H-4) and two methyl (acetylmethyl groups) signals appeared at 2.02 (3 H, acetyl in $-COCH_3$, attached to C-4). MS of **2** (m/z): 320 (M, 0.86), 260 (M - 60, 14), 234 (M - 86, 58), 200 (M - 120, 54), 174 ($C_{13}H_{18}$, 100). From the double quantum filtered COSY of **2**, we can also discover the coupling between H-4a (4.43) and H-3 (2.46), H-5a (2.27) and H-5b (1.75), H-11a (2.20) and H-11b (2.29), and H-7a (1.68) and H-7b (0.69 ppm). The NOE data of **2** are listed in Table I.

MS (m/z) of **4**: 320 (M, 0.56), 260 (M - 60, 20), 200 (M - 120, 40), 185 (26), 174.1404 ($C_{13}H_{18}$, calcd 174.1408, 100), 159 (93), 86 (21), 60 (5). IR of **4**: 1730 cm^{-1} (C=O), hydroxyl signal disappeared. Its ^1H-NMR shows quite similar peaks to that of **3** except that the protons on carbons bonded to oxygen are moved downfield (see above) and the two methyl groups (acetylmethyl groups attached to C-12 and C-5) signals appeared at 2.01 and 1.99 ppm. ^1H-^1H COSY of **4** are presented in the Introduction. NOE results for **4** are listed in Table I.

The structures of **1** and **3** were further confirmed by comparison of the spectral data with surperic acid **6** and their parent sterpurene **5**. The comparable ^1H-NMR data for them are listed in Table II.

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Registry No. 1, 138835-50-4; 2, 138835-52-6; 3, 138835-51-5; 4, 138835-53-7.

Regioselective Bromination and Fluorination of Apogossypol Hexamethyl Ether

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Apogossypol hexamethyl ether (**3**) was brominated upon treatment with any of a number of brominating agents. Each reagent gave a different bromo derivative. Thus, the reaction of **3** with bromine in CCl_4 with ultrasound irradiation gave **4** in 71% yield. When treated with bromine and iron powder in CCl_4 at -5 °C, **3** afforded **5** in 65% yield. The reaction of **3** with pyridinium bromide perbromide in 1,2-dichloroethane at 65-70 °C furnished **6** in 70% yield. Treatment of **3** with NBS in DMF at room temperature afforded **7** in 30% yield. Treatment of **4** and **5** with potassium fluoride and 18-crown-6 in acetonitrile at room temperature furnished **8** and **9**, respectively. An attempt to introduce trifluoromethyl groups at the 8 and 8′ positions of **4**, by treatment with cuprous iodide and sodium trifluoroacetate, failed and gave only **10**. Interestingly, but unexpectedly, **11** and **12** were produced upon treating **4** with silver(I) fluoride.

Introduction

Gossypol (**1**),[1,2] a toxic pigment present in cotton seed, was first isolated, in the form of its crystalline acetic acid complex, by Marchlewski.[3] Its structure was deduced by Adams and co-workers[4] in 1938, but it was not until 1957 that Shirley and Dean[5] provided the first conclusive proof of the structure of gossypol by independently synthesizing its two derivatives apogossypol hexamethyl ether (**3**) and desapogossypol hexamethyl ether. Over the next 20 years, evidence that gossypol and its derivatives have vlue as anticancer agents, antibiotics, and pesticides gradually accumulated.[2] In 1978, Chinese investigators reported gossypol to be an effective male antifertility agent.[6] This revelation generated enormous interest and, furthermore, suggested that fluoro derivatives of gossypol might also be biologically active. Herein, we describe the synthesis of several bromo derivatives of apogossypol hexamethyl ether. Such compounds should prove to be valuable as starting materials for the synthesis of novel compounds structurally related to gossypol, in particular those that contain fluorine.

Results and Discussion

Gossypol (**1**), when treated with base, provides apogossypol (**2**), which can be readily methylated to furnish the corresponding hexamethyl ether **3**.[4,5,7,8] We found that **3** can be brominated by treatment with any of a number of brominating agents. Each reagent gives a different bromo derivative. For example, the bromination of **3** by treatment with bromine in CCl_4 at room temperature gave a separable mixture of **4**, **5**, and **6**. The ratio of these three products did not change significantly as the reaction temperature was increased. However, when a CCl_4 solution of **3** and bromine was irradiated with ultrasound, only the tetrabromide **4** was produced, and in 71% yield. The reaction of **3**, bromine, and iron powder at -5 °C gave the tribromide **5** as the main product (65% yield). Interestingly, when **3** was allowed to react with pyridinium bromide perbromide in 1,2-dichloroethane at 65-70 °C, the dibromide **6** was produced in 70% yield. Treatment of **3** with the NBS-DMF complex[9] at room temperature pro-

