cyclohexane, α −1.949), $[\alpha]^{29.5}_D$ −1235° (c 0.0057, carbon tetrachloride, α −7.103).

(+)-5: $[\alpha]^{29.5}_D$ +1252° (c 0.0012, cyclohexane, α +1.502), $[\alpha]^{29.5}_D$ +1222° (c 0.0063, carbon tetrachloride, α +7.700).

(±)-Bicyclo[2.2.2]octane-2,5-dione (9). A solution of (±)-5 (136 mg, 1 mmol) in 10 mL of ethanol was hydrogenated using 10% Pd/C catalyst at atmospheric pressure until the theoretical amount of hydrogen had been taken up. Filtration and removal of solvent gave 133 mg of crude product. ^{1}H NMR analysis indicated that hydrogenation was incomplete. Recrystallization from benzene gave 110 mg of racemic 9 (80%); mp 203–205 °C (lit.[16] mp 203–205 °C); IR (film) 2910, 2875, 2840, 1720 (split), 1450, 1430, 1380, 1280, 1230, 1070, 920, 850, 840, 785 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.8 (br s, 2 H), 2.55 (d, 4 H), 2.08 (br s, 4 H).

(−)-Bicyclo[2.2.2]octane-2,5-dione (9). Hydrogenation of (−)-5, $[\alpha]^{30}_D$ −1030°, in ethanol over PtO_2 for 30 min in a Parr shaker at 15 psi gave (−)-9 in quantitative yield: mp 201–203 °C; $[\alpha]^{30}_D$ −40.7° (c 0.45, cyclohexane); ORD (c 0.45, cyclohexane) −40.7 (589), −1210 (322), −1250 (312), 0 (297), +1190 (272); CD (c 0.45, cyclohexane) $[\psi]_D$ −1555, $[\psi]_{297}$ −1870, $[\theta]_{max}$ −2581.

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Aflatoxin Precursors: Total Synthesis of (±)-Averufin and (±)-Nidurufin

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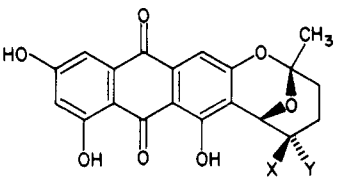
A practical, improved synthesis of 1,3,6,8-tetrahydroxyanthraquinone is described. The latter compound has been used as the starting material in new syntheses of the racemic forms of the *Aspergillus* metabolites averufin and nidurufin. The 2′-endo epimer of nidurufin was also synthesized regiospecifically.

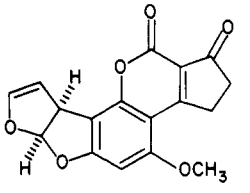
The aflatoxins are a group of mycotoxins produced by certain strains of the mold *Aspergillus*. Aflatoxin B_1 (3), the most widely produced member of this group, is acutely hepatotoxic and carcinogenic. The importance of aflatoxin mycotoxicoses on both animals and in man has spurred intensive studies of the biosynthesis of these compounds.[2] The anthraquinone derivatives averufin[3] and versiconal acetate[4] have been firmly established as intermediates along the complex pathway of aflatoxin biosynthesis.

Until very recently, the minor *Aspergillus* metabolite nidurufin[5] (**2a**) seemed to be a most likely intermediate between averufin (1) and versiconal acetate (4). Model rearrangement studies indirectly supported this view, as did synthetic studies leading to the reassignment of the stereochemistry of nidurufin.[6] Although nidurufin has now been shown to be only poorly incorporated into aflatoxin,[7] the most recent biosynthetic results still point to an as yet unknown intermediate which must be very close structurally and stereochemically to nidurufin.

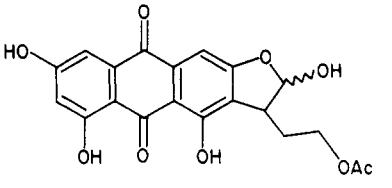
Both averufin and nidurufin may be regarded as structurally elaborated derivatives of 1,3,6,8-tetrahydroxyanthraquinone. In this paper, we describe an improved, practical synthesis of this important intermediate and its elaboration into both (±)-averufin and (±)-nidurufin[8] as well as (±)-2′-*epi*-nidurufin (**2b**). The general synthetic scheme was patterned after our earlier synthesis of the model substance 6,8-dideoxynidurufin.[6]



1, X=Y=H
2a, X=OH; Y=H
2b, X=H; Y=OH



3



4

Results and Discussion

Synthesis of 1,3,6,8-Tetrahydroxyanthraquinone (6). A number of syntheses of 1,3,6,8-tetrahydroxyanthraquinone have been described in the literature.[9] In general, none of these procedures affords a convenient means of obtaining multigram quantities of this compound for further study. The best synthesis reported is that of Brassard and co-workers.[9a] This procedure involves the

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(2) (a) Steyn, P. S.; Vleggaar, R.; Wessels, R. L. In "The Biosynthesis of Mycotoxins", Steyn, P. S., Ed.; Academic Press: New York, 1980; pp 105–155. (b) Biollaz, M.; Buchi, G.; Milne, G. *J. Am. Chem. Soc.* **1970**, *92*, 1035–1043.

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(7) Townsend, C. A.; Christensen, S. B. *J. Am. Chem. Soc.* **1985**, *107*, 270–271.

