3-(Acyloxy)-3-buten-2-ones as Dienophiles in Anthracyclinone Synthesis. An Efficient Route to 4-Demethoxy-7-deoxydaunomycinone Derivatives

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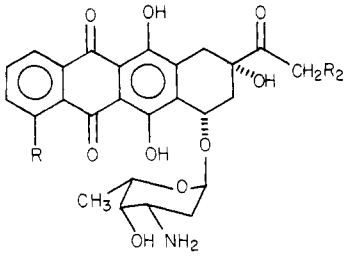
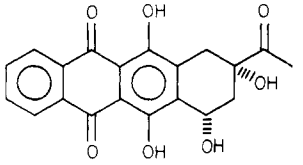
Biacetyl has been converted into a series of 3-(acyloxy)-3-buten-2-ones (13–17) which were characterized both spectroscopically and as their crystalline adducts with 1,3-diphenylisobenzofuran. A comparative study has been made of the reaction of these dienophiles with three related transient anthraquinone–o-quinodimethanes (8) which are readily available from 2,3-dimethylquinizarin. The yield of tetracyclic adduct obtained is highly dependent upon both the structure of the dienophile and the diene; the best yields are quite good (39–46%), establishing the utility of biacetyl enol esters in a very short and practical synthesis of 4-demethoxy-7-deoxydaunomycinones.

The clinical utility of the anthracycline antibiotics daunorubicin (1) and adriamycin (2)[1] has prompted con-



1, $R_1 = OCH_3$; $R_2 = H$
2, $R_1 = OCH_3$; $R_2 = OH$
3, $R_1 = R_2 = H$



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siderable efforts to find, by partial or total synthesis, close analogues having higher anticancer activity and/or lower cardiotoxicity.[2] The initial report of the considerably enhanced activity of the synthetic 4-demethoxydaunorubicin (3)[3] has made the corresponding aglycon, 4-demethoxydaunomycinone (4), a particularly attractive synthetic target. Although a number of varied approaches[4] have now complemented the original Wong synthesis of 4, the synthesis of this aglycon by a short, inexpensive, and experimentally simple route remains a challenging goal.

We recently reported[5] a new and efficient route to the tetracyclic system of the 4-demethoxyanthracyclinones.

Table I

bromide	dienophile	tetracyclic ketone	% yield
5	MVK	9	69[5]
6	MVK	10	75[5]
7	MVK	11	71
5	12	18	12
6	13	19	46
6	14	20	39
6	15	21	18[a]
7	12	22	8[b]
7	13	23	25[c]
7	14	24	17[c]
7	15	25	15[c]
7	16	26	2[c]
7	17	27	2[c]

[a] Isolated as hydroxy ketone 21 after chromatography. [b] Isolated as hydroxy ketone 18 after hydrolysis: HOAc-THF-H_2O (1:2:1), 45 °C, 2 h; NaOH (5%)-THF, 80 °C, 2 h. [c] Isolated as hydroxy ketone 18 after hydrolysis: NaOH (5%)-THF, 80 °C, 2 h.

The key step in this process involved the sodium iodide debromination of either dibromide 5 or 6 (Scheme I) and the trapping of the resulting transient *o*-quinodimethane 8 by methyl vinyl ketone to give, in 69–75% yield, 4-demethoxy-7,9-dideoxydaunomycinone (9) or its dimethyl ether (10). In an attempt to obtain a 9-oxygenated anthracyclinone directly from a similar Diels-Alder reaction, we effected the debromination of dibromide 5 in the presence of a large excess of the enol trimethylsilyl ether of biacetyl [3-[(trimethylsilyl)oxy]-3-buten-2-one, TBO, 12]. The reaction did in fact succeed but, due to the sluggish behavior of TBO as a dienophile,[6] the yield of 4-demethoxy-7-deoxydaunomycinone (18) never exceeded 12%, and the product required extensive chromatographic purification. We now report a simple synthesis of a series of monoenol esters of biacetyl and the results of a study of their utility as dienophiles in the direct synthesis of 4-demethoxy-7-deoxydaunomycinone derivatives.