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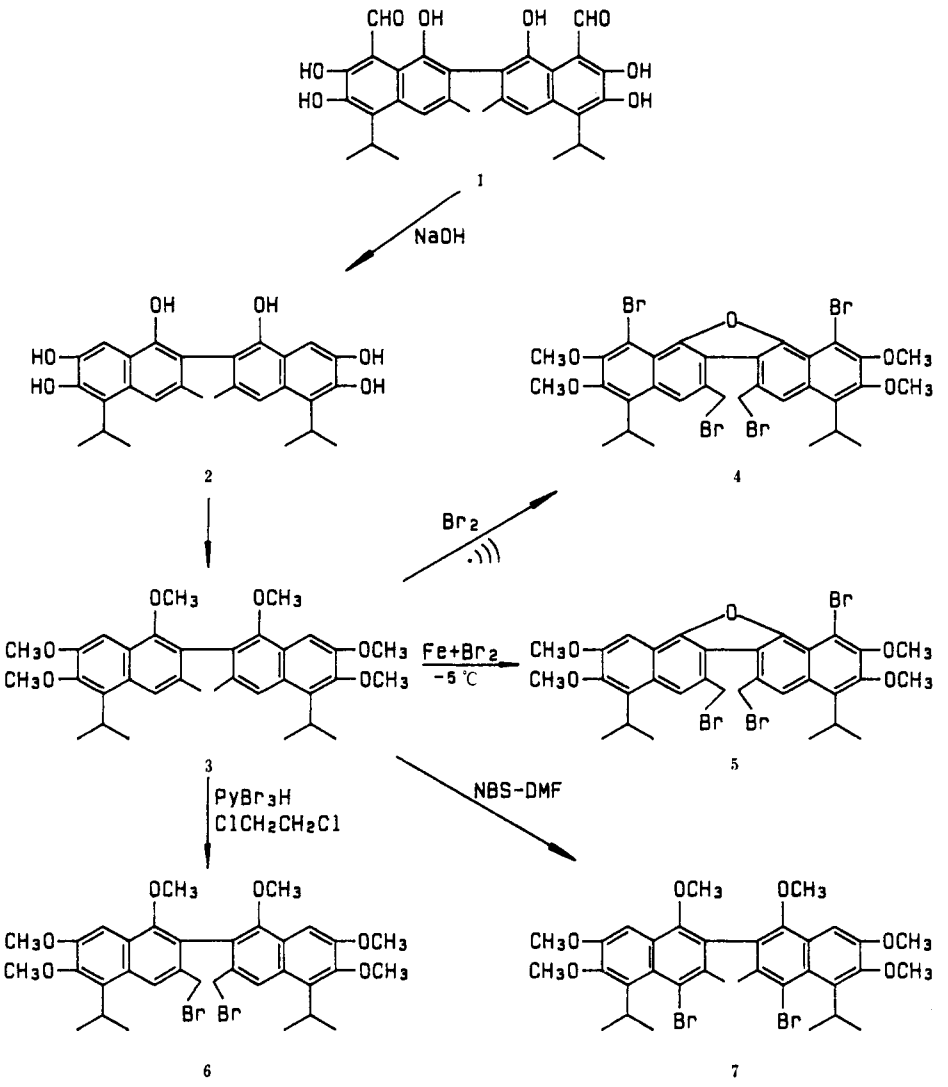
0022-3263/92/1957-2316$03.00/0

Scheme I



vided the dibromide **7**, a regioisomer of **6**, selectively. Compounds **4**, **5**, and **6** were not detected in the reaction mixture. Thus, depending upon which brominating agent was used, either **4**, **5**, **6**, or **7** could be selectively produced in good yield (Scheme I).

