Koten and J. G. Noltes, *J. Chem. Soc., Chem. Commun.*, 575 (1974); *J. Organomet. Chem.*, **84**, 419 (1975); G. van Koten, A. J. Leusink, and J. G. Noltes, *ibid.*, **84**, 117 (1975); G. van Koten and J. G. Noltes, *ibid.*, **84**, 129 (1975).
(28) T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, **98**, 748 (1976); *J. Org. Chem.*, **40**, 3649 (1975).
(29) G. van Koten and J. G. Noltes, *J. Chem. Soc., Chem. Commun.*, 59 (1972).
(30) A. S. Kende, L. S. Liebeskind, C. Kubiak, and R. Eisenberg, *J. Am. Chem. Soc.*, **98**, 6389 (1976).
(31) We are indebted to Professor A. T. Sneden, Virginia Commonwealth University, for this sample.
(32) W. C. Kofron and L. M. Baclawski, *J. Org. Chem.*, **41**, 1879 (1976).
(33) J. Attenburrow, A. F. B. Cameron, J. G. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(34) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).
(35) John Anthony Schwartz, Ph.D. Thesis, Yale University, 1977.
(36) C. D. Gutsche, E. F. Jason, R. S. Coffey, and H. E. Johnson, *J. Am. Chem. Soc.*, **80**, 5756 (1958).
(37) R. Pschorr, *Justus Liebigs Ann. Chem.*, **391**, 23 (1912).
(38) H. M. Fales, E. W. Warnhoff, and W. L. Wildman, *J. Am. Chem. Soc.*, **77**, 5885 (1955).
(39) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(40) Y. Nishizawa, *Bull. Chem. Soc. Jpn.*, **34**, 1170 (1961).
(41) Some of the copper reagents precipitate at this point. Homogeneity is achieved during warming of the reaction mixture.
(42) Hydrolysis with aqueous HOAc/CH_2Cl_2 has been found to be superior to mineral acid hydrolysis. See the Experimental Section, compound **26b**.
(43) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yahima, *J. Chem. Soc.*, 4749 (1956).
(44) I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Verengo, *J. Chem. Soc.*, 1896 (1961).
(45) M. Hanaoka, H. Sussa, C. Shimezawa, and Y. Arata, *Chem. Pharm. Bull.*, 1216 (1974).
(46) Y. Naya and M. Kotake, *Nippon Kagaku Zasshi*, **86**, 313 (1965).
(47) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).

Synthesis of Chartreusin Aglycone

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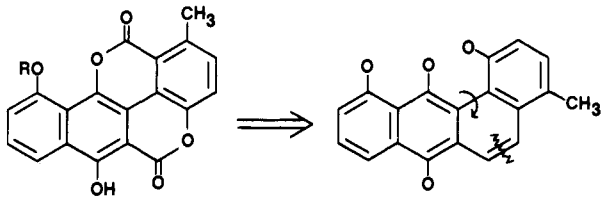
Abstract: A short regiospecific synthesis of chartreusin aglycone (**2**) is described. Diels–Alder addition of **4** and **5** under oxidizing conditions affords benzanthracenedione **6**. Reductive methylation of **6** gives **7** (90%), which is oxidatively cleaved to diacid **8** (54%). Treatment of **8** with HBr/HOAc provides **2** (64%).

The antibiotic chartreusin (**1**)[2] was first fully characterized by Schmid et al. in 1960.[3,4] Although the antibacterial properties of **1** failed to attract lasting attention, recent findings that chartreusin exhibits pronounced activity in a number of anticancer screens[5] led to a resurgence of interest in the pharmaceutical applications of this structurally unique molecule. To date no synthesis of either **1** or its aglycone **2** has appeared. We now report a short, regiospecific preparation of **2**.

The general strategy was based on the perception that **2** might be available by oxidative cleavage of an appropriately