(8) A synthesis of (±)-nidurufin has been previously reported (Townsend, C. A.; Christensen, S. B. *Tetrahedron* **1982**, *39*, 3575–3582); however, no experimental details are given and references are to unpublished results of those laboratories.

(9) (a) Castoguay, A.; Brassard, P. *Can. J. Chem.* **1977**, *55*, 1324–1332. (b) Grandmaison, J.; Brassard, P. *Tetrahedron* **1977**, *33*, 2047–2053. (c) Holmwood, G. M.; Roberts, J. C. *J. Chem. Soc. C* **1971**, 3899–3902. (d) Low, T. F.; Park, R. J.; Sutherland, M. D.; Vessey, I. *Aust. J. Chem.* **1965**, *18*, 182–189.

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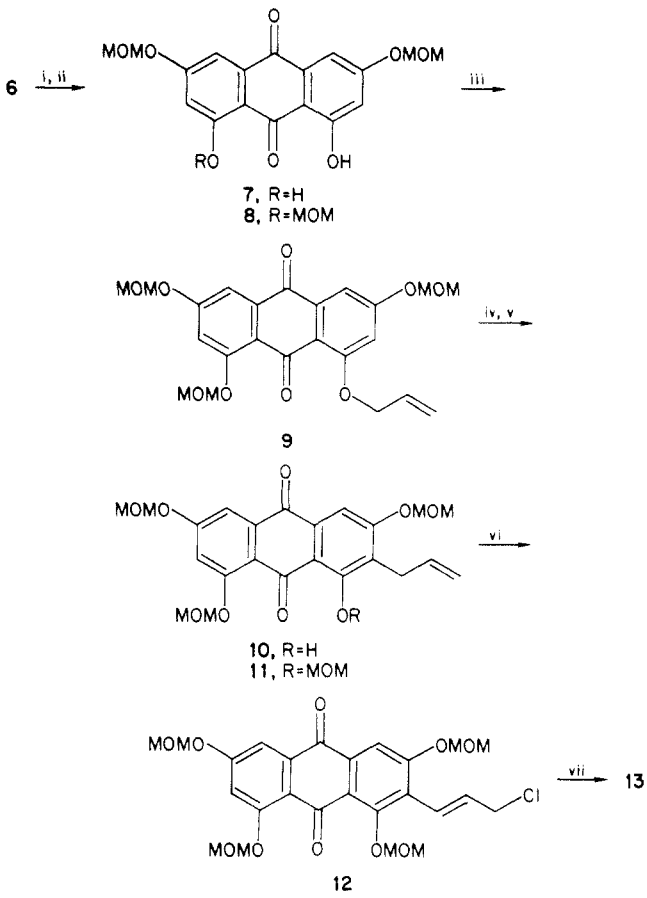
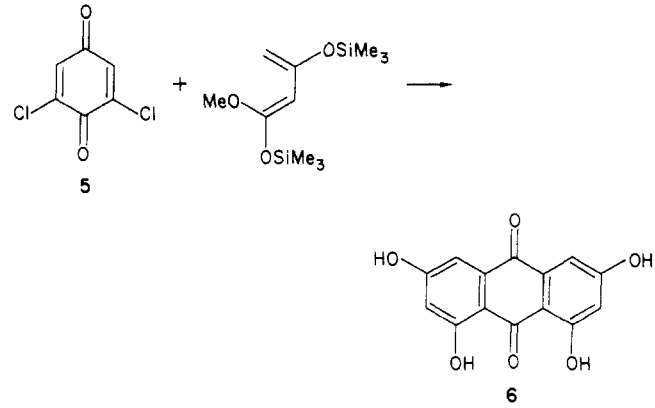
Scheme I[a]



[a] (i) MOMCl, *i*-Pr_2NEt, THF, room temperature; (ii) MOMCl, KO-*t*-Bu, THF, room temperature; (iii) allyl bromide, K_2CO_3, acetone, reflux; (iv) $Na_2S_2O_4$, DMF-H_2O (1:1), 90 °C; (v) MOMCl, KO-*t*-Bu, THF, room temperature; (vi) (a) PhSeCl, CCl_4, 0 °C; (b) H_2O_2, pyr; *t*-BuAA, NaH, Me_2SO, NaI, room temperature.

Diels–Alder reaction of 2,6-dichlorobenzoquinone[10] with an excess of 1,3-dimethoxy-1-[(trimethylsilyloxy]-1,3-butadiene, followed by methylation of the crude reaction product to give 1,3,6,8-tetramethoxyanthraquinone and subsequent fusion of the latter compound with a large quantity of sodium chloride and aluminum chloride to yield the tetrahydroxyanthraquinone in about 30% overall yield. We have now found that the Brassard synthesis can be greatly simplified by employing 1,3-bis[(trimethylsilyl)oxy]-1-methoxy-1,3-butadiene[11] as the diene. In this way, 1,3,6,8-tetrahydroxyanthraquinone can be prepared in multigram quantities in about 50% yield in a one-pot process requiring no chromatography.

