reaction being monitored by ^1H NMR spectroscopy. After 0.5 h, the mixture was cooled to room temperature and the solvent was evaporated. Kugelrohr distillation (80–82 °C/1.5 torr) gave an analytically pure sample of **6** (15.5 g, 0.081 mol, 63%): ^1H NMR ($CDCl_3$) δ 1.49 (6 H, s), 3.77 (3 H, s), 5.93 (1 H, d, J = 16 Hz), 7.04 (1 H, d, J = 16 Hz).

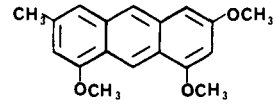
Anal. Calcd for $C_8H_{11}O_3Cl$: C, 50.39; H, 5.77. Found: C, 50.25; H, 6.01.

3,5,7,10-Tetramethoxy-1,1,9-trimethyl-6*H*-benzo[*cd*]pyrene-2(1*H*)-one (8): One-Pot Preparation from 6 and 7. A magnetically stirred mixture of 700 μL (5.2 mmol) of acid chloride **6** and 620 μL (9.55 mmol) of CH_3SO_3H was heated in a 100-mL three-necked flask fitted with a $CaCl_2$ drying tube in a preheated oil bath at 60 °C for 2–3 min; 10 mL of 1,2-dichloroethane was then added. The mixture was heated at 80 °C for 5–6 min and allowed to cool to room temperature. To the light-yellow solution was added 500 mg (1.7 mmol) of **7** in one portion, and the resulting red-colored reaction mixture was heated at reflux in an oil bath (90–95 °C). The progress of the reaction was monitored by TLC by using 7:3 petroleum ether/ethyl acetate (R_f of **7** = 0.82, R_f of **11** = 0.06). When TLC analysis indicated that the reaction had stopped but significant amounts of **7** remained (ca. 10 h), 50 μL (0.36 mmol) of acid chloride **6** and 100 μL of CH_3SO_3H were added. An additional 100 μL of CH_3SO_3H was added to the refluxing mixture after 4 h. When TLC indicated the presence of negligible amounts of **7** in the reaction mixture, the solvent was removed in vacuo. To the residue was added 10 mL of CF_3COOH and 1.5 mL (16.8 mmol) of CF_3SO_3H under an argon atmosphere. The mixture was heated at 70–80 °C for 45 min and concentrated in vacuo. The flask was cooled to 0 °C, and 40 mL of methanol was added. The mixture was heated at 60 °C for 15 min and then cooled to room temperature. The reaction mixture was poured into 400 mL of water and extracted with ethyl acetate (3 × 200 mL). The organic layer was washed with brine until free (pH paper) from acid, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (Florisil) by using 8:2 ethyl acetate/petroleum ether to afford 165 mg (0.39 mmol, 22%) of **8**. A sample recrystallized from methanol under argon melted at 280 °C dec; ^1H NMR ($CDCl_3$) δ 1.57 (6 H, s), 2.89 (3 H, s), 3.98 (12 H, s), 4.12 (2 H, s), 6.45 (1 H, s), 6.70 (1 H, s), 6.96 (1 H, s); high-resolution MS calcd for $C_{26}H_{26}O_5$ 418.1780, found 418.1751.

Intermediates in the conversion of **7** to **8** were prepared and characterized as described below.

Methyl 1,2-Dihydro-4,6,8-trimethoxy-2,2,10-trimethyl-3-oxo-3*H*-benz[*de*]anthracene-1-acetate (11). A magnetically stirred mixture of 140 μL (1.04 mmol) of acid chloride **6** and 120 μL (1.84 mmol) of CH_3SO_3H was heated in a flask fitted with a $CaCl_2$ drying tube in a preheated oil bath at 60 °C for 2–3 min; 2 mL of 1,2-dichloroethane was then added. The mixture was heated at 80 °C for 5–6 min and allowed to cool to room temperature. To the light-yellow solution was added 100 mg (0.35 mmol) of **7** in one portion. The mixture turned red immediately and was heated at reflux in an oil bath (90–95 °C). The progress of the reaction was monitored by TLC by using 7:3 petroleum ether/ethyl acetate (R_f of **7** = 0.82; R_f of **11** = 0.06). When TLC analysis indicated that the reaction had stopped but a significant amount of **7** remained (ca. 10 h), 20 μL (0.30 mmol) of CH_3SO_3H was added and the mixture was heated at reflux for 1 h. An additional 10 μL (0.15 mmol) of CH_3SO_3H was added, and heating was continued for 0.5 h more. The mixture was cooled to room temperature, poured into 25 mL of water, and extracted with ethyl acetate. The organic layer was washed with 5% aqueous $NaHCO_3$ solution followed by water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography over neutral alumina (60 g). Elution with 3:7 ethyl acetate/petroleum ether afforded a mixture of **21** and the anthracene **28**.