The acid-catalyzed acetylation of biacetyl to give the monoenol acetate 13 was described a number of years ago,[7] but only a low yield of product was obtained after a tedious purification. We have now found that acetate 13 may be easily and cleanly obtained by the reaction of biacetyl with acetyl chloride and triethylamine at room temperature. Using the same general procedure, the new enol esters 14–17 were prepared from biacetyl and ethyl chloroformate, methoxalyl chloride, trifluoroacetic anhydride,

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(3) Arcamone, F.; Bernardi, L.; Giardino, P.; Patelli, B.; DiMarco, A.; Casazza, A. M.; Pratesi, G.; Regiani, P. *Cancer Treat. Rep.* **1976**, *60*, 829.

(4) (a) Wong, C. M.; Popien, D.; Schwenk, R.; Te Raa, J. *Can. J. Chem.* **1971**, *49*, 2412. (b) Arcamone, F.; Bernardi, L.; Patelli, B.; DiMarco, A. British Patent 2 601 785, 1975. (c) Suzuki, F.; Glein, R. D.; Trenbeath, S.; Sih, C. J. *Tetrahedron Lett.* **1977**, 2303. (d) Jackson, D. K.; Narashimhan, L.; Swenton, J. S., *J. Am. Chem. Soc.* **1979**, *101*, 3989. (e) Kende, A. S.; Curran, D. P.; Tsay, Y. G.; Mills, J. E. *Tetrahedron Lett.* **1977**, 3537. (f) Wiseman, J. R.; French, N. I.; Hallmark, R. K.; Chiong, K. G. *Ibid.* **1978**, 3765. (g) Kelly, T. R.; Tsong, W. G. *Ibid.* **1978**, 4457. (h) Garland, R. B.; Palmer, J. R.; Schultz, J. A.; Sollman, P. B.; Pappo, R. *Ibid.* **1978**, 3669. (i) Krohn, K.; Tolkiehn, K. *Ibid.* **1978**, 4023.

(5) Kerdesky, F. A.; Ardecky, R. J.; Lakshmikantham, M. V.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1992.

(6) Ardecky, R. J.; Kerdesky, F. A.; Cava, M. P. *J. Org. Chem.* **1981**, *46*, 1483.

(7) Wharton, P. S.; Aw, B. J. *J. Org. Chem.* **1966**, *31*, 3787.