Elaboration of the Anthraquinone Nucleus. Selective protection of three of the hydroxyls of **6** could be accomplished in a convenient two-step procedure (Scheme I). When 1,3,6,8-tetrahydroxyanthraquinone was treated with 2 equiv of chloromethyl methyl ether and *i*-Pr_2NEt, the non-hydrogen bonded 3-OH and 6-OH positions can be selectively protected to give **7**. The triprotected anthraquinone can be obtained by a careful addition of 1 equiv of KO-*t*-Bu to a THF solution of **7** and chloromethyl methyl ether. The triprotected product **8** could also be obtained by the direct treatment of 1,3,6,8-tetrahydroxyanthraquinone with 3 equiv of KO-*t*-Bu and chloromethyl methyl ether although in a somewhat diminished yield. This triprotected anthraquinone **8** was alkylated to give



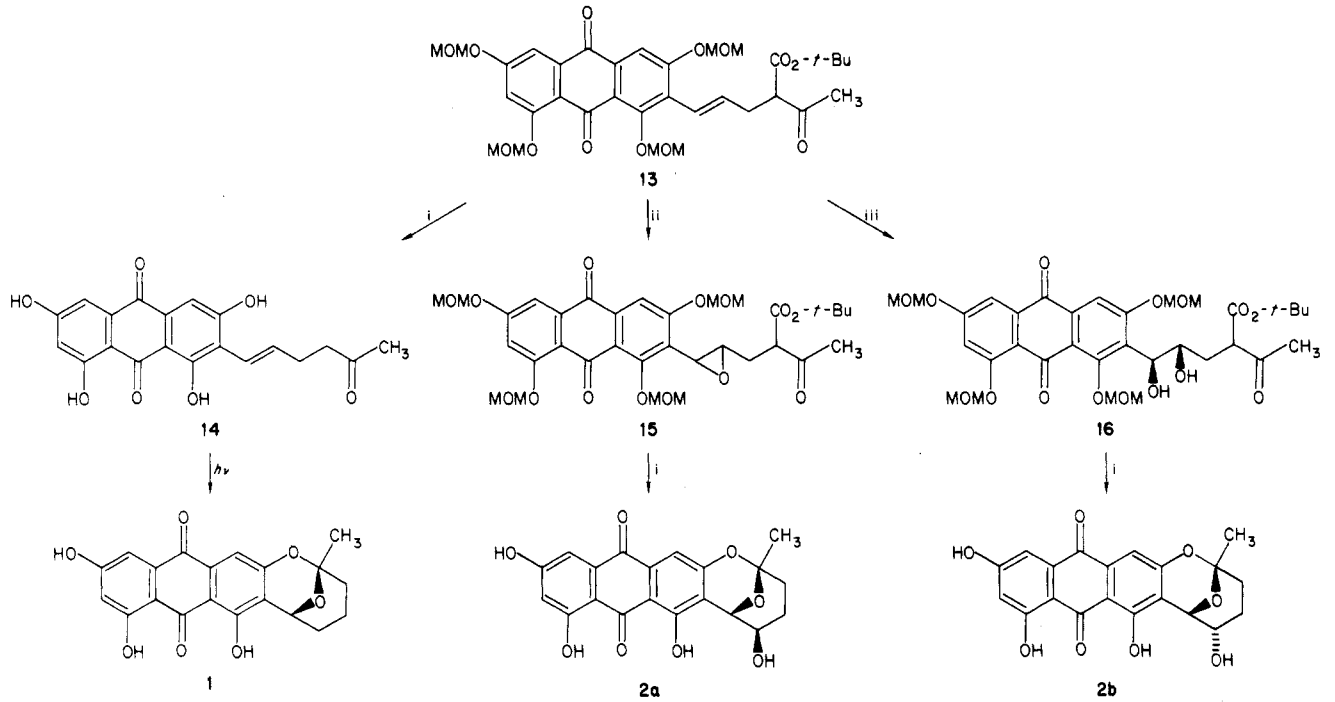
9 which was subjected to reductive Claisen conditions[12] and protected again as the methoxymethyl ether to give the 2-propenylanthraquinone **10**. A three-carbon homologation with transposition of the olefin to the benzylic position was realized in two steps. The allylic chloride **12** was obtained by the kinetic addition–elimination of PhSeCl according to the Raucher[13] procedure. Treatment of this allylic chloride with the anion of *tert*-butyl acetoacetate gave the alkylated product in which the double bond is in the trans configuration. This alkylated compound **13** served as the pivotal intermediate for the synthesis of (±)-averufin and both regioisomers of (±)-nidurufin.

(±)-Averufin and (±)-Nidurufin. The open form of averufin (**14**) was cleanly obtained when **13** was heated in a 1:1 acetic acid–water solution containing a catalytic amount of sulfuric acid.[15] When product **14** was treated with a catalytic amount of *p*-toluenesulfonic acid in hot toluene, (±)-averufin (**1**) resulted in a 50% yield for the two-step procedure (Scheme II). Alternatively, (±)-averufin can be produced directly from **13** by heating in toluene containing *p*-toluenesulfonic acid, although in synthetically unacceptable yields. The 250-MHz ^1H NMR spectrum of (±)-averufin corresponds to that reported in the literature.[14]

The exo isomer of (±)-nidurufin (**2a**) was produced when the *trans*-alkene **13** was epoxidized and subjected to mild cyclization conditions (HOAc–H_2O (1:1), H_2SO_4 catalytic) (Scheme II). The ^1H NMR spectrum of this compound exhibits chemical shifts which are in total agreement with those reported by Aucamp and Holzapfel,[5] including the small coupling constant observed for the benzylic C-1′ proton (reported J = 1.5 Hz, observed J = 1.3 Hz). The endo isomer ((±)-2′-*epi*-nidurufin (**2b**)) was obtained via a cis-glycolization of **13** with OsO_4–$NaClO_3$[16] followed by ketalization with the same mild conditions. Some notable differences in the ^1H NMR spectra of the two isomers of (±)-nidurufin were observed. The benzylic C-1′ proton proved to exhibit the most important differences: in the exo isomer it appeared as a doublet of J = 1.3 Hz at 5.16 ppm, while in the endo isomer it appeared as a doublet of J = 4.08 Hz at 5.33 ppm. These data confirm our earlier contention based upon models that naturally occurring nidurufin is indeed *exo*-2′-hydroxyaverufin.[6]

