8-Ethenyl-1-hydroxy-4-β-D-ribofuranosylbenzo[d]naphtho[1,2-b]pyran-6-one and 8-Ethenyl-1-hydroxy-4-(2′-deoxy-β-D-ribofuranosyl)benzo[d]naphtho-[1,2-b]pyran-6-one. Synthetic C-Glycosides Related to the Gilvocarcin, Ravidomycin, and Chrysomycin Antibiotics

Roger N. Farr,[†,‡] Daw-Iong Kwok,[‡] and G. Doyle Daves, Jr.*[,†]

Departments of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180, and Lehigh University, Bethlehem, Pennsylvania 18015

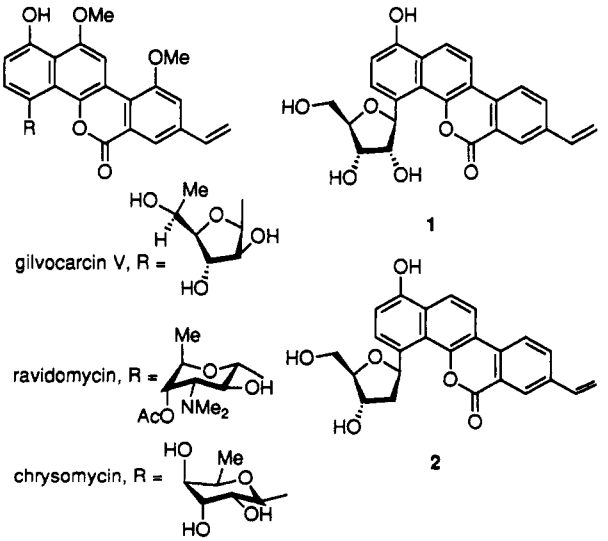
Received October 18, 1991

Syntheses of 8-ethenyl-1-hydroxy-4-β-D-ribofuranosylbenzo[d]naphtho[1,2-b]pyran-6-one (1) and 8-ethenyl-1-hydroxy-4-(2′-deoxy-β-D-ribofuranosyl)benzo[d]naphtho[1,2-b]pyran-6-one (2) have been accomplished. These two compounds are the first synthetic C-glycosides structurally related to the gilvocarcin, ravidomycin, and chrysomycin antibiotic class which possess the aglycon substituents (hydroxyl at C-1 and ethenyl at C-8) considered critical for the photolytic nicking of DNA. Anthracycline C-glycoside 1 was prepared by a route involving Lewis acid-catalyzed C-glycosyl bond formation between the tetracyclic aglycon and 1,2,3,5-tetra-O-acetyl-D-ribose followed by construction of the aglycon 8-ethenyl substituent from the corresponding ethyl group by radical bromination–dehydrobromination. Synthesis of C-glycoside 2 utilized a different, complementary procedure for C-glycosyl bond formation by palladium-mediated coupling of an iodoaglycon derivative with 1,4-anhydro-2-deoxy-3-O-(*tert*-butyldiphenylsilyl)-D-*erythro*-pent-1-enitol, a furanoid glycal designed to form only β C-glycosyl bonds in this reaction. In the synthesis of 2, the 8-ethenyl substituent of the aglycon was installed prior to C-glycosyl bond formation since, in this case, attempted ethyl group bromination led instead to conversion of the carbohydrate moiety to a furan.

Introduction

The benzo[d]naphtho[1,2-b]pyran-6-one C-glycoside antibiotics,[1] ravidomycin,[2] the gilvocarcins[3] (toromycin,[4] anandamycin[5]), and the chrysomycins[6] (virenomycin,[7] the albacarcins[8]), have attracted significant synthetic interest. Syntheses of the anthracyclic aglycon system[9] and of (−)-methyl ravidosaminide,[10] the carbohydrate portion of ravidomycin, have been accomplished. We have reported syntheses of C-glycosides possessing the benzo[d]-naphtho[1,2-b]pyran-6-one aglycon characteristics of this antibiotic class.[11-17]

We now report syntheses of 8-ethenyl-1-hydroxy-4-β-D-ribofuranosylbenzo[d]naphtho[1,2-b]pyran-6-one[18] (1) and 8-ethenyl-1-hydroxy-4-(2′-deoxy-β-D-ribofuranosyl)benzo-[d]naphtho[1,2-b]pyran-6-one (2), the first synthetic C-glycosides which possess the aglycon structural features considered critical[9c,19] for the photolytic nicking of DNA.[19,20] In the synthesis of 1,[15] the C-glycosyl bond was formed by Lewis acid-catalyzed condensation of anthracyclic aglycon and glycone precursors.[21,22] The synthesis



[†] Rensselaer Polytechnic Institute.
[‡] Lehigh University.

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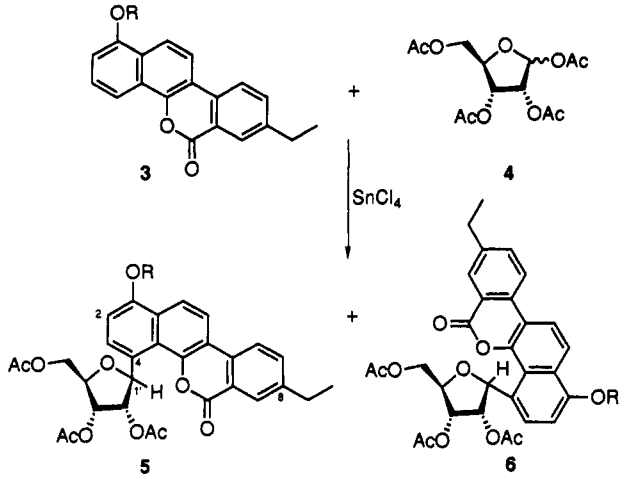
of the closely related 2′-deoxy C-glycoside **2** was accomplished by a completely different, complementary synthetic strategy involving as a key step a palladium-mediated coupling reaction[11] of an iodo aglycon derivative with a glycal (1,2-unsaturated carbohydrate) to form the C-glycosyl bond in a regio- and stereospecific manner.[16]