The novel structure of **4** was inferred from its spectra and the results of elemental analysis. The presence in the mass spectrum of a parent ion at $m/e = 816$ and the results of elemental analysis are consistent with a molecular formula of $C_{32}H_{32}Br_4O_5$. The ^1H NMR spectrum shows signals at δ 1.60 (a doublet, 12 H) and δ 4.06 (a multiplet, 2 H) attributable to the protons of two identical isopropyl groups. Signals (two singlets, 12 H) that can be attributed to the protons of the 6-, 6′-, 7- and 7′-methoxy groups appear at δ 4.01. The absence of a signal characteristic of the functional group Ar-CH_3 (which appears at δ 2.10 in the spectrum of **3**) and the presence of a broad singlet (4 H) at δ 5.71 indicate that **4** bears 3- and 3′-bromomethyl groups. The chemical shift (δ 8.59) and the broadness of the only aromatic proton signal (a singlet, 2 H) suggest that the aromatic protons of **4** are located on the carbon atoms ortho to those that bear the bromomethyl groups. Because no signal attributable to the 1- and 1′-methoxy groups (which appears at δ 4.02 in the spectrum of **3**) is present and also because the results of elemental analysis show that **4** possesses only five oxygen atoms, it can reasonably be assumed that **4** is a cyclic ether that incorporates a C-1–O–C-1′ linkage. The two remaining bromine atoms of **4** must therefore be located at C-8 and C-8′. That the aromatic proton signal appears at δ 8.59, further downfield by 1.2 ppm than any signal in the spectrum of its parent (**3**), cannot be explained in terms of the simple diamagnetic shielding effect exerted by neighboring ring substituents.[9] It can only be the result of the anisotropic deshielding effect of a ring current. Therefore, in **4** the two naphthalene rings must be coplanar. The results of NOE experiments provided additional evidence that the structure of **4** is that which is depicted. A clear enhancement of the aromatic proton signal (δ 8.59) was seen upon irradiation of both the benzylic proton signal (δ 5.71) and the signal due to the tertiary protons of the 5- and 5′-isopropyl groups (δ 4.06). On the other hand, irradiation of the signal due to the 7- and 7′-methoxy groups (δ 4.01) produced no signal enhancement.

The structures of **5**, **6**, and **7** were similarly inferred. How **4** and **5** were formed is as yet unclear. However, it is reasonable to assume that, under the acidic conditions that attend their formation, at least one of the oxygen–aliphatic carbon bonds of **3** (or a bromide derived therefrom) is cleaved. An intramolecular nucleophilic attack

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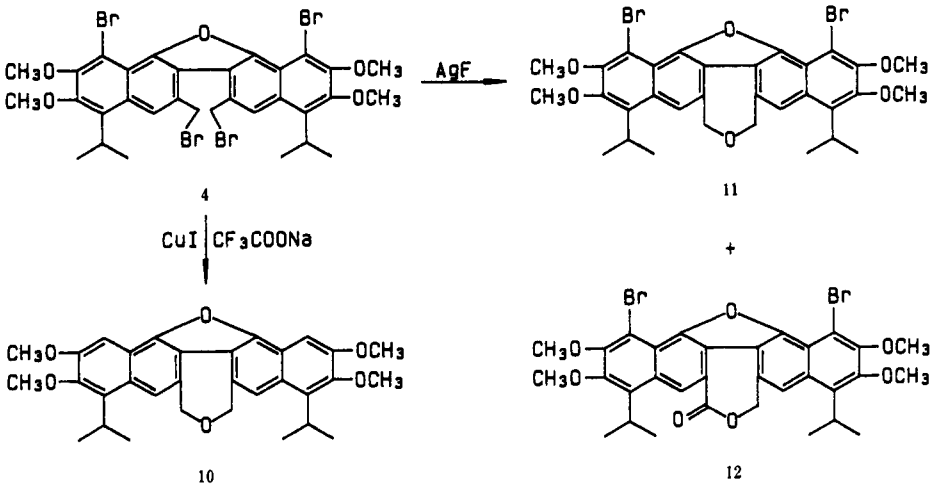
Scheme II

4 R_1=R_2=Br
5 R_1=H, R_2=Br

8 R_1=R_2=Br
9 R_1=H, R_2=Br

Scheme III



by the naphthol so formed, on a suitably positioned aromatic carbon atom that bears a protonated methoxy group (or a methoxy group coordinated with a Lewis acid, e.g., $FeBr_3$), could then yield a cyclic ether. Obviously, thermodynamic factors play an important role in such a nucleophilic attack because the product is a *five*-membered cyclic ether.

Treatment of 4 with KF and 18-crown-6 in acetonitrile[11] at room temperature provided 8 in good yield. A variety of conditions were examined. The best yield (>90%) were obtained when the concentration of KF was about 0.4 M. Similar treatment of 5 furnished 9 in 85% yield (Scheme II).