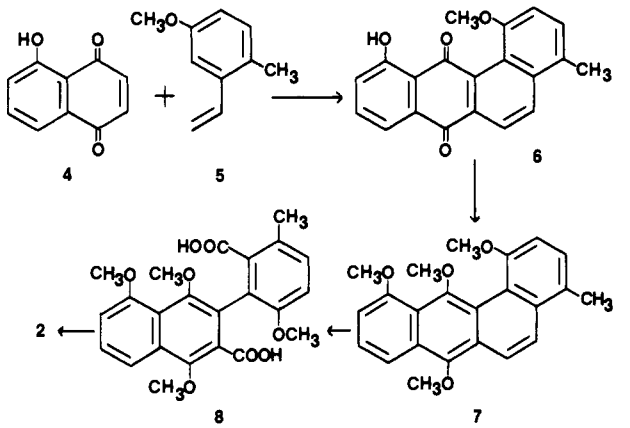
1, R= fucose–digitalose
2, R= H

3

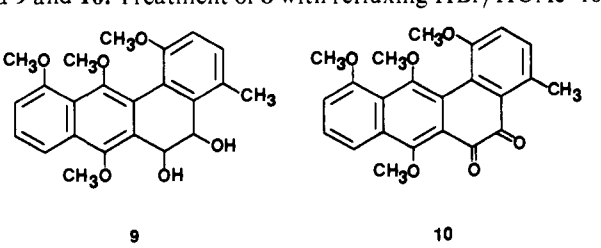
substituted benzanthracene as shown in **3**. The synthesis is outlined in Scheme I. Thus Diels–Alder reaction between 21 g of juglone (**4**) and 33 g of **5**[6] in refluxing toluene for 1 week under oxidizing conditions (chloranil plus O_2 atmosphere) following the procedure of Manning et al.[7,8] affords 14.5 g of **6** regiospecifically. There is no evidence to indicate that any of the alternative regioisomer is produced. The assignment of regiochemistry to **6** was initially based on the known regiochemical propensities of juglone[9] and styrenes[10] in their Diels–Alder reactions with unsymmetrical partners;[11] the eventual obtention of **2** affirms this assignment.

Reductive methylation of **6** ($Na_2S_2O_4$, K_2CO_3, and $(CH_3)_2SO_4$ in refluxing acetone) provides **7** (90%). Attempts to effect conversion of **7** to **8** in a single step (O_3, purple benzene, $IO_4^-/KMnO_4$) failed, but the more circumspect approach employing successive oxidations with $OsO_4/NaClO_3$,[12,13] CrO_3, and H_2O_2[14] gives **8** in 54% overall yield via **9** and **10**. Treatment of **8** with refluxing HBr/HOAc[3] for 16 h followed by workup in hot aqueous acid[3] affords **2** (64%), identical with an authentic sample.

Scheme I



4 5 6 7 8



9 10

Experimental Section

Melting points were determined in Pyrex capillaries and are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-24 spectrometer in $CDCl_3$; chemical shifts are reported in

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parts per million downfield from internal Me_4Si. IR and UV-vis spectra were recorded on Perkin-Elmer spectrometer Models 421 and 575, respectively. Chromatographies were performed on either Merck silica gel 60 (230-400 mesh) or neutral, activity I alumina (80-200 mesh, Fisher Scientific). Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

11-Hydroxy-1-methoxy-4-methylbenz[*a*]anthracene-7,12-dione (6). A solution of 21.0 g of juglone (**4**) and 60.0 g of chloranil in 300 mL of toluene was heated to reflux in a 1-L round-bottom flask. A solution of 33.0 g of 5-methoxy-2-methylstyrene (**5**)[6] in 300 mL of toluene was added and the solution was refluxed for 6 days under an O_2 atmosphere. The mixture was then cooled to room temperature, filtered, washed with 2 × 500 mL of 10% $NaHSO_3$ (to remove residual **4**), dried over Na_2SO_4, filtered twice, and evaporated to dryness. Filtration through 200 g of silica gel using CH_2Cl_2 as eluent and chromatography on 350 g of alumina using 50:1 CH_2Cl_2/AcOH yielded 14.5 g (37%) of pure **6**. Recrystallization from EtOH/CH_2Cl_2 gave an analytical sample as brown crystals: mp 181-182 °C; NMR δ 2.51 (3 H, s), 3.85 (3 H, s), 6.6-7.6 (5 H, m), 8.01 (2 H, s), 11.65 (1 H, s). Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. Found: C, 75.37; H, 4.44.

4-Methyl-1,7,11,12-tetramethoxybenz[*a*]anthracene (7). A suspension of 1.01 g of adduct **6**, 15 g of K_2CO_3, and 10 mL of dimethyl sulfate in 100 mL of acetone was heated at reflux under an N_2 atmosphere. After 3 h 1.0 g of $Na_2S_2O_4$ was added, and the stirred suspension was refluxed for 20 h. After cooling, 100 mL of water with 10 mL of 1 N NaOH was added. After 2 h the solution was concentrated, extracted with CH_2Cl_2, and dried over $MgSO_4$. Chromatography on alumina using CH_2Cl_2 as eluent yielded 1.00 g (90%) of pure **7** as a yellow solid: mp 46 °C dec; NMR δ 2.65 (3 H, s), 3.40 (3 H, s), 3.97 (3 H, s), 4.05 (6 H, s), 6.9-8.1 (7 H, m). Molecular ion calcd for $C_{23}H_{22}O_4$: 362.1518. Found: 362.1528.