Further purification of this mixture by preparative TLC (3:7 ethyl acetate/petroleum ether) gave 8 mg (0.018 mmol, 5%) of **21** (see below for data) and 25 mg (0.08 mmol, 25%) of **28**, which could be converted



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quantitatively to **7** by refluxing with zinc/CH_3COOH, following the procedure described in the conversion of **27** to **7**. An analytical sample of **28**, mp 124–125 °C, was prepared by recrystallization from ethyl acetate/petroleum ether: ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s), 3.81 (3 H, s), 3.91 (6 H, s), 6.33 (1 H, br s), 6.39 (1 H, s), 6.64 (1 H, br s), 7.16 (1 H, s), 7.89 (1 H, s), 8.94 (1 H, s).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.59; H, 6.38. Found: C, 76.65; H, 6.48.

Futher elution of the alumina column with 7:3 ethyl acetate/petroleum ether afforded 46 mg (0.10 mmol) of **11** (40% yield based on starting material consumed). An analytical pure sample, mp 188–189 °C, was prepared by recrystallization from methanol: ^1H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.35 (3 H, s), 2.05–2.40 (2 H, m), 2.56 (3 H, s), 3.52 (3 H, s), 4.04 (3 H, s), 4.08 (3 H, s), 4.12 (3 H, s), 4.2–4.5 (1 H, m), 6.52 (2 H, br s), 7.62 (1 H, br s), 9.05 (1 H, s).

Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.55; H, 6.42. Found: C, 71.57; H, 6.58.

11,11a-Dihydro-3,5,7-trimethoxy-1,1,9-trimethyl-2*H*-benzo[*cd*]pyrene-2,10(1*H*)-dione (12). To 100 mg (0.23 mmol) of **11** was added 3.5 mL of CF_3COOH and 350 μL (3.95 mmol) of CF_3SO_3H under an argon atmosphere. The mixture was heated at 70–80 °C for 1 h, concentrated under vacuum, and cooled to 0 °C; 20 mL of water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed several times with water until free (pH paper) from acid, dried (Na_2SO_4), and evaporated to give 90 mg (0.23 mmol, 98%) of **12**. Crystallization from ethyl acetate/petroleum ether afforded a yellow solid, mp 255 °C

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dec; ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, s), 1.40 (3 H, s), 2.84 (3 H, s), 2.88–2.99 (2 H, m), 3.42–3.72 (1 H, m), 4.11 (3 H, s), 4.16 (3 H, s), 4.20 (3 H, s), 6.57 (1 H, s), 6.60 (1 H, s), 9.06 (1 H, s); high-resolution MS calcd for $C_{25}H_{24}O_5$ 404.1604, found 404.1585.

3,5,7,10-Tetramethoxy-1,1,9-trimethyl-6*H*-benzo[*cd*]pyrene-2(1*H*)-one (8). A solution of *p*-toluenesulfonic acid (6 mg) in 13 mL of methanol was degassed by bubbling argon through it for 10 min. To this solution 49 mg (0.12 mmol) of **12** was added, and argon was bubbled through for an additional 5 min. The mixture was heated at reflux for 45 min under argon and cooled in an ice bath. A greenish-yellow solid precipitated from the reaction mixture which was filtered to give 45 mg (0.10 mmol, 90%) of a compound identical with **8** prepared in the one-pot procedure (vide supra).