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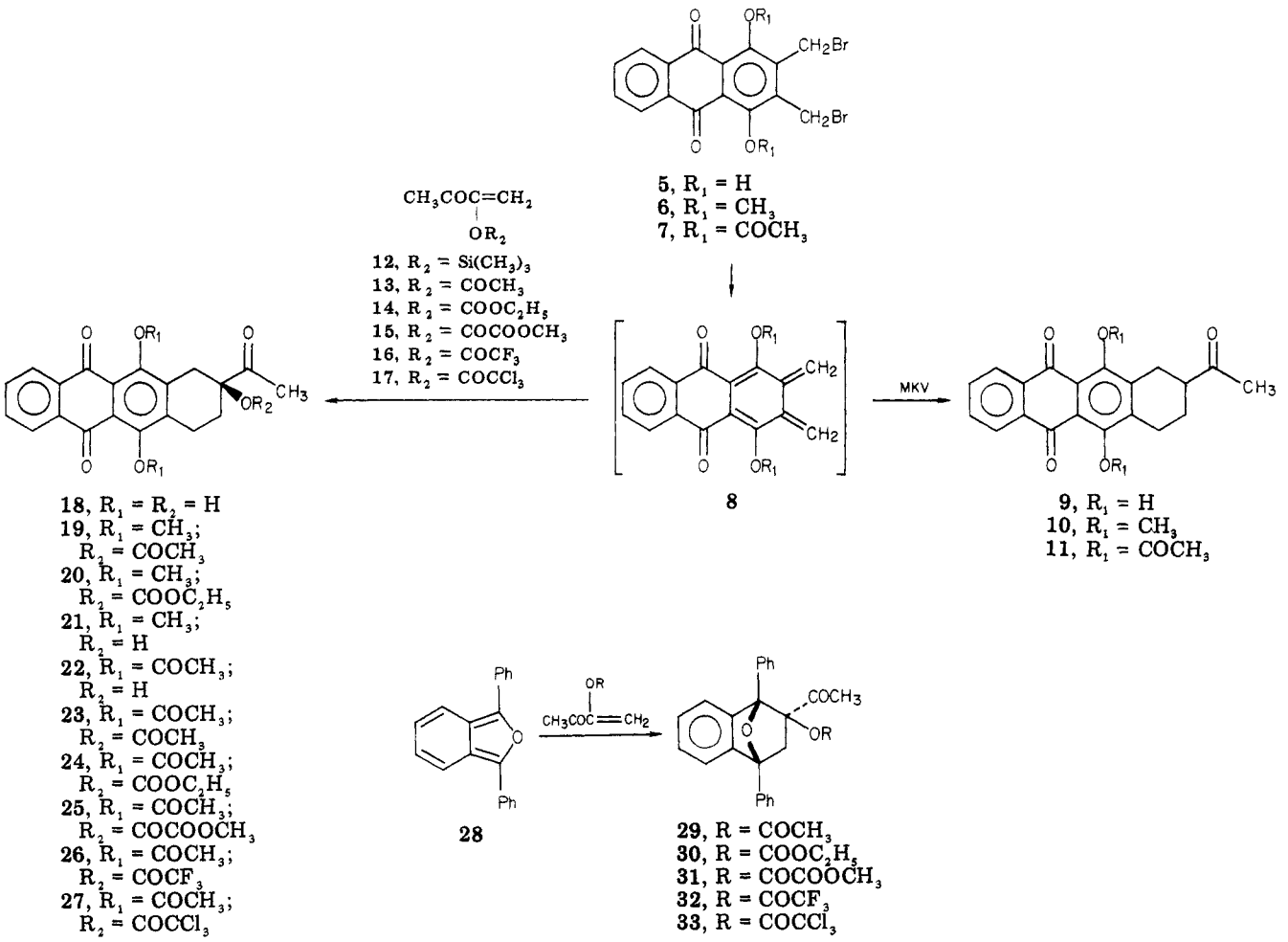
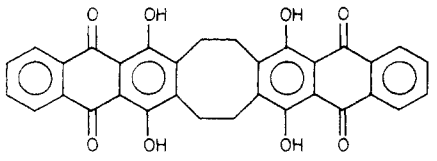
Scheme I



and trichloroacetyl chloride, respectively. The enol esters **13–17** were characterized both spectroscopically and as their nicely crystalline adducts (**29–33**) with 1,3-diphenylisobenzofuran (**28**).

The three anthraquinone dibromides used in this study were the previously described dihydroxy dibromide **5**,[5] its dimethyl ether **6**,[5] and the new diacetate derivative **7**, which was obtained in 94% yield by the acid-catalyzed acetylation of **5**. All Diels–Alder reactions were carried out under similar conditions in dimethylacetamide (DMA) by using excess dienophile and a preparative quantity (1 g) of the appropriate dibromide. The TBO adducts were isolated after aqueous desilylation, and the adduct from dibromide **6** and the enol oxalate **15** could be isolated only as the hydrolyzed product **21**. The adducts from dibromide **7** and the dienophiles **12–17** were isolated as the hydroxy ketone **18**, after alkaline hydrolysis.