4-Methyl-1,7,11,12-tetramethoxybenz[*a*]anthracene-5,6-dione (10). Solutions of 498 mg of compound **7** in 20 mL of THF and 146 mg of $NaClO_3$ in 20 mL of water were mixed. After the addition of 6 mg of OsO_4, the mixture was stirred for 75 h at 50 °C. After cooling to 25 °C, 5 mL of a 10% $NaHSO_3$ solution in water was added. After 1 h the mixture was extracted with ether (3 × 100 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated to dryness, yielding 525 mg of crude product.[15] The crude material was dissolved in 20 mL of pyridine and a solution of 520 mg of CrO_3 in 10 mL of pyridine was added. After stirring for 18 h, the mixture was extracted with 2 × 100 mL of ether. The ether extracts were washed with 1.5 N HCl until all pyridine was removed, dried over Na_2SO_4, and evaporated to dryness. Chromatography on silica gel using ether as eluent yielded 358 mg of diketone **10** (65%). An analytically pure sample was obtained as brown crystals by recrystallization from EtOH: mp 187-188 °C; NMR δ 2.65 (3 H, s), 3.50 (3 H, s), 3.98 (3 H, s), 4.07 (3 H, s), 4.25 (3 H, s), 7.0-8.1 (5 H, m). Anal. Calcd for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.13; H, 5.26.

3-(2-Carboxy-6-methoxy-3-methylphenyl)-1,4,5-trimethoxy-2-naphthoic Acid (8). A solution of 20 mL of THF, 5 mL of H_2O_2 (30%), and 128 mg of diketone **10** was prepared and allowed to stand for 24 h. After this period, 5 mL of 1 N NaOH was added slowly and carefully (very exothermic), and the solution was stirred for 4 h at room temperature. The solution was then acidified with 1.5 N HCl and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated to give a solid which was recrystallized twice from ethyl acetate/heptane, yielding 115 mg (83%) of diacid **8** as colorless crystals, mp 208-209 °C. A mixture of synthetic **8** with naturally derived[3] **8** [mp 207-209 °C (lit.[3] 208-209 °C)] melted at 207-209 °C; NMR (both samples) δ 2.30 (3 H, s), 3.45 (3 H, s), 3.60 (3 H, s), 4.05 (3 H, s), 6.85-7.9 (5 H, m), 9.45 (2 H, bs, exchanges with D_2O).

Chartreusin Aglycone (2). A solution of 58 mg of diacid **8** in 30 mL of AcOH saturated with HBr was heated at reflux for 24 h under N_2. The mixture was evaporated to dryness; 30 mL of 1 N HCl was added and the mixture was stirred under reflux for 18 h. Evaporation to dryness and sublimation of the crude product at 265 °C (0.1 Torr) yielded 29.3 mg (64%) of pure aglycone as chartreuse needles, mp 311-312 °C. A mixture of synthetic **2** and authentic **2** [mp 309-310 °C (lit. 310-311,[3b] 315-316 °C[3a])] melted at 309-310 °C. Aglycone **2** was insufficiently soluble to obtain an NMR spectrum. The IR and UV spectra of synthetic and authentic **2** are superimposable and in agreement with published[3] data.

Acknowledgments. We thank Professor M. Hesse and Mr. H. Kühne (Universität Zürich) for making available samples of **2** and its dimethyl ether prepared in the laboratories of the late Professor Schmid and also Dr. J. Berger (Hoffmann-La Roche)[2] for samples of **1** and **2**. We also thank Drs. J. Douros and M. Suffness of the National Cancer Institute for providing the biological data,[5] Professor L. Vining[4] (Dalhousie University) and Dr. W. B. Manning[7,11] for helpful information, and Dr. H. Dali for preliminary studies. Support of the National Cancer Institute (CA-17631) is gratefully acknowledged. We thank Dr. C. E. Costello of the Mass Spectrometry Facility at Massachusetts Institute of Technology (supported by PHS Grant RR-00317) for recording high-resolution mass spectra.