Attempts to directly fluorinate the aromatic rings of 3 by treatment with F_2, $CsSO_4F$, or CH_3COOF under a variety of conditions failed.[12-14] We then attempted to regiospecifically introduce a trifluoromethyl group into both the 8 and 8′ positions of 3 indirectly. However, the reaction of 4 with CF_3COONa in the presence of CuI[15,16] gave not the expected 8,8′-bis(trifluoromethyl) analogue, but 10 instead. The trifluoromethylation of aryl halides by sodium trifluoroacetate has been studied by Chambers and co-workers.[15] They considered the reaction to be a copper-assisted nucleophilic aromatic substitution. However, the results of the attempted trifluoromethylation of 4 cannot be explained in such terms.

Treatment of 4 with AgF failed to give the expected fluorinated derivative. Instead, two products of cyclization 11 and 12, were formed (Scheme III). Treatment of 4 with sodium sulfide/*tert*-butyl alcohol/benzene also gave 11, in 50% yield. At attempt to replace the benzylic bromine atoms of 4 with pentafluorophenyl groups by treatment of 4 with tetrakis(pentafluorophenyl)tin and $Pd(PPh_3)_4$[17] failed. Again, 11 was produced. The results of all three reactions indicate that, under certain conditions, 4 is quite easily hydrolyzed.

The structure shown for 12 is consistent with the compound's spectra and elemental analysis results. The presence in the mass spectrum of a parent ion at m/e = 684 and the analytical data indicate a molecular formula of $C_{32}H_{30}Br_2O_7$. A strong IR absorption band at 1715 cm^{-1} shows that 12 possesses a carbonyl group. A peak in the mass spectrum at m/e = 640 ($M^+ - 44$), indicative of the loss of the elements of CO_2 from the parent ion, suggests that 12 is an ester, perhaps a lactone. The ^1H NMR spectrum shows signals at δ 1.56–1.65 (two doublets, 12 H) and δ 3.98 (a multiplet, 2 H) attributable to the protons of two different isopropyl groups. The second signal is partially obscured by the first of four singlets (3 H each) which appear at δ 4.01–4.06 and indicate the presence of four methoxy groups, each of which exists in a different environment. A singlet (2 H) attributable to the secondary protons of the functional group $ArCH_2O$ appears at δ 5.78. Two aromatic proton signals (2 H each) are present at δ 8.29 and 9.11. Because no signal that can be attributed to protons present at C-8 and C-8′ appears, it can reasonably be assumed that a bromine atom is present at both of those positions. The signal at δ 9.11 is further downfield by 0.55 ppm than the most downfield signal (δ 8.56) in the spectrum of 4, the parent compound of 12. Such a downfield shift is significantly greater than that which would be expected to be the result of simple diamagnetic deshielding by neighboring ring substituents.[9] It could, however, be a consequence of the anisotropic deshielding effect exerted by a pendant ester carbonyl group attached

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to an adjacent aromatic carbon atom. NOE experiments gave results that supported the belief that 12 is of the structure shown. Thus, an enhancement of the aromatic proton signal at δ 8.29 was seen upon irradiation of the benzylic proton signal at δ 5.78. Irradiation of the signal at δ 3.98 (due to the tertiary protons of the 5- and 5′-isopropyl groups) produced a marked enhancement of both aromatic proton signals.

Because 4, 5, 8, 9, 10, 11, and 12 appear to be planar and have $4n + 2$ ($n = 5$) π electrons, they are presumed to be fully aromatic in character. Indeed, an X-ray crystallographic study of 11 showed that its two naphthalene rings are coplanar and that its carbon–carbon bonds are short as in aromatic compounds. It is the intense diamagnetic ring current of this sizable aromatic system that gives rise to the downfield shifts of the aromatic and benzylic proton signals.

Experimental Section

General. Melting points were determined with an X-4 melting point apparatus and are uncorrected. ^1H and ^{19}F NMR spectra were recoreded with a Varian XL-2900 spectrometer. TMS served as an internal standard for the proton spectra. Infrared spectra of Nujol mulls between KBr plates were measured with a Perkin-Elmer 983 spectrophotometer. Mass spectra were recorded with a Finnigan MAT spectrometer. Column chromatography was performed with glass columns loaded with TLC grade silica gel. 1,2-Dichloroethane and CCl_4 were distilled from P_2O_5. DMF and HMPA were distilled from CaH_2 under reduced pressure. All other solvents and reagents were purified by literature procedures.[18] All reactions requiring anhydrous conditions were performed under N_2 in oven-dried glassware. NMR data are tabulated as chemical shift (multiplicity, number of nuclei, assignment). Mass spectral data are tabulated as m/z (relative abundance).