The yields of tetracyclic ketones derived from dibromides **5–7** and the various biacetyl monoenol derivatives are shown in Table I. The dihydroxy dibromide **5** proved to be synthetically useless in attempted reactions with the enol esters **13–15**: no adduct at all was isolated, either before or after hydrolysis. The major product from these reactions was the dimeric product (**34**). On the other hand, the diacetoxy dibromide **7** gave adducts with all six enol derivatives **12–17**, the best yield (25%) being obtained from enol acetate **13**. The very poor yields (2%) from the trihaloacetyl esters **16** and **17** may be attributed to the instability of trifluoroacetate **16**, which begins to blacken even when freshly distilled, and to the exothermic decomposition of trichloroacetate **17** by iodide ion, a reaction which may liberate dichloroketene by fragmentation. The best yield (**19**, 46%) was obtained from the dimethoxy dibromide **6** and enol acetate **13**; the yield of the product (**20**, 39%) from **6** and enol carbonate **14** was almost as good. Since compound **6** may be prepared in 78% yield from 2,3-dimethylquinizarin (see Experimental Section), compound **19** is now available from 2,3-dimethylquinizarin in 36% overall yield. A search for efficient methods of conversion of **19** to 4-demethoxydaunomycinone (**4**) is actively being pursued in our laboratory.



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Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass, infrared (KBr), and ultraviolet spectra were determined by using Perkin-Elmer 270B, 137, and 202 spectrometers, respectively. NMR spectra were recorded on Varian 60, Varian EM-360, and Bruker 250 FT machines of $CDCl_3$ solutions (unless otherwise stated) containing Me_4Si as an internal standard and are reported in δ units (J values are in hertz). Elemental analyses were performed by Galbraith Laboratories. All organic extracts were washed and dried over anhydrous Na_2SO_4 prior to filtration and evaporation.

1,4-Dihydroxy-2,3-bis(bromomethyl)anthraquinone (5). In a 2000-mL three-necked flask were placed 20.00 g of 2,3-dimethylquinizarin, 1.00 g of benzoyl peroxide, and 1000 mL of

tetrachloroethylene. The mixture was heated until all the solid dissolved, and then 48.0 g of bromine in 50 mL of tetrachloroethylene was added slowly with irradiation with a sunlamp. The reaction mixture was refluxed while being irradiated for 20 h and then cooled. Filtration of the resulting red dibromide gave 29.9 g (94%) of (5).[5]

1,4-Dimethoxy-2,3-bis(bromomethyl)anthraquinone (6). In a 500 mL round-bottom flask were placed 5.00 g of 1,4-dimethoxy-2,3-dimethylanthraquinone, 5.00 g of 1,3-dibromo-5,5-dimethylhydantoin, and 300 mL of CCl_4. The reaction was refluxed for 4 h and cooled. The precipitate was filtered off and the filtrate concentrated (Buchi). The residue was recrystallized from hexane–CH_2Cl_2, giving 6.50 g (98%) of 6.[5]

1,4-Diacetoxy-2,3-bis(bromomethyl)anthraquinone (7). In a 500-mL flask was placed 5.00 g of 1,4-dihydroxy-2,3-bis(bromomethyl)anthraquinone (5) and 400 mL of acetic anhydride and 0.1 mL of concentrated sulfuric acid. The mixture was refluxed for 1 h and cooled. The acetic anhydride was removed (Buchi) and the residue recrystallized from CH_2Cl_2–MeOH, giving yellow needles: 5.62 g (94%); mp 216–218 °C; NMR δ 2.56 (s, 6 H, OAc), 4.62 (br, 4 H, CH_2Br), 7.73–8.16 (m, 4 H, Ar); IR 1782 cm^{-1}; UV (CH_3CN) λ_{max} 259 nm (log ϵ, 4.78), 280 (4.18), 345 (3.75); mass spectrum m/e (relative intensity) 426 (M^+, 26), 347 (10), 266 (100). Anal. Calcd for $C_{20}H_{14}O_6Br_2$: C, 48.31; H, 2.70; Br, 30.61. Found: C, 48.09; H, 2.89; Br, 30.85.