(10) Kehrmann, F.; Tiesler, W. *J. Prakt. Chem.* **1889**, *40*, 480–497.
(11) Yamamoto, K.; Suzuki, S.; Tsuji, J. *Chem. Lett.* **1978**, 649.
(12) Rutledge, P. et al. *Tetrahedron Lett.* **1982**, 4407.
(13) (a) Raucher, S. *Tetrahedron Lett.* **1977**, 3909. (b) Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, 4977.
(14) Isolation: Holker, J. S. E.; Kagal, S. A.; Mulheirn, L. J.; White, P. M. *J. Chem. Soc., Chem. Commun.* **1966**, *24*, 911–913. Synthesis: Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885–6888. See also ref 9a.
(15) Compound **14** was characterized as the tetramethylether derivative (IR, NMR, HRMS).
(16) Wiesner, K.; Chan, K. K.; Demerson, C. *Tetrahedron Lett.* **1965**, 2893–2897.

Scheme II[a]



[a] (i) HOAc-H_2O (1:1), catalytic H_2SO_4; (ii) *m*-CPBA, $CHCl_3$, room temperature; (iii) $NaClO_3$, OsO_4 catalytic, THF-H_2O (1:1), room temperature; (iv) *p*-TsOH, toluene, 90 °C.

Thus, with an improved preparation of 1,3,6,8-tetrahydroxyanthraquinone, we have accomplished the total synthesis of (±)-averufin and (±)-nidurufin by an efficient route in overall yields of 20% and 24%, respectively, from **6**. The key intermediate **13** in the sequence was also used to complete a synthesis of (±)-*epi*-2′-nidurufin.

Experimental Section

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Mass spectra were determined on a Perkin-Elmer 270B spectrometer. NMR spectra were recorded on a Bruker 250 FT instrument with Me_4Si as an internal standard and are reported in δ units. Elemental analyses were performed by Galbraith Laboratories. All organic extracts were washed and dried over anhydrous Na_2SO_4 prior to filtration and evaporation. All solvents were dried prior to use.

1,3,6,8-Tetrahydroxyanthraquinone (6). To a stirred solution of 2,6-dichloro-1,4-benzoquinone[10] (5 g, 28.2 mmol) and 50 mL of distilled THF in a flame-dried, N_2-flushed flask at −78 °C was added (*E*)-1,3-bis[(trimethylsilyl)oxy]-1-methoxybuta-1,3-diene[11] (23 g, 84.6 mmol) in 30 mL of THF. The solution was warmed to room temperature and stirred for 2 h. All volatiles were removed in vacuo, and the resulting dark tar was pyrolyzed overnight at 120 °C. A solution of 3:1 MeOH/10% HCl(aq) was added to the residue, and the mixture was refluxed for 0.5 h, cooled, diluted with water (1:1), and filtered. The resulting dark brown solid was dissolved in EtOAc and filtered. When the EtOAc was removed in vacuo 3.9 g (50%) of **6** was obtained, which was used without further purification. The crude product can be chromatographed (silica gel, hexane–EtOAc (1:1)) to give **6** as an orange solid: mp >350 °C, ^1H NMR (Me_2SO-d_6) 12.18 (s, 2 H, OH), 7.09 (d, 2 H, *J* = 2.2 Hz, Ar H), 6.57 (d, 2 H, *J* = 2.2 Hz, Ar H).

1,8-Dihydroxy-3,6-bis(methoxymethoxy)anthraquinone (7). To a stirred solution of 1,3,6,8-tetrahydroxyanthraquinone (2.0 g, 7.35 mmol) and chloromethyl methyl ether (1.29 g, 16.0 mmol) in 40 mL of dry THF was added diisopropylethylamine (2.1 g, 16.2 mmol) in 10 mL of THF. The mixture was allowed to stir 0.5 h and was monitored by TLC. Upon completion of the reaction, the mixture was diluted with 100 mL of CH_2Cl_2 and washed successively with 10% HCl(aq) dilute $NaHCO_3$, and water. The organic layer was dried and removed in vacuo. The resulting solid was chromatographed (silica gel, hexane–EtOAc (2:1)), and 2.3 g (88%) of **7** were obtained, which could be crystallized from EtOH: mp 181–182 °C; ^1H NMR ($CDCl_3$) 3.50 (s, 6 H, OCH_3), 5.28 (s, 4 H, OCH_2O), 6.84 (d, 2 H, *J* = 2.4 Hz, Ar H), 7.42 (d, 2 H, *J* = 2.4 Hz, Ar H), 12.27 (s, 2 H, Ar OH); MS(EI), *m/e* (relative intensity) 360 (M^+, 100), 330 (16), 300 (7). Anal. Calcd for $C_{18}H_{16}O_8$: C, 59.99; H, 4.48. Found: C, 60.21; H, 4.65.