3,5,7,10-Tetramethoxy-1,1,9-trimethyl-2*H*-benzo[*cd*]pyrene-2,6-(1*H*)-dione (10, Resistomycin Tetramethyl Ether). To a solution of 80 mg (0.020 mmol) of **8** in 8 mL of acetone cooled to 0 °C was added 550 μL (0.054 mmol) of a 0.11 M standard solution of RuO_4 in CH_2Cl_2.[8a] The mixture was stirred at room temperature for 0.5 h. The progress of the reaction was monitored by TLC (20:1 ethyl acetate/methanol), which indicated the presence of starting material. The reaction mixture was cooled again to 0 °C, 550 μL (0.054 mmol) of the RuO_4 solution was added, and the reaction was stirred at room temperature for 0.5 h. The process was repeated 2 times more. When TLC indicated the absence of starting material, 5 mL of isopropyl alcohol was added and the reaction mixture was stirred at room temperature for 0.5 h. Insoluble material was filtered off and washed with 15 mL of THF. The combined filtrate and wash were concentrated in vacuo, and the residue was purified by column chromatography (silica gel) using 20:1 ethyl acetate/methanol to afford 35 mg (0.081 mmol, 43%) of resistomycin tetramethyl ether (**10**) as a yellow solid, which is identical by TLC comparison with an authentic sample (prepared[2] from **1**) in a variety of solvent systems. A sample crystallized from methanol melted at 273–276 °C dec [lit.[2] mp 278 °C dec; mixture melting point with authentic material having mp 270–273 °C dec: 270–274 °C dec]; ^{1}H NMR ($CDCl_3$) δ 1.63 (6 H, s), 2.95 (3 H, s), 4.05 (6 H, s), 4.08 (3 H, s), 4.12 (3 H, s), 6.58 (1 H, s), 6.94 (1 H, s), 7.14 (1 H, s).

3,5,7,10-Tetrahydroxy-1,1,9-trimethyl-2*H*-benzo[*cd*]pyrene-2,6-(1*H*)-dione (1, Resistomycin). To 25 mg (0.058 mmol) of synthetic resistomycin tetramethyl ether (**10**) was added 1.1 g of freshly distilled[9b] anhydrous pyridinium hydrochloride. The reaction mixture turned red immediately. The solid mixture was heated under argon at 180–190 °C for 3.5 h while the solid melted and the color of the mixture turned from red to dark yellow. The reaction mixture was cooled, 10 mL of water was added, and the mixture was extrcted with ethyl acetate. The ethyl acetate layer was washed with 3% hydrochloric acid, followed by 3% sodium bicarbonate and water. The organic layer was dried (Na_2SO_4); evaporation of the solvent afforded 19 mg (0.050 mmol, 90%) of resistomycin (**1**). A sample crystallized from dioxane/petroleum ether melted at 335–336 °C (vacuum) [lit.[2] mp 330 °C (vacuum); mixture melting point with authentic sample having mp 330–333 °C (vacuum): 330–334 °C (vacuum)]; ^{1}H NMR (THF-d_8) δ 1.63 (6 H, s), 2.98 (3 H, s), 6.35 (1 H, s), 7.06 (1 H, s) 7.14 (1 H, s), 10.74, 13.99, 14.27, 14.64 (4 H, phenolic OH's).

9,10-Dihydro-1,3,8-trimethoxy-6-methyl-4-(2-methyl-1-oxopropyl)-anthracene (14). To a magnetically stirred mixture of 229 mg (1.71 mmol) of $AlCl_3$ and 80 μL (0.48 mmol) of isobutyric anhydride was added 2.5 mL of 1,2-dichloroethane in a flask fitted with a $CaCl_2$ drying tube. The mixture was heated at 45 °C for 15 min and then cooled to 0 °C. To the cooled mixture was added 100 mg (0.35 mmol) of **7** in one portion. The mixture was stirred for 10 min at 0 °C and 1.5 h at room temperature. The reaction mixture was poured into 3 N HCl and extracted with CH_2Cl_2. The organic layer was washed with 10% aqueous Na_2CO_3 solution followed by water, dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC (8:2 petroleum ether/ethyl acetate) to give 15 mg (0.053 mmol, 15% of **7** and 60 mg (0.27 mmol) of **14** as a light-yellow solid (57% yield based on unrecovered starting material). An analytically pure sample of **14**, mp 164–165 °C, was obtained by recrystallization from ethyl acetate/petroleum ether: ^{1}H NMR ($CDCl_3$) δ 1.14 (6 H, d, J = 8 Hz), 2.28 (4 H, overlapping 3 H, s and 1 H, m), 3.76 (13 H, br s), 6.31 (1 H, s), 6.49 (1 H, s), 6.59 (1 H, s).

Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.57; H, 7.34. Found: C, 74.64; H, 7.29.