Results and Discussion

8-Ethenyl-1-hydroxy-4-β-D-ribofuranosylbenzo[*d*]naphtho[1,2-*b*]pyran-6-one (1). Hurd and Bonner[21] in the 1940s first reported Lewis acid-catalyzed glycosylation for preparation of aryl C-glycosides. This reaction is restricted to relatively electron-rich aglycons; nonetheless, this method of C-glycosyl bond formation has proved useful[22] owing to its inherent simplicity. We established in a preliminary study[13] that 8-ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (**3a**) possesses sufficient electron density to permit Lewis acid-catalyzed glycosylation using 1,2,3,5-tetra-O-acetyl-D-ribose[23] (**4**) in the presence of stannic chloride. This reaction yielded a 1:1 mixture of α and β C-glycoside anomers **5a** and **6a** in a combined 60% isolated yield.[13] Importantly, this successful Lewis acid-catalyzed coupling reaction also established that condensation occurred regiospecifically at C-4 of the aglycon; no C-glycosyl bond formation at C-2 was detected.



a, R = Me; **b**, R = H; **c**, R = Ac; **d**, R = Si(iPr)$_3$

Attempts to incorporate C-glycoside **5a** into a synthetic sequence leading to **1** were unsuccessful because all conditions found which effected removal of the methyl group from the C-1 oxygen of the aglycon disrupted the stereochemistry of the anomeric center (C-1′) of the ribofuranosyl moiety. As a result, a brief study was made of Lewis acid-catalyzed condensation reactions of ribose derivative **4**[23] with the corresponding phenolic aglycon (**3b**) and with the acetyl (**3c**) and triisopropylsilyl (**3d**) derivatives. No C-glycosyl product was isolated following treatment of a mixture of acetyl glycoside **4** and either **3b** or **3c** with stannic chloride. However, treatment of a mixture of **4** and **3d** with stannic chloride, like the similar condensation of **4** with **3a**, resulted in formation of a 1:1 mixture of the corresponding β and α C-glycosides **5d** and **6d**. For synthetic purposes, this condensation reaction leading to C-glycosides **5** and **6** was superior to that employing O-methyl aglycon **3a**[13] in three respects. First, the yield of the stannic chloride catalyzed condensation reaction when **3d** was used as the aglycon precursor was higher (87%) and second, because of more favorable solubility and chromatographic properties, anomers **5d** and **6d** were more readily separated. Most critically, however, treatment of these C-glycosides with fluoride ion readily removed the triisopropylsilyl protective group from the aglycon C-1 hydroxyl without affecting the stereocenter at C-1′ of the carbohydrate moiety.

Efforts to improve the stereoselectivity of the coupling reaction by changing Lewis acid catalyst, reaction solvent, or reaction temperature were unsuccessful. Careful monitoring of the course of the reaction revealed that the β C-glycoside anomer (**5d**) forms first and, under the reaction conditions, undergoes equilibration with the α anomer (**6d**). The equilibrium, about 1:1 at room temperature, can be adjusted by carrying out the condensation at lower temperature. At −40 °C the reaction takes several days but yields a ratio of **5d**:**6d** of about 5:1; this ratio is achieved more readily by simply cooling the reaction mixture formed at room temperature to −40 °C. Unfortunately, attempts to use this procedure synthetically were not successful; we were not able to stabilize the reaction mixture with this ratio of C-glycoside products for isolation. However, in the current study focused on the preparation of β C-glycoside **1**, we were able to achieve practical yields of key intermediate **5d** of about 70% by reprocessing chromatographic fractions rich in the α-anomer **6d** by exposure to stannic chloride which restored the 1:1 equilibrium mixture of anomers.

Following construction of the C-glycosyl bond in formation of **5d**, attention was directed to conversion of the 8-ethyl substituent of the aglycon into a vinyl group. This conversion was accomplished during synthesis of the aglycon of gilvocarcin by a radical bromination–dehydrobromination sequence.[9c] Bromination of **5d** using N-bromosuccinimide (NBS) and catalytic benzoyl peroxide led to a complex mixture of products which, on the basis of ^{1}H NMR spectra, appeared to involve bromination of the triisopropylsilyl group. Therefore, **5d** was desilylated using cesium fluoride, and the resulting phenolic group of the aglycon was acetylated (acetic anhydride/pyridine) to produce **5c**. Treatment of **5c** with NBS and catalytic benzoyl peroxide produced the desired benzylic bromination product **7c** in about 60% yield after chromatographic separation.[24] Dehydrobromination of **7c** to introduce an 8-vinyl substituent (**8c**) was accomplished catalytically using tetrakis(triphenylphosphine)palladium(0); we found this procedure to be preferable to base catalyzed dehy-

(22) For recent examples of Lewis acid-catalyzed C-glycosylation and leading references to earlier uses, see: ref 13. Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 4629–4632. Cai, M. S.; Qiu, D.-X. *Synth. Commun.* **1989**, *19*, 851–855. Rao, S. P.; Rao, K. V. B.; Otter, B. A.; Klein, R. S.; Ren, W.-Y. *Tetrahedron Lett.* **1988**, *29*, 3537–3540. Herscovici, J.; Muleka, K.; Boumaiza, L.; Antonakis, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1995–2009. Girgis, N. S.; Michael, M. A.; Smee, D. F.; Alaghamandan, H. A.; Robins, R. K.; Cottam, H. B. *J. Med. Chem.* **1990**, *33*, 2750–2755.

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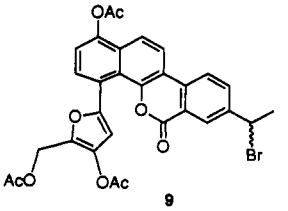
(24) A second, highly unstable product was also isolated. Based on mass and NMR spectra, we have assigned structure **9** to this material.