1-Hydroxy-3,6,8-tris(methoxymethoxy)anthraquinone (8). To a stirred solution of bis(methoxymethyl ether) **7** (2.0 g, 5.5 mmol) and chloromethyl methyl ether (0.55 g, 6.6 mmol) in 40 mL of dry THF was added potassium *tert*-butoxide in small portions until the reaction was complete (TLC). The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (3 × 50 mL). The organic layer was dried, and the solvent was removed in vacuo. The resulting solid was chromatographed (silica gel, hexane–EtOAc (2:1)), and 2.1 g (95%) of **8** were obtained, which could be crystallized from EtOH: mp 140 °C; ^1H NMR ($CDCl_3$) 3.49 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3), 5.27 (s, 2 H, OCH_2O), 5.32 (s, 2 H, OCH_2O), 5.40 (s, 2 H, OCH_2O), 6.88 (d, 1 H, *J* = 2.4 Hz, Ar H), 7.17 (d, 1 H, 2.4 Hz, Ar H), 7.39 (d, 1 H, 2.4 Hz, Ar H), 7.64 (d, 1 H, *J* = 2.4 Hz, Ar H), 13.31 (s, 1 H, Ar OH); MS(EI), *m/e* (relative intensity) 404 (M^+, 100), 389 (25), 373 (27), 344 (80). Anal. Calcd for $C_{20}H_{20}O_9$: C, 59.39; H, 4.99. Found: C, 59.26; H, 5.01.

1-(Allyloxy)-3,6,8-tris(methoxymethoxy)anthraquinone (9). To a stirred solution of tris(methoxymethyl ether) **8** (0.9 g, 2.2 mmol) and allyl bromide (0.81 g, 6.7 mmol) in dry acetone (20 mL) was added ground anhydrous K_2CO_3 (0.92 g, 6.7 mmol). The reaction mixture was refluxed under nitrogen for 12 h. The mixture was cooled, diluted with CH_2Cl_2, and washed with water. The resulting product was filtered through basic alumina (CH_2Cl_2), and 0.95 g (97%) of the yellow compound **9** was obtained: 113–114 °C mp; ^1H NMR ($CDCl_3$) 3.50 (s, 6 H, OCH_3), 3.57 (s, 3 H, OCH_3), 4.74–4.76 (m, 2 H, $OCH_2CH{=}CH_2$), 5.28 (s, 4 H, OCH_2O), 5.34 (s, 2 H, OCH_2O), 5.35 (d, 1 H, $C{=}CH_2$), 5.55 (d, 1 H, *J* = 17.3 Hz, $C{=}CH_2$), 6.09 (m, 1 H, $CH{=}C$), 6.90 (d, 1 H, *J* = 2.2 Hz, Ar H), 7.16 (d, 1 H, *J* = 2.2 Hz, Ar H), 7.46 (d, 1 H, *J* = 2.2 Hz, Ar H), 7.54 (d, 1 H, *J* = 2.2 Hz, Ar H); MS(EI), *m/e* (relative intensity) 444 (0.7 M^+), 403 (34.9), 399 (100). Anal. Calcd for $C_{23}H_{24}O_9$: C, 62.14; H, 5.44. Found: C, 62.14; H, 5.64.

1-Hydroxy-3,6,8-tris(methoxymethoxy)-2-(2′-propenyl)-anthraquinone (10). To a stirred solution of **9** (2.8 g, 6.23 mmol) and $NaHCO_3$ (0.25 g) in DMF–H_2O (1:1, 60 mL) was added sodium dithionite (1.68 g, 9.6 mmol). The mixture was heated at 90 °C under N_2 and monitored by TLC. Upon completion of

the reaction, the mixture was allowed to cool while air was bubbled through for 1 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed repeatedly with water. The crude product was concentrated in vacuo and chromatographed (silica gel, hexane–EtOAc (1:1)), and 2.5 g (89%) of **10** were obtained as a yellow solid which was crystallized from EtOH: mp 132–134 °C, ^{1}H NMR ($CDCl_3$) 3.49 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 5.00 (d, J = 8.1 Hz, C=CH_2), 5.12 (d, 1 H, J = 17 Hz, C=CH_2), 5.31 (s, 2 H, OCH_2O) 5.36 (s, 2 H, OCH_2O), 5.38 (s, 2 H, OCH_2O), 5.99 (m, 1 H, CH=C), 7.16 (d, J = 2.4 Hz, Ar H), 7.48 (s, 1 H, Ar H), 7.63 (d, J = 2.4 Hz, Ar H), 13.51 (s, 1 H, Ar OH); MS(EI), m/e (relative intensity) 444 (M^1, 0.2), 398 (9.3), 356 (14.4), 272 (100). Anal. Calcd for $C_{23}H_{24}O_9$: C, 62.14; H, 5.44. Found: C, 62.44; H, 5.63.