References and Notes

(1) Recipient of NIH Career Development Award (CA-00040), 1975-1980.
(2) Leach, B. E.; Calhoun, K. M.; Johnson, L. E.; Teeters, C. M.; Jackson, W. G. *J. Am. Chem. Soc.* **1953,** *75,* 4011. Berger, J.; Sternbach, L. H.; Pollock, R. G.; La Sala, E. R.; Kaiser, S.; Goldberg, M. W. *Ibid.* **1958,** *80,* 1636.
(3) (a) Simonitsch, E.; Eisenhuth, W.; Stamm, O. A. *Helv. Chim. Acta* **1960,** *43,* 58; **1964,** *47,* 1459. Eisenhuth, W.; Stamm, O. A.; Schmid, H. *Ibid.* **1964,** *47,* 1475. (b) For other studies on the structure of **1** see: Sternbach, L. H.; Kaiser, S.; Goldberg, M. W. *J. Am. Chem. Soc.* **1958,** *80,* 1639.
(4) For biosynthetic studies which suggest that **2** arises from oxidative cleavage of a benzopyrene and emerges via an intermediate akin to **8**, see: Canham, P.; Vining, L. C.; McInnes, A. G.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1976,** 319.
(5) For an account of some of this work see: McGovern, J. P.; Neil, G. L.; Crampton, S. L.; Robinson, M. I.; Douros, J. D. *Cancer Res.* **1977,** *37,* 1666. T/C's against B-16 melanoma and P-388 and L-1210 leukemia in mice are 277, 231, and 166, respectively; the chemotherapeutic potential of **1** is seriously compromised by its rapid excretion through the bile (personal communications from Drs. J. Douros and M. Suffness, NCI). Whether this limitation can be overcome with analogues is presently unknown, but is under investigation in other laboratories (cf. Beisler, J. A.; Takai, M.; Vehara, Y. "Abstracts of Papers", 178th National Meeting of the American Chemical Society, Washington, D.C., Sept 1979; American Chemical Society: Washington, D.C., 1979; MEDI 47).
(6) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977,** 3859.
(7) Manning, W. B.; Tomaszewski, J. E.; Muschik, G. M.; Sato, R. I. *J. Org. Chem.* **1977,** *42,* 3465. See also ref 11.
(8) For Diels-Alder-based synthesis of benzanthraquinones employing 1,4-phenanthraquinone as the dienophile see: Rosen, B. I.; Weber, W. P. *J. Org. Chem.* **1977,** *42,* 3463. Harvey, R. G.; Fu, P. P.; Cortez, C.; Pataki, J. *Tetrahedron Lett.* **1977,** 3533. Wunderly, S. W.; Weber, W. P. *J. Org. Chem.* **1978,** *43,* 2277.
(9) See: Kelly, T. R.; Montury, M. *Tetrahedron Lett.* **1978,** 4311, and references cited therein.
(10) Onishchenko, A. S. "Diene Synthesis"; Israel Program for Scientific Translations: Jerusalem, 1964; Chapter V.
(11) After the regiospecific preparation of **6** had been achieved, Manning and colleagues reported that the Diels-Alder reaction between juglone and styrene itself gives a 2:1 mixture of regioisomers; the major regioisomer has a structure consistent with the structure assigned to **6**: Manning, W. B.; Muschik, G. M.; Tomaszewski, J. E. *J. Org. Chem.* **1979,** *44,* 699. Manning, W. B. *Tetrahedron Lett.* **1979,** 1661.
(12) Cook, J. W.; Schoental, R. *J. Chem. Soc.* **1948,** 170. Badger, G. M.; Lynn, K. R. *Ibid.* **1950,** 1726.
(13) Wiesner, K.; Chan, K. K.; Demerson, C. *Tetrahedron Lett.* **1966,** 5939. Büchi, G.; Demole, E.; Thomas, A. *J. Org. Chem.* **1973,** *38,* 123.
(14) Kyburz, E.; Riniker, B.; Schenk, H. R.; Heusser, H.; Jeger, O. *Helv. Chim. Acta* **1953,** *36,* 1891.
(15) In a similar experiment this mixture was separated by silica gel chromatography using 4:1 CH_2Cl_2/Et_2O, yielding 38% of diol **9** and 20% of diketone **10**. An analytically pure sample of diol **9** was obtained as colorless crystals by recrystallization from EtOH/CH_2Cl_2: mp 205 °C; NMR δ 2.45 (3 H, s), 2.65 (1 H, bs, D_2O exchanges), 3.40 (3 H, s), 3.85 (3 H, s), 4.0 (6 H, s), 5.05 (2 H, bs), 6.35 (1 H, bs, D_2O exchanges), 6.9-7.8 (5 H, m). Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.56; H, 6.14.