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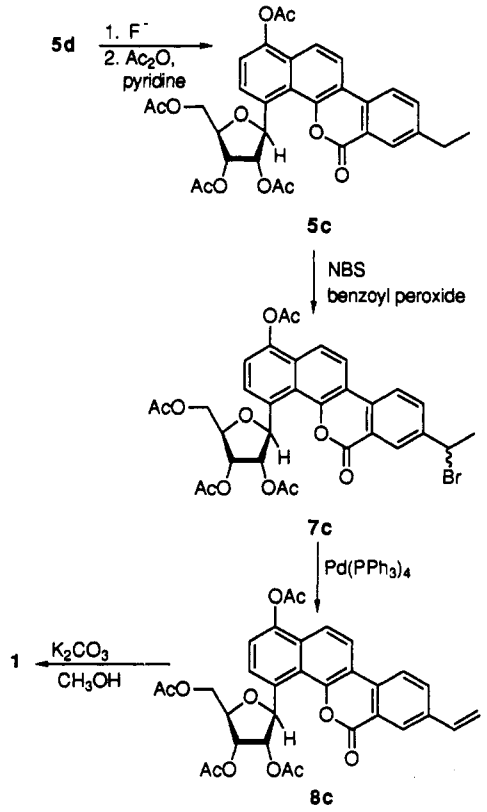
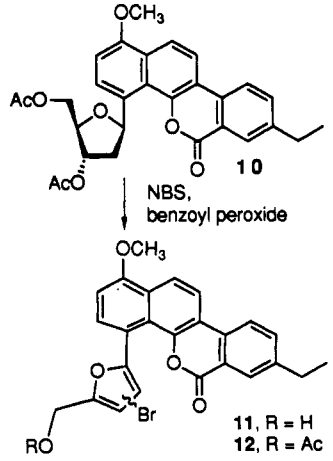


drobromination or dehydrobromination using lithium bromide and lithium carbonate.[9c] Completion of the synthesis of anthracycline C-glycoside **1** was accomplished by removal of the four acetyl groups of **8c** using potassium carbonate in methanol.

8-Ethenyl-1-hydroxy-4-(2′-deoxy-β-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (2). In an earlier study[16] involving in part palladium-catalyzed coupling reactions of 4-iodo-8-ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one, we prepared C-glycoside **10** which was used to determine whether, in the 2′-deoxy series, the 8-ethyl substituent of the aglycon can be dehydrogenated to form a vinyl group. Unfortunately, treatment of **10** with NBS in the presence of benzoyl peroxide led to preferential reaction at the sterically accessible C-1′ carbohydrate center[24] yielding two unstable products assigned structures **11** and **12** on the basis of spectrometric data. This result and the previously noted



inability to remove the phenolic methyl group of **10** and related C-glycosides[15] without disruption of the stereochemical integrity of the carbohydrate anomeric center led us to develop a synthetic approach to **2** which (a) introduces the vinyl substituent of the aglycon prior to palladium-mediated glycal-aglycon coupling and (b) uses an aglycon derivative with a readily removable substituent on the phenolic (C-1) oxygen.

Aglycon Chemistry. A number of studies of the aglycon system were carried out in order to find an appropriate derivative for palladium-mediated glycal-aglycon coupling.[11,16] 8-Ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]-pyran-6-one[9c,13] (**13**) was brominated selectively at C-4 using NBS to yield **14**,[16] which was further brominated under radical conditions (NBS, benzoyl peroxide) at the benzylic carbon of the ethyl side chain (**14** → **15**). The phenolic oxygen of **15** was then O-demethylated with boron tribromide, and the resulting hydroxyl was esterified using pivaloyl chloride and 4-(dimethylamino)pyridine to yield key intermediate **16**. Alternatively, **16** was prepared from **14** by changing the C-1 oxygen function prior to benzylic bromination; in both sequences excellent yields were achieved in all reactions.

Derivative **16** was further transformed into the aglycon precursor (**18**) used for the palladium-mediated coupling reaction by (a) dehydrobromination of the bromoethyl side chain to an 8-vinyl substituent and (b) replacement of the 4-bromo substituent by iodo. This latter change was necessary owing to the poor performance of bromo aglycon derivatives in palladium-catalyzed coupling reactions with enol ethers.[16] Conversion of **16** to **18** was accomplished in either of two ways. Dehydrobromination of **16** was effected using catalytic tetrakis(triphenylphospine)palladium(0) in dimethylformamide to form **18** (74%) which underwent halogen exchange in the presence of cuprous iodide and potassium iodide[16,27] to yield **18** (76%). Alternatively, **16** was converted directly to **18** in 54% yield by treatment with a mixture of cuprous and potassium iodides; in this reaction the nonhalogenated 8-vinyl derivative[9c] was a side product. That aryl iodination prior to ethyl group halogenation was inappropriate was shown using 8-ethyl-4-iodo-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one[16] (**10**), prepared from **14** by halogen exhange using cuprous and potassium iodides[16] or from **13**[9c,13] by direct iodination using *N*-iodosuccinimide and an acid catalyst. Attempts to brominate the ethyl group of **10** under radical conditions led, instead, to deiodination; as a result iodination at C-4 was delayed until after ethyl group bromination had been accomplished.