5,5′-Diisopropyl-1,1′,6,6′,7,7′-hexamethoxy-3,3′-dimethyl-2,2′-binaphthalene (3). A mixture of gossypol–acetic acid (1) (10.0 g, 0.017 mol) and 40% aqueous NaOH (100 mL) was heated at 90 °C under N_2 for 4 h. The mixture was then poured into a mixture of ice and concd H_2SO_4. The resultant precipitate was collected by filtration and extracted with Et_2O. The extract was washed with water, dried (Na_2SO_4), and concentrated in vacuo to yield crude apogossypol (2), which was immediately dissolved in acetone (420 mL). Dry powdered K_2CO_3 (47 g, 0.34 mol) was added dropwise. The stirred mixture, under N_2, was refluxed for 20 h and then cooled to rt. The solid that separated from the solution was collected by filtration. It was washed (acetone and water) and dried to yield 6.3 of 3. The filtrate was concentrated in vacuo. The yellow solid that separated was collected by filtration. It was washed (water and Et_2O) and dried to yield an additional 3.0 g of 3 such that the total yield of the reaction was 9.3 g (92%) with a melting point of 271–273 °C.

6,6′,7,7′-Tetramethoxy-5,5′-diisopropyl-8,8′-dibromo-3,3′-bis(bromomethyl)dinaphtho[2,1-*b*:2′,1′-*d*]furan (4). A solution of 3 (2.27 g, 0.004 mol), Br_2 (8.0 g, 0.05 mol), and CCl_4 (130 mL) was kept in a water bath in an ultrasonic laboratory cleaner (35 W, 32 kHz) for 10 h. The resultant dark red solution was washed with 5% aqueous $NaHSO_3$ and water. After being dried over anhydrous Na_2SO_4, the organic phase was concentrated to provide a yellow foam, which was purified by column chromatography to yield 4 as a light yellow solid (2.41 g, 71%), mp 217–218 °C. ^1H NMR (CD_3COCD_3): δ 1.60 [d, 12 H, 2 $CH(CH_3)_2$], 4.01 (d, 12 H, 4 OCH_3), 4.06 [m, 2 H, 2 $CH(CH_3)_2$], 5.71 (s, 4 H, 2 $BrCH_2Ar$), 8.59 (s, 2 H, ArH). IR: 1573, 1538, 1038 cm^{-1}. MS: m/e 814 (35) 816 (52), 818 (35, M^+). Anal. Calcd for $C_{32}H_{32}O_5Br_4$: C, 47.06; H, 3.92; Br, 39.22. Found: C, 46.73; H, 3.90; Br, 39.10.

6,6′,7,7′-Tetramethoxy-5,5′-diisopropyl-8-bromo-3,3′-bis(bromomethyl)dinaphtho[2,1-*b*:2′,1′-*d*]furan (5). Fe powder (60 mg, 1 mmol) was added to a stirred solution (−5 °C) of 3 (550 mg, 1 mmol), Br_2 (970 mg, 6 mmol), and CCl_4 (40 mL). The resultant dark red mixture was stirred at the same temperature under N_2 for 5 h. The mixture was filtered. The filtrate was washed with 5% aqueous $NaHSO_3$ and water, dried (Na_2SO_4), and concentrated to provide a yellow foam. Purification of the foam by column chromatography (1:20 ethyl acetate/light petroleum ether) yielded 5 as yellow crystals (480 mg, 65%), mp 190–191 °C. ^1H NMR (CD_3COCD_3): δ 1.56–1.61 [q, 12 H, 2 $CH(CH_3)_2$], 4.16–3.95 [m, 14 H, 4 OCH_3, 2 $CH(CH_3)$], 5.69 (s, 4 H, 2 $BrCH_2Ar$), 8.00 (s, 1 H, ArH-8), 8.40 (s, 1 H, ArH-4), 8.50 (s, 1 H, ArH-4). IR: 1586, 1458, 1038 cm^{-1}. MS: m/e 734 (9), 736 (28), 738 (29), 740 (11, M^+), 655 (50), 657 (100), 659 (54, M^+ − Br). Anal. Calcd for $C_{32}H_{33}Br_3O_5$: C, 52.10; H, 4.48; Br, 32.56. Found: C, 52.44; H, 4.63; Br, 32.51.