8-Acetyl-7,8,9,10-tetrahydro-6,11-diacetoxy-5,12-naphthacenedione (11). In a 250-mL flask were placed 26.0 mL of DMA, 53 mL of methyl vinyl ketone, and 38 g of sodium iodide. The mixture was stirred and heated to 65–70 °C. At this point a solution of 5.00 g of 1,4-diacetoxy-2,3-bis(bromomethyl)-anthraquinone (7) in 60 mL of DMA was slowly added. After 2 h the mixture was poured into 800 mL of water and ice. The resulting yellow precipitate was chromatographed (SiO_2; C_6H_6/CH_2Cl_2/CH_2Cl_2–EtOAc (5%)), giving 2.9 g (71%) of 11: mp 197–199 °C; NMR δ 1.92 (br, 2 H, CH_2), 2.26 (br, 1 H, CH), 2.28 (s, 3 H, CH_3), 2.52 (s, 3 H, OAc), 2.53 (s, 3 H, OAc), 2.60–3.20 (br, 4 H, benzylic), 7.36–8.17 (m, 4 H, Ar); IR 1702, 1760 cm^{-1}; UV (CH_3CN) λ_{max} 256 nm (log ϵ, 4.92), 277 (4.36), 390 (3.78); mass spectrum, m/e (relative intensity) 420 (M^+, 1), 378 (11), 336 (100), 293 (63). Anal. Calcd for $C_{24}H_{20}O_7$: C, 68.57; H, 4.80. Found C, 68.25; H, 4.77.

Preparation of 3-(Acyloxy)-3-buten-2-ones. A standard procedure for the preparation of dienophiles 13–17 from 2,3-butanedione is illustrated below. To a stirred solution of 2,3-butanedione (0.2 mol, 17.2 g) and Et_3N (0.2 mol, 20.2 g) in CH_2Cl_2 (200 mL) at 0 °C was added slowly a solution of the acetylating agent (0.2 mol) in 50 mL of CH_2Cl_2. The reaction mixture was allowed to warm to room temperature and stirred overnight. To the stirred solution was added 200 mL of hexane. The precipitate was filtered, and the solution was concentrated (Buchi) and distilled bulb to bulb (Kugelrohr), giving the dienophiles 13–17.

3-Acetoxy-3-buten-2-one (13): 10.9 g (43%); bp 90–95 °C (2.5 mm); NMR δ 2.21 (s, 3 H, OAc), 2.35 (s, 3 H, CH_3), 5.63 (d, 1 H, J = 2, vinyl), 5.94 (d, 1 H, J = 2, vinyl); IR 1714, 1767 cm^{-1}; mass spectrum, m/e (relative intensity) 128 (M^+, 23), 111 (100), 85 (70).

3-[(Ethoxycarbonyl)oxy]-3-buten-2-one (14): 20.27 g (64%); bp 115–120 °C (0.5 mm); NMR δ 1.36 (t, 3 H, J = 7, CH_3), 2.40 (s, 3 H, CH_3), 4.29 (q, 2 H, J = 7, CH_2), 5.74 (d, 1 H, J = 2.6, vinyl), 5.99 (d, 1 H, J = 2.6, vinyl); IR 1707, 1765 cm^{-1}; mass spectrum, m/e (relative intensity) 129 (40), 111 (100), 86 (98).

3-(Methoxalyloxy)-3-buten-2-one (15): 20.8 g (68%); bp 120–130 °C (0.5 mm); NMR δ 2.41 (s, 3 H, CH_3), 4.00 (s, 3 H, OMe), 5.94 (d, 1 H, J = 3.2, vinyl), 6.24 (d, 1 H, J = 3.2, vinyl); IR 1695, 1754, 1770 cm^{-1}; mass spectrum, m/e (relative intensity) 86 (21), 72 (21), 70 (32), 59 (100).

3-(Trifluoroacetoxy)-3-buten-2-one (16): 18.64 g (51%); bp 80–85 °C (0.5 mm); NMR δ 2.41 (s, 3 H, CH_3), 5.93 (d, 2 H, J = 3.4, vinyl), 6.17 (d, 1 H, J = 3.4, vinyl); IR 1711, 1814 cm^{-1}; mass spectrum, m/e (relative intensity) 182 (M^+, 9), 113 (22), 97 (11), 69 (100).