Glycal–Aglycon Coupling. The utility of a pivaloyl-protected aglycon derivative was established in a preliminary experiment. 8-Ethyl-4-iodo-1-(pivaloyloxy)benzo-[*d*]naphtho[1,2-*b*]pyran-6-one (**19**) was obtained from **14** in three steps (demethylation with BBr_3, pivaloylation, and halogen exchange with CuI and KI[27]). This aglycon derivative and 1,4-anhydro-2-deoxy-3-*O*-(*tert*-butyldiphenylsilyl)-D-*erythro*-pent-1-enitol (**20**), a furanoid glycal specifically designed[25] for synthesis of β C-glycosides, were coupled using a catalytic portion of palladium acetate in dimethylformamide. This reaction effected regio- and stereospecific C-glycosyl bond formation[11,28-30] yielding, after desilylation of the intermediate silylenol ether, 2′-deoxy-3′-keto C-glycoside **21** in 88% isolated yield. Stereospecific reduction of the keto group of **21** using sodium triacetoxyborohydride[25,26] followed by removal of the pi-

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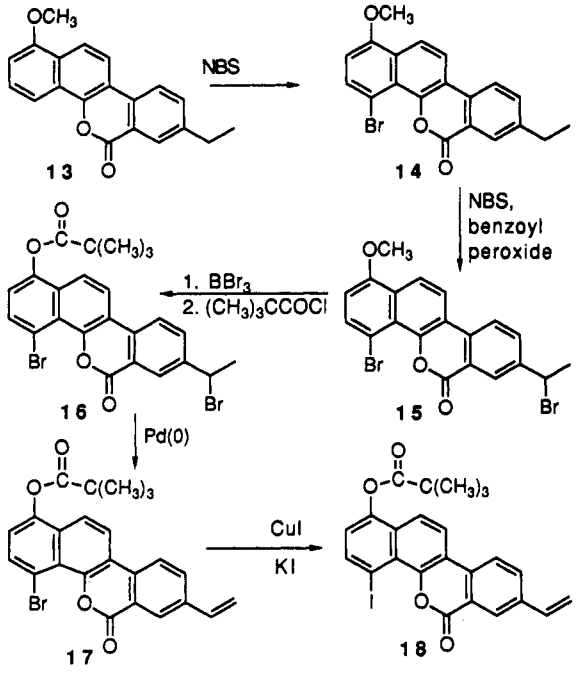
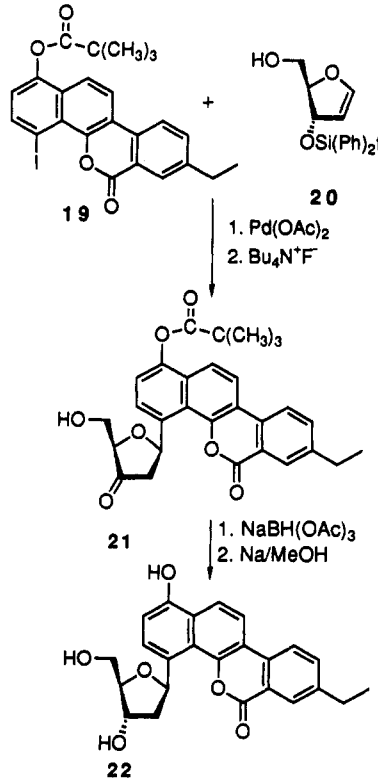
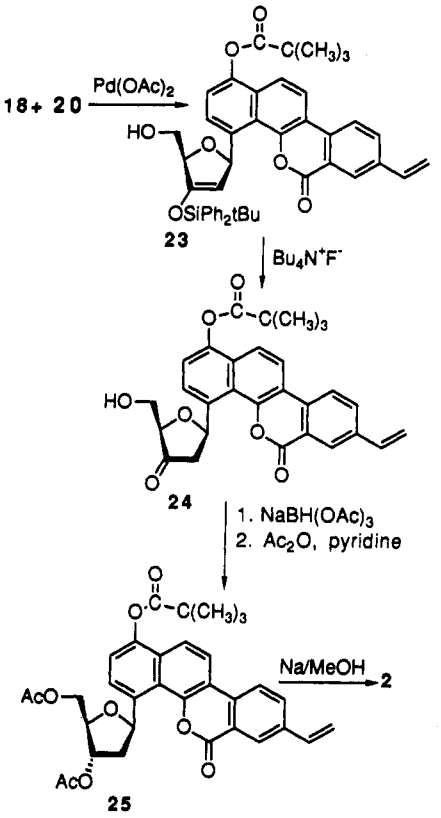


valoyl protective group produced **22** in 91% yield.



Similarly, palladium-mediated coupling of iodo aglycon derivative **18** and glycal **20**[25] was accomplished and the synthesis of 4-(2′-deoxy-β-D-ribofuranosyl)-8-ethenyl-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (**2**) was completed in straightforward manner. Thus, the initially formed *C*-glycosyl intermediate **23** was desilylated without isolation using tetra-*n*-butylammonium fluoride to yield keto derivative **24**. Stereospecific reduction of the keto group of **24** using sodium triacetoxyborohydride[25,26] followed by acetylation produced triester **25**. The ester groups of **25** were then removed to yield **2** (81% from **25**).



Conclusion

Our current efforts have culminated in the synthesis of the first synthetic benzo[*d*]naphtho[1,2-*b*]pyran-6-one *C*-glycosides which possess the aglycon structural features considered critical[9c,19] for the photolytic nicking of DNA.[19,20] The Lewis acid and palladium-catalyzed coupling reactions offer complementary convergent syntheses of 2′-hydroxy and 2′-deoxy analogues. With the problems of protection and step ordering having been overcome, together with the recent improvements in the palladium-catalyzed syntheses of β *C*-glycosides,[16,25] concise routes to biologically important benzo[*d*]naphtho[1,2-*b*]pyran-6-one *C*-glycosides have been elucidated.