1,1′,6,6′,7,7′-Hexamethoxy-5,5′-diisopropyl-3,3′-bis(bromomethyl)-2,2′-binaphthalene (6). To a stirred solution of pyridinium bromide perbromide (1.4 g, 4.4 mmol) in 1,2-dichloroethane (30 mL) at rt was added a solution of 3 (1.0 g, 1.8 mmol) in 1,2-dichloroethane (30 mL) dropwise. The mixture was stirred at 65–70 °C under N_2 for 5 h; then it stood overnight at rt. The resulting solution was washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown oil. This was purified by column chromatography (EtOAc/light petroleum ether) to give 6 as light yellow rhombic crystals (0.9 g, 70%), mp 202–204 °C. ^1H NMR (CD_3COCD_3): δ 1.57 [d, 12 H, 2 $CH(CH_3)_2$], 3.63 (s, 4 H, $BrCH_2$), 3.93 (s, 6 H, 2 OCH_3), 4.03 (s, 6 H, 2 OCH_3), 4.56–4.74 [m, 2 H, 2 $CH(CH_3)_2$], 7.47 (s, 2 H, ArH), 8.37 (s, 2 H, ArH), 8.37 (s, 2 H, ArH). IR (KBr): 1612, 1584, 1031 cm^{-1}. MS: m/e 702 (47), 704 (100), 706 (55, M^+), 523 (60), 625 (68, M^+ − Br). Anal. Calcd for $C_{34}H_{40}Br_2O_6$: C, 57.95; H, 5.68; Br, 22.72. Found: C, 58.20; H, 5.85; Br, 22.50.

5,5′-Diisopropyl-1,1′,6,6′,7,7′-hexamethoxy-3,3′-dimethyl-4,4′-dibromo-2,2′-binaphthalene (7). *N*-Bromosuccinimide (720 mg, 4 mmol) was added at rt to a solution of 3 (550 mg, 1 mmol) in DMF (50 mL). The resultant solution was stirred at rt for 18 h; then 5% aqueous $NaHSO_3$ (50 mL) was added. The solid that separated from solution was collected by filtration and was extracted with Et_2O. The extract was added to the filtrate and two resulting layers were separated. The organic layer was washed (5% $NaHSO_3$, water), dried (Na_2SO_4), and concentrated in vacuo to give a brown oil. Purification of the oil by column chromatography on silica gel (EtBr/light petroleum ether, 1:2) yielded 7 (220 mg, 30%) as light yellow needles, mp 184–185 °C. ^1H NMR ($CDCl_3$): δ 2.3 (s, 6 H, 2 $ArCH_3$), 3.50 (s, 6 H, 2 OCH_3), 4.00 (d, 12 H, 4 OCH_3), 4.50 [m, 2 H, 2 $CH(CH_3)_2$], 7.40 (s, 2 H, ArH). IR: 1590, 1530, 1045 cm^{-1}. MS: m/e 703 (48), 704 (100), 706 (51, M^+), 623 (55), 625 (60, M^+ − Br). Anal. Calcd for $C_{34}H_{40}O_6Br_2$: C, 57.95; H, 5.68; Br, 22.73. Found: C, 58.03; H, 5.85; Br, 22.92.

1,12-Dibromo-4,9-diisopropyl-2,3,10,11-tetramethoxy-6,7-bis(fluoromethyl)dinaphtho[1,2-*b*:2′,1′-*d*]furan (8). KF (350 mg, 6 mmol) was heated at 200 °C in vacuo for 3 h. The white powder was cooled to rt and CH_3CN (15 mL) and 18-crown-6 (1.58 g, 6 mmol) were added. The mixture was stirred for 30 min at rt and then 4 (0.41 g, 0.5 mmol) was added. The mixture was refluxed until the reaction was complete (2 h). Then ether (10 mL) was added and the mixture was washed with water. The organic phase was dried over Na_2SO_4. Evaporation of the solvent yielded 8 (91%), mp 221–222 °C. ^1H NMR ($CDCl_3$): δ 1.57 [d, 12 H, 2 $CH(CH_3)_2$], 3.99 [d, 14 H, 4 OCH_3, 2 $CH(CH_3)_2$], 5.96–6.20 (d, 4 H, 2 CH_2F), 8.24 (d, 2 H, ArH). ^{19}F NMR (CF_3COOH): δ +117 (t, 2 F, 2 CH_2F). IR: 1580, 1540, 1120, 1054 cm^{-1}. MS: m/e 692 (48), 694 (100), 696 (53, M^+), 672 (18), 673 (8), 674 (11, M^+ − F), 614 (11), 616 (12, M^+ − Br). Anal. Calcd for $C_{32}H_{32}Br_2F_2O_5$: C, 55.33, H, 4.61; F, 5.48. Found: C, 55.12; H, 4.74; F, 5.56.