11,11-a-Dihydro-5,7,9-trimethoxy-1,1,3-trimethyl-2*H*-benzo[*cd*]pyrene-2,10(1*H*)-dione (19). A homogeneous solution was prepared by heating a mixture of 800 mg of P_2O_5 and 8.0 g (83 mmol) of CH_3SO_3H at 60–70 °C for ca. 1 h. This solution was then added to a magnetically stirred mixture of 100 mg (0.35 mmol) of **7** and 140 μL (1.04 mmol) of acid chloride **6** under an argon atmosphere. The resulting mixture was heated at 110 °C for 45 min, cooled to room temperature, poured into cold water, and extracted with ethyl acetate. The organic layer was washed with water until free from acid, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (neutral alumina) with 8:2 ethyl acetate/petroleum ether to afford 87 mg (0.22 mmol, 61%) of **19**. Recrystallization from ethyl acetate under an argon atmosphere afforded orange crystals, mp 250 °C dec: ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.40 (3 H, s), 2.80 (3 H, s), 2.87–3.03 (2 H, m), 3.45–3.90 (1 H, m), 4.12 (9 H, br s), 6.59 (2 H, s), 9.05 (1 H, s); high-resolution MS calcd for $C_{25}H_{24}O_5$ 404.1604, found 404.1634.

Methyl 1,2-Dihydro-6,8,10-trimethoxy-2,2,4-trimethyl-3-oxo-3*H*-benz[*de*]anthracene-1-acetate (21). A mixture of ca. 2 g of P_2O_5 and 20.0 g (208 mmol) of CH_3SO_3H was heated at 70 °C (ca. 1 h) until a clear solution resulted. This solution was added in one portion to a mixture of 215 mg (0.75 mmol) of dihydroanthracene **7** and 455 mg (2.4 mmol) of acid chloride **6**. The mixture was heated at 60 °C for 2.5 h under an argon atmosphere, cooled to room temperature, and poured into water. The resulting mixture was extracted with ethyl acetate (2 × 200 mL), washed with water until free from acid, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (neutral alumina). Elution with 7:3 petroleum ether/ethyl acetate gave 135 mg (0.31 mmol, 41%) of **21** as yellow crystals. A sample recrystallized from methanol melted at 185–186 °C (compound softens at 95–100 °C); ^{1}H NMR ($CDCl_3$) δ 1.10 (3 H, s), 1.36 (3 H, s), 2.07–2.72 (2 H, m), 2.84 (3 H, s), 3.60 (3 H, s), 4.02 (3 H, s), 4.04 (3 H, s), 4.10 (3 H, s), 4.17–4.52 (1 H, m), 6.48 (1 H, br s), 6.58 (1 H, s), 7.23 (1 H, s), 9.09 (1 H, s); high-resolution MS calcd for $C_{26}H_{28}O_6$ 436.1917, found 436.1886.

Further elution of the alumina column with 8:2 ethyl acetate/petroleum ether gave 55 mg (0.13 mmol, 18%) of **19**.

Methyl 1,2,8,11-Tetrahydro-4,6-dimethoxy-2,2,10-trimethyl-3,8,11-trioxo-3*H*-benz[*de*]anthracene-1-acetate (29).[15] To a solution of 50 mg (0.11 mmol) of **11** in 7 mL of CH_2Cl_2 was added 125 mg (0.57 mmol) of pyridinium chlorochromate, and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered, and the filtrate was concentrated. The residue was purified by preparative TLC (7:3 ethyl acetate/petroleum ether) to give 39 mg (0.089 mmol, 78%) of **29**. Crystallization from ethyl acetate gave a yellow solid, mp 155–158 °C: ^{1}H NMR ($CDCl_3$) δ 1.11 (3 H, s), 1.36 (3 H, s), 2.25 (3 H, br s), 2.51–2.91 (2 H, m), 3.48 (3 H, s), 4.12 (3 H, s), 4.15 (3 H, s), 5.05 (1 H, apparent t, $J \simeq 6.5$ Hz), 6.65–6.91 (2 H, m), 8.96 (1 H, s); high-resolution MS calcd for $C_{25}H_{24}O_7$ 436.1522, found 436.1531.