Experimental Section[31]

8-Ethyl-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (3b). BBr_3 (12 mL, 1.0 M in CH_2Cl_2) was added slowly with stirring into a solution of 8-ethyl-1-methoxybenzo[*d*]naphtho-[1,2-*b*]pyran-6-one (**3a**)[13] (1.0 g, 3.3 mmol) in 40 mL of CH_2Cl_2 at room temperature. A bright yellow precipitate appeared within 10 min. TLC (benzene–ethanol, 15:1) showed that reaction was complete in 90 min, at which time the reaction mixture was a clear brown solution. The reaction mixture was then added to a heated solution (50–60 °C) of ethanol and aqueous $NaHCO_3$. The precipitate which formed was filtered and dried in an oven (110 °C) for 3 h to afford 0.92 g (97%) of 8-ethyl-1-hydroxybenzo[*d*]-naphtho[1,2-*b*]pyran-6-one (**3b**) as a light beige solid: mp 250–258 °C dec; MS *m/z* 290 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, *J* = 7.6 Hz, CH_3), 2.77 (2 d, 2 H, benzylic), 7.02 (d, 1 H, $J_{2,3}$ = 7.6 Hz, H-2), 7.48 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, H-3), 7.79 (d, 1 H, H-4), 7.81 (dd, 1 H, $J_{9,10}$ = 8.3 Hz, H-9), 8.06 (d, 1 H, $J_{11,12}$ = 9.0 Hz), 8.10 (d, 1 H, $J_{7,9}$ = 1.8 Hz, H-7), 8.23 (d, 1 H, $J_{11,12}$ = 9.0 Hz), 8.37 (d, 1 H, H-10); HRMS calcd for $C_{19}H_{14}O_3$ 290.0943, found 290.0946.

8-Ethyl-1-[(triisopropylsilyl)oxy]benzo[*d*]naphtho[1,2-*b*]pyran-6-one (3d). Triisopropylsilyl chloride (1.1 g, 5.7 mmol) was added to a solution of **3b** (1.01 g, 3.4 mmol) and imidazole (0.98 g, 10.4 mmol) in 9 mL of dimethylformamide (DMF). The reaction mixture was stirred at room temperature for 10 h. The white crystals which formed were filtered at ice temperature and recrystallized from $CHCl_3$/ethanol to yield 1.42 g (92%) of 8-ethyl-1-[(triisopropylsilyl)oxy]benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**3d**): mp 169 °C; MS *m/z* 446 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 1.17

(31) For general procedures see ref 17.

(d, 18 H, J = 7.5 Hz, CH_3), 1.32 (t, 3 H, J = 7.6 Hz, CH_3), 1.43 (h, 3 H, isopropyl CH), 2.79 (2 d, 2 H, benzylic), 6.99 (d, 1 H, $J_{2,3}$ = 7.6 Hz, H-2), 7.45 (dd, 1 H, H-3), 7.67 (dd, 1 H, $J_{9,10}$ = 8.2 Hz, H-9), 8.04 (d, 1 H, $J_{11,1}{}^2$ = 9.0 Hz), 8.08 (d, 1 H, H-10), 8.16 (d, 1 H, $J_{3,4}$ = 8.4 Hz, H-4), 8.19 (d, 1 H, $J_{11,12}$ = 9.0 Hz), 8.26 (d, 1 H, H-7); ^{13}C NMR ($CDCl_3$) δ 13.02 (CH_3), 15.16 (CH), 18.06 (CH_3), 28.58 (benzylic), 113.41, 114.01 (C-2), 114.74 (C-4), 118.13, 119.20 (C-11, C-12), 121.08, 122.07 (C-3), 125.41, 127.23 (C-10), 128.08, 129.14 (C-7) 133.08, 135.06 (C-9), 145.12, 146.74, 151.99 (C-1), 161.53 (C=O); HRMS calcd for $C_{28}H_{34}O_3Si$ 446.2277, found 446.2274.

8-Ethyl-1-[(triisopropylsilyl)oxy]-4-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (5d) and 8-Ethyl-1-[(triisopropylsilyl)oxy]-4-(2′,3′,5′-tri-*O*-acetyl-α-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (6d). To a stirred solution of **3d** (1 g, 2.2 mmol) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[23] (4) (3 g, 9.4 mmol) in 80 mL of 1,2-dichloroethane was added stannic chloride (20 mL of a 1 M solution in 1,2-dichloroethane). After 20 h at room temperature, the reaction mixture was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ solution. The organic phase was separated, washed with water, and then concentrated. The resulting residue was separated by preparative TLC ($CHCl_3$–ethyl acetate, 10:1) to yield unreacted **3d** (0.03 g, 3%) and **5d** (668 mg, 42%) as off-white crystals, mp 87–88 °C, and **6d** (704 mg, 45%) as white crystals, mp 73–74 °C.

For **5d**: MS m/z 704 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 1.19 (apparent t, 18 H, CH_3), 1.30 (t, 3 H, CH_3), 1.44 (h, 3 H, J = 7.6 Hz, isopropyl CH), 2.00, 2.19, 2.31 (3 s, 9 H, acetyl), 2.76 (2 d, 2 H, benzylic), 4.48 (dd, 1 H, $J_{5',5'}$ = 12.1 Hz, $J_{4',5'}$ = 5.1 Hz, H-5′), 4.55 (dd, 1 H, $J_{4',5'}$ = 2.4 Hz, H-5′), 4.58 (ddd, 1 H, $J_{3',4'}$ = 9.5 Hz, H-4′), 5.20 (dd, 1 H, $J_{2',3'}$ = 4.3 Hz, H-3′), 5.63 (d, 1 H, H-2′), 6.61 (s, 1 H, H-1′), 6.98 (d, 1 H, $J_{2,3}$ = 8.3 Hz, H-2), 7.66 (dd, 1 H, $J_{9,10}$ = 8.2 Hz, $J_{7,9}$ = 1.4 Hz, H-9), 8.00 (d, 1 H, H-10), 8.08 (d, 1 H, $J_{11,12}$ = 9.0 Hz), 8.10 (d, 1 H, H-3), 8.16 (d, 1 H, H-7), 8.30 (d, 1 H, $J_{11,12}$ = 9.0 Hz, H-12); HRMS calcd for $C_{39}H_{48}O_{10}Si$ 704.3013, found 704.3026.