1-Bromo-2,3,10,11-tetramethoxy-4,9-diisopropyl-6,7-bis(fluoromethyl)dinaphtho[1,2-*b*:2′,1′-*d*]furan (9). Treatment of 5 in the manner described for the synthesis of 8 provided an 85% yield of 9, mp 160–161 °C. ^1H NMR ($CDCl_3$): δ 1.59 [q, 12 H, 2 $CH(CH_3)_2$], 4.02 [m, 14 H, 4 OCH_3, 2 $CH(CH_3)_2$], 6.00, 6.06, 6.24, 6.30 (q, 4 H, 2 CH_2F), 7.97 (s, 1 H, ArH), 8.30 (d, 1 H, ArH), 8.42 (d, 1 H, ArH). IR: 1630, 1600, 1120, 1029 cm^{-1}. MS: m/e 614 (96), 616 (100, M^+), 595 (10), 597 (10, M^+ − F), 635 (2, M^+ − Br). Anal. Calcd for $C_{32}H_{33}O_5BrF_2$: C, 62.44; H, 5.37; F, 6.18. Found: C, 62.11; H, 5.35; F, 6.07.

2,3,10,11-Tetramethoxy-4,9-diisopropyl-6,7-(methanoxymethano)diaptho[1,2-*b*:2′,1′-*d*]furan (10). A stirred mixture

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of 4 (125 mg, 0.15 mmol), sodium trifluoroacetate (160 mg, 1.1 mmol), CuI (110 mg, 0.5 mmol) and hexamethylphosphoramide (2.5 mL) was heated at 160 °C under N_2 for 6 h. The cooled mixture was poured into water and then extracted with Et_2O. The extract was washed with water, dried (Na_2SO_4), and concentrated to give a brown oil. This was purified by column chromatography (EtOAc/light petroleum ether). White cubic crystals of **10** were obtained (10 mg, 10%), mp 129–130 °C. ^1H NMR (CD_3COCD_3): δ 1.57 [d, 12 H, 2 $CH(CH_3)_2$], 3.94 (s, 6 H, 2 OCH_3), 4.02 [m, 2 H, 2 $CH(CH_3)_2$], 4.16 (s, 6 H, 2 OCH_3), 5.40 (s, 4 H, 2 OCH_2Ar), 7.77 (s, 2 H, ArH), 7.80 (s, 2 H, ArH). IR: 1593, 1036 cm^{-1}. MS: *m/e* 514 (100), 515 (34, M^+, $M^+ + 1$). Anal. Calcd for $C_{32}H_{34}O_6$: C, 74.71; H, 6.61. Found, C, 74.59; H, 6.73.

1,12-Dibromo-2,3,10,11-tetramethoxy-4,9-diisopropyl-6,7-(methanoxymethano)dinaptho[1,2-*b*:2′,1′-*d*]furan (11) and **1,12-Dibromo-2,3,10,11-tetramethoxy-4,9-diisopropyl-14-oxo-6,7-(methanoxymethano)dinaptho[1,2-*b*:2′,1′-*d*]furan (12). Method A.** AgF (0.78 g, 6 mmol) was heated at 200 °C in vacuo for 5 h and cooled to rt under N_2. Then a solution of **4** (0.5 g, 0.6 mmol) in glyme (10 mL) was added. The reaction mixture was stirred at 120 °C under N_2 for 2 h and at 130 °C for 8 h. The resultant black mixture was poured into water (50 mL) and extracted with Et_2O. The extract was washed with water and dried over Na_2SO_4. Concentration of the extract in vacuo provided a brown oil which was purified by column chromatography (1:20 ethyl acetate/light petroleum ether) to yield crystalline **11** (20 mg) and **12** as rhombic crystals (10 mg). **11**: mp 264–265 °C. ^1H NMR (CD_3COCD_3): δ 1.55 [d, 12 H, 2 $CH(CH_3)_2$], 3.95 (d, 12 H, 4 OCH_3), 4.00 [m, 2 H, 2 $CH(CH_3)_2$], 5.37 (s, 4 H, 2 OCH_2Ar), 8.00 (s, 2 H, ArH-4). IR: 1568, 1344, 1039 cm^{-1}. MS: *m/e* 670 (49), 672 (100), 674 (52, M^+). Anal. Calcd for $C_{32}H_{32}Br_2O_6$: C, 57.14; H, 4.76. Found: C, 56.98; H, 4.82. **12**: mp 210–212 °C. ^1H NMR (CD_3COCD_3): δ 1.56–1.65 [q, 12 H, 2 $CH(CH_3)_2$], 3.98 [m, 2 H, 2 $CH(CH_3)_2$], 4.01–4.06 (q, 12 H, 4 OCH_3), 5.78 (s, 2 H, $ArCH_2O$), 8.29 (s, 1 H, ArH), 9.11 (s, 1 H, ArH). IR: 1715, 1452, 1022 cm^{-1}. MS: *m/e* 684 (49), 686 (100), 688 (53, M^+), 640 (4, $M^+ - CO2$). Anal. Calcd for $C_{32}H_{30}O_7Br_2$: C, 55.98; H, 4.37. Found: C, 55.83; H, 4.46.