3-(Trichloroacetoxy)-3-buten-2-one (17): 20.3 g (44%); bp 110–115 °C (0.5 mm); NMR δ 2.30 (s, 3 H, CH_3), 5.78 (d, 1 H, J = 3.2, vinyl), 6.05 (d, 1 H, J = 3.2, vinyl); IR 1711, 1800 cm^{-1}; mass spectrum, m/e (relative intensity) 117 (100), 113 (50), 69 (23).

Diels–Alder Reactions of 3-(Acyloxy)-3-buten-2-ones with Diphenylisobenzofuran (28). A standard procedure for the preparation of the adducts 29–33 from diphenylisobenzofuran 28 and dienophiles 13–17 is illustrated below.

Diphenylisobenzofuran (0.5 g) was dissolved in 8 mL of CH_2Cl_2 (dry). To this mixture was added 0.5 g of the dienophile, and the progress of the reaction was checked by TLC. After approximately 2 h the CH_2Cl_2 was removed under vacuum (Buchi), and the resulting oil was chromatographed by using silica gel and methylene chloride to yield a white crystalline compound that was crystallized from MeOH–CH_2Cl_2.

Adduct 29: 0.38 g (52%); mp 148–150 °C; NMR δ 1.96 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3), 2.50 (d, 1 H, J = 13.6, CH_2), 3.48 (d, 1 H, J = 13.6, CH_2), 7.18–7.73 (m, 14 H, Ar); IR 1716, 1766 cm^{-1}; UV (CH_3CN) λ_{max} 250 nm (log ϵ, 4.74), 257 (5.11), 265 (5.14), 271 (4.74); mass spectrum, m/e (relative intensity) 270 (100), 241 (22). Anal. Calcd for $C_{27}H_{22}O_5$: C, 72.04; H, 5.20. Found: C, 72.17; H, 5.20.

Adduct 30: 0.60 g (75%); mp 167–169 °C; NMR δ 1.26 (t, 3 H, J = 7.0, CH_3), 1.99 (s, 3 H, CH_3), 2.63 (d, 1 H, J = 13.6, CH_2), 3.47 (d, 1 H, J = 13.6, CH_2), 4.10 (m, 2 H, CH_2), 7.20–7.80 (m, 14 H, Ar); IR 1724, 1763 cm^{-1}; UV (CH_3CN) λ_{max} 247 nm (log ϵ, 5.08), 253 (5.44), 260 (5.52), 268 (5.11); mass spectrum, m/e (relative intensity) 270 (100), 241 (25). Anal. Calcd for $C_{27}H_{24}O_5$: C, 75.68; H, 5.65. Found: C, 75.38; H, 5.72.

Adduct 31: 0.72 g (85%); mp 158–160 °C; NMR δ 2.04 (s, 3 H, CH_3), 2.63 (d, 1 H, J = 13.6, CH_2), 3.45 (d, 1 H, J = 13.6, CH_2), 3.87 (s, 3 H, CH_3), 7.20–7.80 (m, 14 H, Ar); IR 1716, 1760 cm^{-1}; UV (CH_3CN) λ_{max} 246 nm (log ϵ, 4.60), 253 (5.30), 260 (5.30), 268 (4.87); mass spectrum m/e (relative intensity) 270 (100), 241 (25). Anal. Calcd for $C_{27}H_{22}O_6$: C, 72.04; H, 5.20. Found: C, 72.17; H, 5.20.

Adduct 32: 0.40 g (47%); mp 140–141 °C; NMR δ 2.05 (s, 3 H, CH_3), 2.64 (d, 1 H, J = 13.6, CH_2), 3.42 (d, 1 H, J = 13.6, CH_2), 7.20–7.70 (m, 14 H, Ar); IR 1726, 1798 cm^{-1}; UV (CH_3CN) λ_{max} 246 nm (log ϵ, 4.60), 253 (5.30), 260 (5.30), 268 (4.87); mass spectrum, m/e (relative intensity) 270 (100), 241 (21). Anal. Calcd for $C_{26}H_{19}O_4F_3$: C, 69.02; H, 4.26; F, 12.60. Found: C, 69.20; H, 4.26; F, 12.74.