For **6d**: MS m/z 704 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 1.16 (d, 18 H, J = 7.5 Hz, CH_3), 1.33 (t, 3 H, CH_3), 1.43 (h, 3 H, J = 7.5 Hz, isopropyl CH), 1.54, 2.05, 2.20 (3 s, 9 H, acetyl), 2.81 (2 d, 2 H, benzylic), 4.37 (dd, 1 H, $J_{4',5'}$ = 4.8 Hz, $J_{5',5'}$ = 12.0 Hz, H-5′), 4.52 (dd, 1 H, $J_{4',5'}$ = 2.9 Hz, H-5′), 4.55 (m, 1 H, H-4′), 5.72 (dd, 1 H, $J_{2',3'}$ = 4.8 Hz, $J_{3',4'}$ = 7.7 Hz, H-3′), 6.37 (dd, 1 H, $J_{1',2'}$ = 3.4 Hz, H-2′), 6.83 (d, 1 H, H-1′), 7.02 (d, 1 H, $J_{2,3}$ = 8.2 Hz, H-2), 7.70 (dd, 1 H, $J_{7,9}$ = 1.9 Hz, $J_{9,10}$ = 8.0 Hz, H-9), 7.91 (d, 1 H, H-10), 8.05 (d, 1 H, $J_{11,12}$ = 8.1 Hz), 8.12 (d, 1 H, H-3), 8.26 (s, 1 H, H-7), 8.26 (d 1 H, $J_{11,12}$ = 8.1 Hz); HRMS calcd for $C_{39}H_{48}O_{10}Si$ 704.3013, found 704.3023.

8-Ethyl-1-[(triisopropylsilyl)oxy]-4-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (5d) from 6d. To a stirred solution of **6d** (1.65 g, 2.3 mmol) in 30 mL of 1,2-dichloroethane was added stannic chloride (20 mL of a 1 M solution in 1,2-dichloroethane). TLC indicated the presence of a 1:1 mixture of **5d** and **6d**. The reaction mixture was then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was washed several times with water and then dried over Na_2SO_4. Volatiles were removed in vacuo, and the residue was separated by preparative TLC to afford 760 mg (46%) of **5d** and 795 mg (48%) of **6d** which contained a small quantity of **5d**.

1-Acetoxy-8-ethyl-4-(2′,3′,5′-tri-*O*-acetyl-β-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (5c). To a stirred solution of **5d** (460 mg, 1 mmol) and CsF (1.16 g, 7.6 mmol) in 30 mL of CH_2Cl_2 was added 18-crown-6 ether (300 mg, 0.88 mmol). The solution changed from colorless to orange in a few seconds, while sonication was applied. The reaction was finished within 10 min (TLC), and then 5 mL of CH_3OH was added to the reaction mixture. The solution was concentrated and applied to a silica gel column which was eluted with CH_2Cl_2–ethyl acetate (14:1) to remove CsF and crown ether. The isolated intermediate phenol was then dissolved in 4 mL of pyridine, and acetic anhydride (560 mg, 5.5 mmol) was added. The reaction mixture was stirred at room temperature; after 16 h, TLC (CH_2Cl_2–ethyl acetate, 14:1) showed the reaction to be complete. Then 100 mL of CH_2Cl_2 was added, and the resulting solution was washed with water several times. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The resulting residue was crystallized from CH_2Cl_2–ethanol to yield 371 mg (96%) of **5c** as white crystals: mp 190 °C; MS m/z 590 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H, CH_3), 2.00, 2.20, 2.32, 2.49 (4 s, 12 H, acetyl), 2.79 (2 d, 2 H, benzylic), 4.46 (dd, 1 H, H-5′), 4.57 (dd, 1 H, $J_{5',5'}$ = 12.1 Hz, H-5′), 4.60 (ddd, 1 H, $J_{4',5'}$ = 2.5, 4.3 Hz, H-4′), 5.19 (dd, 1 H, $J_{3',4'}$ = 9.4 Hz, H-3′), 5.65 (d, 1 H, $J_{2',3'}$ = 4.3 Hz, H-2′), 6.62 (s, 1 H, H-1′), 7.73 (d, 1 H, H-2), 7.68 (dd, 1 H, H-9), 7.83 (d, 1 H, $J_{11,12}$ = 9.0 Hz), 8.08 (d, 1 H, $J_{9,10}$ = 8.2 Hz, H-10), 8.09 (d, 1 H, $J_{11,12}$ = 9.0 Hz), 8.16 (d, 1 H, $J_{7,9}$ = 1.3 Hz, H-7), 8.22 (d, 1 H, $J_{2,3}$ = 8.9 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 15.13 (CH_3), 20.46, 20.91, 21.04, 21.18 (acetyl), 30.89 (benzylic), 62.71 (C-5′), 76.21, 76.60 (C-2′, C′-4), 82.42 (C-1′), 115.25, 118.42 (C-11), 118.99 (C-2), 120.23 (C-12), 120.27, 122.28, 122.37 (C-10), 125.23 (C-3), 128.48, 128.82 (C-7), 132.40, 133.29, 135.26 (C-9), 145.77, 146.33, 159.99 (lactone C=O), 169.01, 169.64, 170.59, 170.70 (acetyl C=O); HRMS calcd for $C_{32}H_{30}O_{11}$ 590.1785, found 590.1781.