Method B. To a stirred solution of **4** (130 mg, 0.16 mmol) in HMPA (2 mL) under N_2 were added tetrakis(triphenylphosphine)palladium (30 mg) and tetrakis(pentafluorophenyl)tin (300 mg, 0.37 mmol). The resulting yellow solution was heated at 80 °C for 40 h. Water (5 mL) was added. The solid that separated from solution was collected by filtration and was extracted with Et_2O. The extract was added to the filtrate. The resulting two layers were separated and the organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by preparative TLC (EtOAc/light petroleum ether, 9:1) and extraction (Et_2O) of the single chromophoric band gave, upon concentration of the extract, **11** as light yellow crystals (30 mg, 30%).

Method C. A mixture of **4** (100 mg, 0.12 mmol), Na_2S (43 mg, 0.55 mmol), benzene (3 mL), *t*-BuOH (10 mL), and water (2 mL) was refluxed for 10 h. The mixture was cooled to rt and Et_2O (50 mL) was added. The two layers were separated. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/light petroleum ether) to yield **11** as light yellow crystals (41 mg, 50%).

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Unsaturated Phosphonates as Acyclic Nucleotide Analogues. Anomalous Michaelis–Arbuzov and Michaelis–Becker Reactions with Multiple Bond Systems[1]

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Reaction of adenallene (**4a**) with methanesulfonyl chloride in pyridine afforded 4′-chloro-4′-deoxyadenallene (**6a**). A similar reaction with toluene-4-sulfonyl chloride (NEt_3, CH_2Cl_2) led to elimination of the unsaturated moiety and formation of N^9-(4-toluenesulfonyl)adenine (**8a**). Michaelis–Arbuzov reaction of *E*- and *Z*-unsaturated chlorides **13a** and **16b** with triethyl phosphite afforded phosphonates **14a** and **17b**. Dealkylation of the latter products, coupled in case of **17b** with acid hydrolysis, led to phosphonic acids **15a** and **18**. By contrast, Michaelis–Arbuzov reaction with butynyl chlorides **19a** and **19b** led to elimination of unsaturated moiety and alkylation of the released heterocyclic bases to give N^9-ethyl derivatives **20a** and **20b**. In the presence of iodide ion, N^9-(2,3-butadien-1-yl)adenine (**30a**, from **19a**) and/or unsaturated diphosphonates **25a** and **25b** were obtained. The Michaelis–Arbuzov reaction of chloroallene **6a** led to 2′-phosphonate **33a** which, after dealkylation, afforded phosphonic acid **35a**. When iodide ion was present, both 2′- and 4′-phosphonates **33a** and **36a** were obtained. Compound **36a** was also prepared by Michaelis–Becker reaction of chloroallene **6a** with sodium diethyl phosphite in THF–HMPA. In DMSO, both phosphonates **33a** and **36a** were formed. Under similar conditions (DMF), chlorobutyne **19a** gave 4′-phosphonate **36a**. Dealkylation of **36a** furnished phosphonic acid **37a**. Adenallene (**4a**) and diethyl chlorophosphite in pyridine afforded phosphonate **33a** whereas butynol **39a** afforded only adenine (**10a**). The probable reaction course of these transformations and spectral properties of the reaction products will be discussed.

Unsaturated analogues of nucleosides, cyclic and acyclic, are a focus of much current attention as antiviral and antitumor agents (Chart I). Thus, compounds **1a–1c** are effective agents[3] against human immunodeficiency virus (HIV), a cause of acquired immunodeficiency syndrome (AIDS). Neplanocin A (**2a**), a naturally occurring antibiotic, and its cytosine analogue **2b** exhibit a broad spectrum of antiviral and antitumor activities.[4] In the acyclic series, alkenediols **3a–3c** were found to be only moderately

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(2) Dedicated to my esteemed teacher Dr. Zdeněk Arnold on the occasion of his 70th birthday.

(3) Recent review: Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533.

(4) Recent review: Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* (*London*) **1986**, *6*, 1.

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