Adduct 33: 0.72 g (76%); mp 199–201 °C; NMR δ 2.02 (s, 3 H, CH_3), 2.56 (d, 1 H, J = 13.6, CH_2), 3.45 (d, 1 H, J = 13.6, CH_2), 7.00–7.80 (m, 14 H, Ar); IR 1726, 1782 cm^{-1}; UV (CH_3CN) λ_{max} 245 nm (log ϵ, 4.74), 253 (5.22), 260 (5.30), 269 (4.90); mass spectrum, m/e (relative intensity) 270 (100), 241 (24), 117 (26). Anal. Calcd for $C_{26}H_{19}O_4Cl_3$: C, 62.23; H, 3.82; Cl, 21.20. Found: C, 62.01; H, 3.81; Cl, 21.39.

***o*-Quinodimethane Trapping with 3-(Acyloxy)-3-buten-2-ones.** A standard procedure for the preparation of adducts 19–27 from the dibromides 6 and 7 and dienophiles 12–17 is illustrated.

Dibromide 6 or 7 (1.00 g) dissolved in 24 mL of DMA was added slowly to a mixture of 7 g sodium iodide, 8 mL of DMA, and 6 g of the dienophile at 65–70 °C. The addition was completed after approximately 0.5 h, and the mixture was checked for the disappearance of the dibromide by TLC (approximately 2 h). The mixture was then added to 400 mL of water and filtered. The precipitate was either chromatographed (19–21) or hydrolyzed and chromatographed (22–27) to yield the corresponding tetracyclic ketone.

8-Acetyl-8-acetoxy-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (19): 0.43 g (46%); mp 174–175 °C; NMR δ 2.00–2.42 (m, 2 H, CH_2), 2.06 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 2.80–3.16 (m, 2 H, benzylic), 3.25 (d, 1 H, J = 18, benzylic), 3.39 (d, 1 H, J = 18, benzylic), 3.91 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 7.74–8.21 (m, 4 H, Ar); IR 1724, 1753 cm^{-1}; UV (CH_3CN) λ_{max} 257 nm (log ϵ 4.55), 275 (4.55), 367 (3.63) mass spectrum, m/e (relative intensity) 422 (M^+, 5), 362 (100), 347 (34), 337 (43). Anal. Calcd for $C_{24}H_{22}O_7$: C, 68.24; H, 5.25. Found: C, 68.40; H, 5.42.

8-Acetyl-8-[(ethoxycarbonyl)oxy]-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (20): 0.39 g (39%); mp 168–169 °C; NMR δ 1.29 (t, 3 H, J = 7.0, CH_3), 2.00–2.47 (m, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.83–3.17 (m, 2 H, benzylic), 3.30 (d, 1 H, J = 18, benzylic), 3.43 (d, 1 H, J = 18, benzylic), 3.91 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.23 (m, 2 H, CH_2), 7.72–8.21 (m, 4 H, Ar); IR 1731, 1745 cm^{-1}; UV (CH_3CN) λ_{max} 256 nm (log ϵ 4.54), 278 (4.05), 366 (3.68); mass spectrum, m/e (relative intensity) 452

(M^+, 2), 362 (100), 347 (29), 331 (23). Anal. Calcd for $C_{25}H_{24}O_8$: C, 66.37; H, 5.35. Found: C, 66.59; H, 5.52.

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Registry No. 5, 77422-59-4; 6, 67122-25-2; 7, 79919-76-9; 9, 77422-62-9; 10, 77422-60-7; 11, 76811-56-8; 12, 42082-94-0; 13, 13207-03-9; 14, 79899-11-9; 15, 79899-12-0; 16, 79899-13-1; 17, 79899-14-2; 18, 76527-50-9; 19, 79899-15-3; 20, 79899-16-4; 21, 77422-64-1; 22, 79899-17-5; 23, 65818-84-0; 24, 79899-18-6; 25, 79899-19-7; 26, 79899-20-0; 27, 79899-21-1; 28, 5471-63-6; 29, 79899-22-2; 30, 79899-23-3; 31, 79899-24-4; 32, 79899-25-5; 33, 79899-26-6; 1,4-dihydroxy-2,3-dimethylanthraquinone, 25060-18-8; 1,4-dimethoxy-2,3-dimethylanthraquinone, 67122-24-1; methyl vinyl ketone, 78-94-4; 2,3-butanedione, 431-03-8.