1,3,6,8-Tetrakis(methoxymethoxy)-2-(2′-propenyl)-anthraquinone (11). To a stirred solution of **10** (2.0 g, 4.5 mmol) and chloromethyl methyl ether (0.47 g, 5.85 mmol) in dry THF (50 mL) was added potassium *tert*-butoxide in small portions until the reaction was complete on the basis of TLC observations. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 × 50 mL). The methylene chloride was removed in vacuo, and the resulting solid was chromatographed on neutral alumina to afford **11** (2.0 g, 91%) as a yellow solid which was crystallized from EtOH: mp 122 °C; ^{1}H NMR ($CDCl_3$), 3.48 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 5.01 (d, 1 H, J = 9.65 Hz, Ar CH_2), 5.06 (d, 1 H, J = 16.7 Hz, C=CH_2), 5.19 (s, 2 H, OCH_2O), 5.29 (s, 2 H, OCH_2O), 5.33 (s, 2 H, OCH_2O), 5.36 (s, 2 H, OCH_2O), 5.99 (m, 1 H, CH_2CH=), 7.13 (d, 1 H, J = 1.9 Hz, Ar H), 7.53 (s, 1 H, Ar H), 7.70 (d, 1 H, J = 1.9 Hz, Ar H); MS(CI), m/e (relative intensity) 489 (M^+ + H, 50), 445 (100), 413 (60), 401 (46). Anal. Calcd for $C_{25}H_{28}O_{10}$: C, 61.47; H, 5.78. Found: C, 61.09; H, 5.95.

1,3,6,8-Tetrakis(methoxymethoxy)-2-(3′-chloro-1′-propenyl)anthraquinone (12). To a stirred solution of phenylselenium chloride (514 mg, 268 mmol) and dry CCl_4 (110 ml) at 0 °C in a flame-dried, N_2-flushed flask was added **11** (1.1 g, 226 mmol), and the solution was allowed to stir for several hours. Upon completion of the reaction (TLC), pyridine (0.5 mL) and 30% H_2O_2 (3 mL) were added at 0 °C, and the solution was stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 × 50 mL). The methylene chloride layer was dried, and the solvent was removed in vacuo. The resulting solid was chromatographed on neutral alumina (CH_2Cl_2), giving the allylic chloride **12** (0.98 g, 83%) as a yellow solid: mp 135 °C; ^{1}H NMR ($CDCl_3$) 3.50 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 4.30 (d, 2 H, J = 6.4 Hz, CH_2Cl), 5.16 (s, 2 H, OCH_2O), 5.29 (s, 2 H, OCH_2O), 5.34 (s, 2 H, OCH_2O), 5.39 (s, 2 H, OCH_2O), 6.87–6.96 (m, 1 H, CH=C$H$$CH_2$), 7.03 (d, 1 H, J = 15.8 Hz, Ar CH=), 7.13 (d, 1 H, J = 2.4 Hz, Ar H), 7.52 (d, 1 H, J = 2.4 Hz, Ar H), 7.71 (s, 1 H, Ar H); MS(CI), m/e (relative intensity) 523 (M + H, 20), 489 (45), 449 (38), 435 (23). Anal. Calcd for $C_{25}H_{27}O_{10}Cl$: C, 57.46; H, 5.21. Found: C, 57.39; H, 5.27.

1,3,6,8-Tetrakis(methoxymethoxy)-2-[5′-oxo-4′-[(*tert*-butyloxy)carbonyl]-1-hexenyl]anthraquinone (13). To a stirred solution of sodium hydride (79 mg, 1.99 mmol; 60% oil dispersion washed several times with hexane) in dry Me_2SO (5 mL) was added *tert*-butyl acetoacetate (315 mg, 1.99 mmol) dropwise via a syringe. The mixture was allowed to stir under N_2 for 1 h before adding a solution of allyl chloride **12** (0.80 g, 1.53 mmol) and NaI (52 mg, 0.3 mmol) in Me_2SO (5 mL) dropwise via a syringe. The reaction mixture was stirred under N_2 for 12 h, diluted with methylene chloride (100 mL), and washed repeatedly with water. The methylene chloride was removed in vacuo, and the resulting product was chromatographed (silica gel, hexane–ethyl acetate (1:1)), giving 695 mg (70%) of the alkylated product: mp 75 °C; ^{1}H NMR ($CDCl_3$) 1.47 (s, 9 H, *t*-BuO), 2.27 (s, 3 H, $COCH_3$), 2.79 (t, 1 H, J = 6.4 Hz, $CH(COCH_3)(CO_2$-*t*-Bu)), 3.50 (s, 6 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 5.12 (s, 2 H, OCH_3O), 5.28 (s, 2 H, OCH_2), 5.32 (s, 2 H, OCH_2O), 5.35 (s, 2 H, OCH_2O), 6.65–6.80 (m, 2 H, Ar CH=CH_2), 7.11 (d, 1 H, J = 2.3 Hz, Ar H), 7.52 (d, 1 H, J = 2.3 Hz, Ar H), 7.62 (s, 1 H, Ar H); MS(EI), m/e (relative intensity) 543 (1.5), 397 (88). Anal. Calcd for $C_{33}H_{40}O_{13}$: C, 61.47; H, 6.26. Found: C, 61.23; H, 5.99.

Epoxide of the Keto Ester 15. To a stirred solution of the alkylated product **13** (100 mg, 0.155 mmol) in $CHCl_3$ (15 mL) was added *m*-CPBA (48 mg, 0.186 mmol). The mixture was allowed to stir under N_2 overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with dilute $NaHCO_3$ and then water. The methylene chloride extract was dried, the solvent was removed in vacuo, and the resulting product was chromatographed on a short column (silica gel, hexane–ethyl acetate (1:2)), giving 95 mg (93%) of **15** as a gummy yellow solid: ^{1}H NMR ($CDCl_3$) 1.47 (s, 9 H, *t*-Bu), 2.31 (s, 3 H, $COCH_3$), 3.50 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.64 (m, 1 H, C-2′H), 5.23 (m, 1 H, C-1′H), 5.29 (s, 2 H, OCH_2O), 5.32 (s, 2 H, OCH_2O), 5.33 (s, 2 H, OCH_2), 5.35 (s, 2 H, OCH_2O), 7.13 (br s, 1 H, Ar H), 7.53 (br s, 1 H, Ar H), 7.74 (s, 1 H, Ar H); MS(CI), m/e (relative intensity) 661 (M^+ + H, 77.3), 630 (37.3), 6.15 (57.5), 605 (99.2). Anal. Calcd (CI high resolution mass spectrum) for $C_{33}H_{40}O_{14}$ (M + H) 661.2496, found 661.2478.