Methyl 1,2,8,11-Tetrahydro-6,10-dimethoxy-2,2,4-trimethyl-3,8,11-trioxo-3*H*-benz[*de*]anthracene-1-acetate (30).[15] To a magnetically stirred solution of 100 mg (0.23 mmol) of **21** in 20 mL of CH_2Cl_2 was added 150 mg (0.69 mmol) of pyridinium chlorochromate. The mixture was stirred at room temperature for 15 min at which time TLC analysis (7:3 ethyl acetate/petroleum ether) indicated the absence of starting material. The mixture was filtered and the filtrate was concentrated. The residue was purified by preparative TLC (7:3 ethyl acetate/petroleum ether) to give 75 mg (0.17 mmol, 75%) of **30**. A sample crystallized from CH_2Cl_2/petroleum ether melted at 207–209 °C: ^{1}H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.38 (3 H, s), 1.95–2.69 (2 H, m), 2.85 (3 H, s), 3.48 (3 H, s), 4.07 (3 H, s), 4.11 (3 H, s), 4.92 (1 H, apparent t, $J \simeq 6$ Hz), 6.05 (1 H, s), 6.90 (1 H, s), 8.72 (1 H, s); high-resolution MS calcd for $C_{25}H_{24}O_7$ 436.1522, found 436.1530.

4-Carbomethoxy-4-methylpent-2-enoic Acid (24) and Methyl 5-Chloro-2,2-dimethyl-5-oxopent-3-enoate (25). To 50 mL of freshly distilled CH_2Cl_2 was added 8.68 g (45 mmol) of $TiCl_4$ at −78 °C under argon. The mixture was stirred magnetically, and a solution of 3.19 g (45 mmol) of propiolic acid in 25 mL of CH_2Cl_2 was added dropwise over a period of 45 min. After stirring at −78 °C for an additional 15 min, a solution of 7.83 g (45 mmol) of ketene acetal **23**[18] in 25 mL of CH_2Cl_2 was added dropwise at −78 °C over 45 min. The reaction mixture was stirred for 10 min at −78 °C and quenched at −78 °C with 50 mL of 5% aqueous K_2CO_3 solution. The organic layer was washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated to afford 1.16 g of crude half acid **24**, which was used in the next step without any further purification. Pure **24** was obtained as indicated below.

To a solution of 1.16 g of crude half acid **24** in 5 mL of CH_2Cl_2 was added dropwise a solution of 0.9 mL (10.3 mmol) of oxalyl chloride in 20 mL of CH_2Cl_2 over a period of 10 min at 0 °C. The mixture was heated at reflux for 0.5 h (the progress of the reaction was monitored by ^{1}H NMR). The mixture was cooled to room temperature, and the solvent was evaporated. Kugelrohr distillation (115 °C/1.5 torr) gave 1.1 g (5.7 mmol, 12%) of **25** as a colorless oil (because **25** proved to have limited utility—see discussion section—no attempt was made to optimize its preparation): ^{1}H NMR ($CDCl_3$) δ 1.40 (6 H, s), 3.72 (3 H, s), 6.97 (1 H, d, J = 16 Hz), 7.32 (1 H, d, J = 16 Hz).

A satisfactory combustion analysis could not be obtained for **25**, but hydrolysis to **24** (aqueous K_2CO_3 overnight at room temperature, acidify

with dilute HCl, and extract into CH_2Cl_2) and recrystallization from ether/petroleum ether gave analytically pure **24**, mp 70–73 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (6 H, s), 3.71 (3 H, s), 5.83 (1 H, d, J = 16 Hz), 7.21 (1 H, d, J = 16 Hz), 10.48 (1 H, br s).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 6.97. Found: C, 55.43; H, 6.91.

Se-Methyl 4-Carbomethoxy-2,2-dimethylbut-3-eneselenoate (26). A 50-mL three-necked flask was equipped with a dry ice condenser, and ca. 20 mL of NH_3 was condensed. To the flask a total of 0.30 g (0.013 g atom) of sodium and 1.20 mL (14.7 mmol) of dimethyl diselenide were added alternately in several portions.[19b] After the addition was over, excess NH_3 was removed at room temperature. Dilute sulfuric acid was slowly added to the solid residue, and the evolved gas was carried in a current of nitrogen through two $CaCl_2$ drying tubes and condensed in a trap cooled in dry ice–acetone. The trap containing methyl selenol[19b] was allowed to attain room temperature slowly, and the gas was passed, via a current of nitrogen, through a mixture of 3.90 g (20.4 mmol) of acid chloride **6** and 1.97 mL (24.2 mmol) of pyridine in 5 mL of CH_2Cl_2 at −78 °C. The mixture was allowed to warm to room temperature and filtered. The filtrate was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by Kugelrohr distillation (130 °C/1.5 torr) to give 4.2 g (16.8 mmol, 82%) of **26**: ^{1}H NMR ($CDCl_3$) δ 1.36 (6 H, s), 2.16 (3 H, s), 3.71 (3 H, s), 5.91 (1 H, d, J = 16 Hz), 7.07 (1 H, d, J = 16 Hz).