Synthesis of Selectively Protected Tri- and Hexaamine Macrocycles

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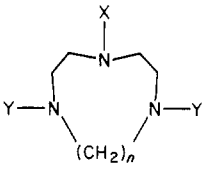
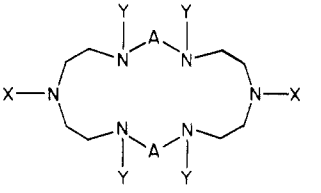
A general route to tri- and hexaamine macrocycles containing selectively protected diethylenetriamine units has been developed. Condensation of the *N'*-benzoyl-*N,N''*-bis(*p*-tolylsulfonyl)diethylenetriamine *N,N''*-disodium salt with bissulfonate esters of two-, four-, and six-carbon diols at high reactant concentrations gave the corresponding 9- and 18- (85% and <1%), 11- and 22- (30% and 20%), and 13- and 26- (56% and 17%) membered tri- and hexaamine macrocycles, respectively. The benzoyl group was selectively removed with potassium *tert*-butoxide in ca. 90% yield, and the macrocycles were conveniently separated by chromatography. Details of the synthetic procedures and characterization of the new selectively protected tri- and hexaamine macrocycles are described.

A significant property of macrocyclic polyamines is their ability to form stable complexes with transition metal ions. In this regard, cyclic tetraamines have been the most extensively studied macrocycles.[1,2] However, there is now considerable interest in elucidating the coordination properties of tri- and hexaamine macrocycles due to the novel structural features of the resulting metal complexes. Recent studies[3-5] with small, cyclic triamines such as **1a** (n = 2, 3) indicate that the metal complexes have cis coordination geometries and distorted structures. Current work with the larger hexaamines **2a** (n = 5)[6] and **2b**[7] shows that they readily bind two metals to yield discrete binuclear complexes. Binuclear compounds of these ligands may be especially useful as models for bimetallic metalloproteins and as bimetallic catalysts.

Synthesis of the triamines **1a** (n = 2, 3) is conveniently accomplished by using Richman and Atkins'[8] modification of the method of Koyama and Yoshino.[9] The symmetric 18-membered hexaamine **2a** (n = 2) has been synthesized by an adaptation of this general procedure.[10] The synthetic method relies on the condensation of bissulfonamide sodium salts and compounds having sulfonate ester leaving groups to facilitate ring closure at high reactant concentrations. This obviates the need for employing high-dilution or template techniques. When compounds **1b** (n = 5, 6) were synthesized by this procedure, it was noted that the corresponding 2:2 cyclization products **2c** were also formed in 10-15% yield.[8] It has been suggested[11] that restricted rotation in the tosylated reactants (i.e., internal entropy effects) are the reason for the high yields achieved in these cyclizations. We are unaware of any reports detailing the application of this procedure to provide selectively protected macrocycles of types **1d** and **2f**, although this possibility has been mentioned as an extension of this method.[8] A route to the 24-membered selectively protected hexaamine **2d** which uses high-dilution methods in the



1a, X = Y = H
b, X = Y = tosyl
c, X = benzoyl; Y = tosyl
d, X = H; Y = tosyl



2a, X = Y = H; A = $(CH_2)_n$
b, X = Y = H; A = $(CH_2CH_2)_2O$
c, X = Y = tosyl; A = $(CH_2)_n$
d, X = H; Y = tosyl; A = $(CH_2CH_2)_2O$
e, X = benzoyl; Y = tosyl; A = $(CH_2)_n$
f, X = H; Y = tosyl; A = $(CH_2)_n$

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