1-Acetoxy-8-(1-bromoethyl)-4-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (7c). A solution of **5c** (162 mg, 0.27 mmol), NBS (63.5 mg, 0.36 mmol), and benzoyl peroxide (2 mg, 0.008 mmol) in 25 mL of CCl_4 was heated under reflux for 18 h. The solution was then evaporated to almost dryness and separated by preparative TLC (CH_2Cl_2–ethyl acetate, 10:1) to afford 118 mg (65%) of **7c** R_f = 0.42 as a light yellow solid, mp 194–196 °C dec, and 52 mg (24%) of **9**[24] as a light brown solid. For **7c**: MS m/z 607 (M – HOAc)$^+$, 588 (M – HBr)$^+$; ^1H NMR ($CDCl_3$) δ 2.12, 2.13 (each d, 3 H, J = 6.8 Hz, CH_3), 2.00, 2.21, 2.32, 2.49 (4 s, 12 H, acetyl), 4.47 (dd, 1 H, H-5′), 4.57 (dd, 1 H, $J_{5',5'}$ = 7.9 Hz, H-5′), 4.60 (ddd, 1 H, $J_{4',5'}$ = 2.4, 4.1 Hz, H-4′), 5.19, 5.20 (each dd, 1 H, $J_{3',4'}$ = 9.3 Hz, H-3′), 5.31 (2 d, 1 H, benzylic), 5.65 (d, 1 H, $J_{2',3'}$ = 4.4 Hz, H-2′), 6.56 (s, 1 H, H-1′), 7.32 (d, 1 H, H-2), 7.82, 7.82 (each d, 1 H, $J_{11,12}$ = 9.0 Hz), 7.94 (apparent dt, 1 H, J = 3.3, 9.1 Hz), 8.03, 8.04 (each d, 1 H, $J_{11,12}$ = 9.0 Hz), 8.12 (d, 1 H, $J_{9,10}$ = 8.2 Hz, H-10), 8.21 (d, 1 H, $J_{2,3}$ = 8.2 Hz, H-3), 8.33, 8.36 (each d, 1 H, $J_{7,9}$ = 2.0 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 20.47, 20.93, 21.03, 21.19, 26.30, 26.36, 47.30, 62.66, 69.23, 76.15, 76.59, 82.36, 114.62, 118.69, 119.37, 120.14, 120.30, 120.37, 122.12, 123.06, 123.11, 125.48, 127.77, 127.91, 128.79, 133.39, 133.96, 134.14, 134.53, 144.34, 144.37, 146.27, 147.95, 159.38, 169.65, 170.41, 170.58.

For **9**:[24] ^1H NMR ($CDCl_3$) δ 2.06, 2.13, 2.15, 2.50 (each s, 3 H each, acetyls), 2.09 (d, 3 H, J = 6.9 Hz, CH_3), 5.12 (s, 2 H, furan), 5.25 (m, 1 H, benzylic), 6.74 (s, 1 H, furan), 7.38–8.32 (complex, 7 H, aglycon).

1-Acetoxy-8-ethenyl-4-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (8c). A solution of **7c** (85 mg, 0.144 mmol), tetrakis(triphenylphosphine)-palladium(0) (30 mg, 0.026 mmol), and $NaHCO_3$ (47 mg, 0.56 mmol) in 10 mL of CH_3CN was stirred at room temperature for 24 h. The solution was then evaporated to almost dryness, and the residue was separated by preparative TLC (CH_2Cl_2–ethyl acetate, 10:1) to yield 62 mg (73%) of **12c** as colorless crystals: mp 186 °C; MS m/z 588 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 2.00, 2.20, 2.32, 2.49 (4 s, 12 H, acetyl) 4.46 (dd, 1 H, $J_{4',5'}$ = 2.3 Hz, $J_{5',5'}$ = 12.1 Hz, H-5′), 4.70 (dd, 1 H, $J_{4',5'}$ = 4.4 Hz, H-5′), 4.61 (ddd, 1 H, H-4′), 5.20 (d, 1 H, $J_{3',4'}$ = 9.5 Hz, H-3′), 5.66 (d, 1 H, $J_{2',3'}$ = 4.2 Hz, H-2′), 6.61 (s, 1 H, H-1′), 5.43, 5.93, 6.78 (d, d, dd, 3 H, J = 10.9, 17.5 Hz, vinyl), 7.35 (d, 1 H, H-2), 7.83 (d, 1 H, $J_{11,12}$ = 9.3 Hz), 7.87 (dd, 1 H, H-9), 8.07 (d, 1 H, $J_{11,12}$ = 9.3 Hz), 8.10 (d, 1 H, $J_{9,10}$ = 8.4 Hz, H-10), 8.22 (d, 1 H, $J_{2,3}$ = 8.2 Hz, H-3), 8.29 (d, 1 H, $J_{7,9}$ = 1.7 Hz, H-7). ^{13}C NMR ($CDCl_3$) δ 20.48, 20.93, 21.06, 21.20 (4 acetyl CH_3), 62.71 (C-5′), 69.27 (C-3′), 76.21, 76.62 (C-2′, C-4′), 82.36 (C-1′), 114.77, 116.35, 118.45, 119.01, 120.03, 120.23, 121.98, 122.48, 125.22, 127.50, 128.46, 132.30, 133.15, 133.55, 134.88, 138.31, 146.19, 147.43, 159.63 (lactone C=O), 168.84, 169.66, 170.59, 170.63 (4 acetyl C=O); HRMS calcd 588.1630, found 588.1627. Anal. Calcd for $C_{32}H_{28}O_{11}$: C, 65.3; H, 4.80. Found: C, 64.9; H, 4.55.