1,3,6,8-Tetrakis(methoxymethoxy)-2-[5′-oxo-4′-[(*tert*-butyloxy)carbonyl]-1′,2′-dihydroxyhexanyl]anthraquinone (16). To a stirred solution of the alkylated adduct **13** (0.11 g, 0.17 mmol) and sodium chlorate (0.036 g, 0.34 mmol) in THF (10 mL) and water (5 mL) was added osmium tetraoxide (3–5 drops of a 0.005% aqueous solution). The mixture was allowed to stir under nitrogen at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed, diluted with $NaHCO_3$ and water, and dried. The methylene chloride was removed in vacuo, and the crude product was chromatographed (silica gel, hexane–EtOAc (1:2)) to give 0.10 g (87%) of **16** as an oil: ^{1}H NMR ($CDCl_3$) 1.43 (s, 9 H, *t*-Bu), 2.27 (s, 1 H, $COCH_3$), 3.50 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.64 (m, 1 H, $CH(OH)CH_2$), 5.25 (d, 1 H, J = 8.8 Hz, Ar CH(OH)), 5.29 (s, 2 H, OCH_2O), 5.32 (s, 2 H, OCH_2O), 5.33 (s, 2 H, OCH_2O), 5.38 (s, 2 H, OCH_2O), 7.14 (br s, 1 H, Ar H), 7.53 (br s, 1 H, Ar H), 7.75 (s, 1 H, Ar H); MS(CI), m/e (relative intensity) 679 (M + H, 1), 633 (6.3), 589 (11.2), 543 (100). Anal. Calcd (CI high resolution mass spectrum) for $C_{33}H_{42}O_{14}$ (M + H) 679.2602, found 679.2540.

(±)-Averufin (1). The alkylation product **13** (120 mg, 0.185 mmol) was dissolved in a 1:1 acetic acid–water solution (50 mL) containing a catalytic amount of H_2SO_4. This solution was heated under nitrogen at 90 °C for 3 h. The mixture was allowed to cool and extracted with EtOAc, and the organic phase was washed with dilute $NaHCO_3$ and washed and then dried. The EtOAc was removed in vacuo, and the resulting solid **14** was dissolved in toluene and heated with a catalytic amount of *p*-toluenesulfonic acid under nitrogen. When the reaction was complete (TLC), the product was extracted into EtOAc, which was then washed several times with dilute $NaHCO_3$ and water. The EtOAc was dried and removed in vacuo, and the crude product was chromatographed (silica gel, hexane–EtOAc (2:1)) to give 34.5 mg (50%) of (±)-averufin: mp 279 °C dec (recrystallized from chloroform–methanol) lit.[5] mp 280 °C; ^{1}H NMR (Me_2SO-d_6) 1.18–2.29 (m, 6 H), 1.53 (s, 3 H, CH_3), 5.24 (br s, 1 H, 1′ H), 6.55 (d, 1 H, J = 2.3 Hz, Ar H), 6.97 (s, 1 H, Ar H), 7.07 (d, 1 H, J = 2.3 Hz), 11.3 (br s, 1 H, 6-OH), 12.04 (s, 1 H, Ar OH), 12.42 (s, 1 H, Ar OH); MS (EI), m/e (relative intensity) 368 (m^+, 56.6), 325 (94.9), 310 (100), 297 (58.8), 286 (66.3). Anal. Calcd (CI high resolution mass spectrum) for $C_{20}H_{16}O_7$ (M + H) 369.0974, found 369.0934.

(±)-Nidurufin (2a). The epoxide **15** (100 mg, 0.15 mmol) was dissolved in a 1:1 acetic acid–water solution (50 mL) containing a catalytic amount of H_2SO_4, and the solution was heated at 90 °C under nitrogen for 4 h. The reaction mixture was diluted with ethyl acetate (100 mL), and the organic phase was washed with dilute $NaHCO_3$ and then water. The ethyl acetate layer was dried, and the solvent was removed in vacuo. The crude product was chromatographed (silica gel, hexane–EtOAc (1:1)) to give 40 mg (69%) of (±)-nidurufin as an orange solid: mp 190 °C dec (recrystallized from chloroform–methanol) (lit.[5] mp 188 °C); ^{1}H NMR (acetone-d_6) 1.58 (s, 3 H, $COCH_3$), 1.3–2.2 (m, 4 H), 3.97 (m, 1 H, CHOH), 5.17 (d, 1 H, 1.3 Hz, benzylic proton), 6.65 (d, 1 H, J = 2.3 Hz, Ar H), 7.13 (s, 1 H, Ar H), 7.25 (d, 1 H, 2.3 Hz); MS (EI), m/e (relative intensity) 384 (M^+, 9.9), 366 (20.9), 323 (17.7), 310 (16.2), 299 (6.8), 266 (30), 99 (100), 71 (57.5). Anal. Calcd (CI high resolution mass spectrum) for $C_{20}H_{16}O_8$ (M + H) 385.0923, found 385.0908.