Anal. Calcd for $C_9H_{14}O_3Se$: C, 43.38; H, 5.60. Found: C, 43.16; H, 5.77.

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Registry No. 1, 20004-62-0; **3**, 518-82-1; **5**, 96328-29-9; **6**, 96328-30-2; **7**, 96328-31-3; **8**, 96328-32-4; **9**, 31469-25-7; **10**, 22852-03-5; **11**, 96328-33-5; **12**, 96328-34-6; **14**, 96328-35-7; **19**, 96328-36-8; **21**, 96328-37-9; **23**, 31469-15-5; **24**, 96328-38-0; **25**, 96328-39-1; **26**, 96328-40-4; **27**, 6414-42-2; **28**, 96328-41-5; **29**, 96328-42-6; **30**, 96328-43-7; methyl propiolate, 922-67-8; methylselenol, 6486-05-1.

Synthesis and Valence Orbital Structures of Azacycl[3.3.3]azines in a Systematic Series

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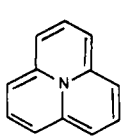
Abstract: The syntheses and spectroscopic properties of unsubstituted 1,3,4,6,7-pentaazacycl[3.3.3]azine (1,3,4,6,7,9b-hexaazaphenalene), 1,3,4,6-tetraazacycl[3.3.3]azine (1,3,4,6,9b-pentaazaphenalene), and 1,3,4,6,8-pentaazacycl[3.3.3]azine (1,3,4,6,8,9b-hexaazaphenalene) are reported. The syntheses were abbreviated in that they consisted of a two-step procedure whereby the appropriate diaminoazine was treated with methyl *N*-cyanomethanimidate and NaOMe in MeOH to give the corresponding bis(*N'*-cyano-*N*-formamidino)azines and these were subjected to short vacuum pyrolysis to afford the azacycl[3.3.3]azines. The valence orbital electronic structure of this series of molecules was examined using UV photoelectron spectroscopy. Interpretation of the spectra was aided by results from HAM/3 and GAUSSIAN 80 (STO-3G) ab initio SCF–MO quantum mechanical calculations. Spectroscopic and theoretical studies were also carried out on 1,3,4-triazacycl[3.3.3]azine and 1,3,6-triazacycl[3.3.3]azine. The results from studies of electronic structure were compared with those previously reported for 1,3,4,6,7,9-hexaazacycl[3.3.3]azine (tri-*s*-triazine) and for cycl[3.3.3]azine. In all of the azacycl[3.3.3]azines studied the highest occupied molecular orbital is a π orbital while the second and third highest occupied orbitals are lone-pair orbitals associated with N atoms. There is a significant variation (>1.3 eV) in the first π ionization potentials of these molecules, and the ionization potential decreases as the number of nitrogen atoms decreases. The ionization potentials of the highest occupied lone-pair orbitals, by contrast, do not change greatly when the number of N atoms changes or when the positions of the N atoms are varied. The quantum mechanical calculations indicate that the entire manifold of upper occupied π orbitals exhibits great sensitivity to heteroatom substitution. Both the HAM/3 and the ab initio GAUSSIAN 80 calculations predict that the ionization potentials of all six of the highest occupied orbitals decrease monotonically as the number of N atoms decreases. The empirically parameterized HAM/3 calculations predict that the total stabilization of the six highest occupied π orbitals is 1.9 eV for each peripheral N atom added. It is likely that these large differences in the stability of the manifold of upper occupied π orbitals play a large role in determining the different reactivities of members of this series of cycl[3.3.3]azines.

The cyclazines as a class of compounds consist of a fused conjugated ring system held planar by three covalent bonds to an internal nitrogen atom.[1,2] The first member of one series, cycl[3.3.3]azine (**1**),[3,4] isoelectronic with the phenalene anion,[5,6] is nonaromatic, contrary to early predictions.[1,7]



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Cycl[3.3.3]azine (**1**) was found to be a highly reactive compound, exhibiting a strong paramagnetic shift in the ^{1}H NMR signals[3,4,8] and a high susceptibility toward oxidation[3,4,9,10] and

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