2′-*endo*-Nidurufin (2c). The diol **16** (30 mg, 0.04 mmol) was dissolved in a 1:1 acetic acid–water solution (25 mL) containing

a catalytic amount of H_2SO_4, and the solution was heated at 90 °C under nitrogen for 45 min. The reaction mixture was diluted with ethyl acetate (100 mL), and the solution was washed with dilute $NaHCO_3$ and then water. The ethyl acetate was dried and then removed in vacuo. The crude product was purified by preparative plate chromatography (hexane–EtOAc (1:1)) to give 12 mg of the nidurufin epimer as an orange solid (71%): mp 190–192d °C (recrystallized from chloroform–methanol); ^1H NMR (acetone-d_6) 1.52 (s, 3 H, $COCH_3$), 4.20 (m, 1 H, C*H*(OH)O), 5.33 (d, 1 H, J = 4.08 Hz, benzylic proton), 6.66 (d, 1 H, J = 2.2 Hz, Ar H), 7.14 (s, 1 H, Ar H), 7.26 (d, 1 H, J = 2.2 Hz, Ar H); MS(CI), m/e (relative intensity) 385 (M + H, 1), 313 (0.9), 299 (0.9), 219 (7.5), 99 (52.8), 71 (95). Anal. Calcd (CI high resolution mass spectrum) for $C_{20}H_{16}O_8$ (M + H) 385.0923, found 385.0933.

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Reductive Carbon–Carbon Cleavage in Caged Systems. A New General Synthesis of Linearly Fused *cis-syn-cis*-Triquinanes

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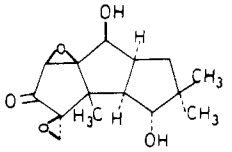
A concise and flexible approach to *cis-syn-cis*-tricyclo[6.3.0.$0^{2,6}$]undecane-4,10-dione derivatives bearing the linearly fused tricyclopentanoid framework has been established. The key concept in this synthetic theme is sequential, reductive carbon–carbon bond cleavage in readily and abundantly available pentacyclo-[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (Cookson's dione **7**). Reaction of **7** with zinc dust in acetic acid under sonic irradiation resulted in the formation of tetracyclic dione **8** in excellent yield through C_1–C_7 bond reduction. The second C–C bond reduction (C_9–C_{10} in pentacyclic dione **7**) was achieved by treating the tetracyclic dione **8** with an excess of Na–K alloy in the presence of trimethylchlorosilane to give *cis-syn-cis*-tricyclo[6.3.0.$0^{2,6}$]-undecane-4,10-dione (**6**). Several interesting transformations of the readily available *cis-syn-cis*-triquinane dione **6** are described. In an analogous manner, methyl-substituted derivatives **21** and **22** of the Cookson's caged dione are transformed to tricyclopentanoids **24** and **26**, respectively, in moderate yields. The three hexacyclic diones **29**, **34**, and **35** sharing common structural features with **7** also undergo sequential C–C bond reductions to furnish novel polyquinanes **31**, **36**, and **37**, respectively. These examples support the generality and preparative utility of the approach delineated here.

The high level of contemporary interest in the synthetic design of linearly fused tricyclopentanoids (triquinanes) stems from their wide occurrence in nature with a promising biological profile [e.g., coriolin (**1**)] and their likely role as the building blocks for the syntheses of "exotic" all carbon polyhedra, e.g., [4]peristylane (**2**) and dodecahedrane.[1] Consequently, a variety of novel approaches to



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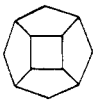
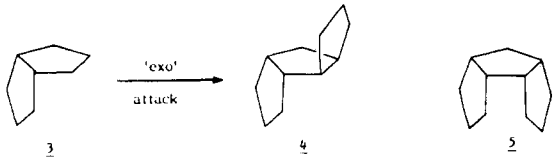


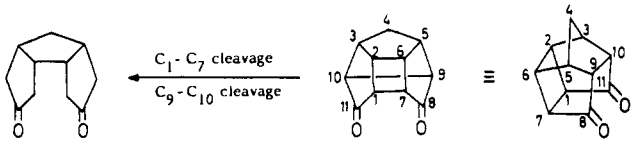
2

this ring system have been delineated in the recent past. The most direct and commonly employed approach to linearly fused tricyclopentanoids is the 5,5 → 5,5,5 ring route in which a cyclopentane ring is annulated to a preformed *cis*-bicyclo[3.3.0]octane framework. This approach is eminently suited for generating the cis-anti-cis stereochemical pattern **4** of natural products as the incoming cyclopentane ring is preferentially appended on the convex face of the folded *cis*-bicyclo[3.3.0]octane moiety **3**. Indeed, most synthesis of triquinane natural products have followed this common strategy.[1b] On the other hand, the



3 **4** **5**

Scheme I



6 **7**

sterically more hindered *cis-syn-cis*-triquinane system, e.g., **5**, has proved difficult to negotiate, and only two methods reported by us[2] and Eaton[3] provide reliable and direct access to this ring system. In pursuit of our work[4] on convex polyquinanes related to dodecahedrane and **2**, we identified the symmetrically functionalized *cis-syn-cis*-triquinanedione **6** as a key building block.[5] It was clear at the outset that neither the existing methodologies[1-3] nor the 5,5 → 5,5,5 route was suited for access to **6** and the desirability of evolving a de novo approach was indicated.

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