8-Ethenyl-1-hydroxy-5-β-D-ribofuranosylbenzo[*d*]naphtho[1,2-*b*]pyran-6-one (1). A mixture of **8c** (55 mg, 0.09 mmol) and K_2CO_3 (50 mg, 0.4 mmol) in 25 mL of methanol was stirred at room temperature. The reaction was complete in 2 h as shown by TLC (ethyl acetate–ethanol, 20:1). Acetic acid (1 mL) was then added, and the volatiles were removed in vacuo. Water (15 mL) was then added, and the resulting light yellow powder was collected by filtration to afford 34 mg (87%) of **1** as a light yellow solid: MS (FAB, matrix: thioglycerol/DMSO) m/z

443 (M + Na)$^+$, 385 ($MH^+ - 2H_2O$), 279 (aglycon + H^+, base peak); ^1H NMR (DMF-d_7) δ 3.88 (dd, 1 H, $J_{4',5'}$ = 4.4 Hz, $J_{5',5'}$ = 11.9 Hz, H-5'), 4.03 (dd, 1 H, $J_{4',5''}$ = 2.0 Hz, H-5''), 4.08 (dd, 1 H, $J_{2',3'}$ = 4.7 Hz, $J_{3',4'}$ = 9.0 Hz, H-3'), 4.18 (ddd, 1 H, H-4'), 4.36 (dd, 1 H, $J_{1',2'}$ = 0.8 Hz, H-2'), 5.50 (d, 1 H, J_{cis} = 11.0 Hz, vinyl), 6.08 (br s, 1 H, H-1'), 6.15 (d, 1 H, J_{trans} = 17.6 Hz, vinyl), 7.02 (dd, 1 H, vinyl), 7.11 (d, 1 H, $J_{2,3}$ = 8.2 Hz, H-2), 8.22 (dd, 1 H, $J_{1',3}$ = 0.6 Hz, H-3), 8.25 (dd, 1 H, $J_{7,9}$ = 1.8 Hz, $J_{9,10}$ = 8.5 Hz, H-9), 8.30 (d, 1 H, $J_{11,12}$ = 9.0 Hz, H-11,12), 8.41 (d, 1 H, H-7), 8.42 (d, 1 H, H-11,12), 8.61 (d, 1 H, H-10); ^{13}C NMR (DMF-d_7) δ 61.79 (C-5'), 69.71, 78.06, 82.78, 86.33, (C-1',2',3',4'), 110.03, 114.97, 116.80, 118.79, 120.15, 120.29, 122.50, 124.16, 126.72, 127.18, 127.29, 128.51, 133.33, 135.30, 135.65, 138.78, 147.87, 153.01, 162.70. Anal. Calcd for $C_{24}H_{20}O_7 \cdot 0.5H_2O$: C, 67.1; H, 4.93. Found: C, 66.7; H, 4.82.

Peracetylation of 1. 8-Ethenyl-1-hydroxy-4-β-D-ribofuranosylbenzo[*d*]naphtho[1,2-*b*]pyran-6-one (1) (3.0 mg) and acetic anhydride (80 mg) in 1 mL of pyridine was kept for 24 h at room temperature. The reaction mixture was then evaporated, and the resulting residue was dissolved in CH_2Cl_2 and applied on a short silica gel column. Elution (CH_2Cl_2–ethyl acetate, 10:1) yielded 3 mg of white solid which exhibited a ^1H NMR spectrum indistinguishable from that of **8c**.

Radical Bromination of 4-[2'-Deoxy-3',5'-di-*O*-acetyl-β-D-ribo(=arabino)furanosyl]-8-ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one[16] (10). A solution of **10** (225 mg, 0.45 mmol), NBS (103 mg, 0.58 mmol), and benzoyl peroxide (20 mg) in 30 mL of CCl_4 was heated under reflux for 16 h. The solution was then evaporated to almost dryness and separated by preparative TLC ($CHCl_3$–ethyl acetate, 40:1) to afford 122 mg (60%) of **12** as a light yellow solid and 26 mg (14%) of **11** as a light yellow solid. For **12**: ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, CH_3), 2.10 (s, 3 H, acetyl), 2.81 (2 d, 2 H, benzylic), 4.03 (s, 3 H, OCH_3), 5.15 (s, 2 H, H-5',5''), 6.70 (s, 1 H, H-2'), 6.93 (m, 1 H, H-2), 7.55–8.28 (complex, 6 H, H-3,7,9,10,11,12); MS (FAB, matrix: *m*-nitrobenzyl alcohol) *m/z* 521 ($M^{\cdot+}$), 462 (M – OAc, base peak), 382 (M – OAc, –Br). For **11**: ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H, CH_3), 2.85 (2 d, 2 H, benzylic), 4.10 (s, 3 H, OCH_3), 4.62 (s, 2 H, H-5',5''), 6.60 (s, 1 H, H-2'), 7.00–8.35 (complex, 7 H, aromatic).

4-Bromo-8-(1-bromoethyl)-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (15). A solution of 4-bromo-8-ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one[16] (14) (2.25 g, 5.9 mmol), NBS (1.07 g, 6 mmol), and benzoyl peroxide (300 mg) in 200 mL of CCl_4 was heated under reflux for 2 h. Volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and separated by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 2.31 g (85%) of **15** as off-white crystals: mp 212–214 °C; ^1H NMR ($CDCl_3$) δ 2.14 (3 H, d, *J* = 7.0 Hz, CH_3), 4.01 (3 H, s, $ArOCH_3$), 5.34 (1 H, q, benzylic), 6.76 (1 H, d, $J_{2,3}$ = 8.4 Hz, H-2), 7.82 (1 H, d, 1 H, H-3), 7.98 (1 H, dd, $J_{7,9}$ = 2.1 Hz, $J_{9,10}$ = 8.5 Hz, H-9), 8.07 (1 H, d, $J_{11,12}$ = 9.1 Hz), 8.22 (1 H, d, H-10), 8.26 (1 H, d, H-11,12), 8.47 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 26.40, 47.44, 55.94, 106.74, 107.05, 114.69, 119.15, 119.24, 121.07, 122.37, 123.14, 124.96, 127.85, 128.37, 133.88, 134.60, 134.88, 144.32, 154.60, 159.80. Anal. Calcd for $C_{20}H_{14}O_3Br_2$: C, 52.0; H, 3.05. Found: C, 52.2; H, 2.81.

4-Bromo-8-(1-bromoethyl)-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one. To a stirred solution of 4-bromo-8-(1-bromoethyl)-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (15) (1.5 g, 3.25 mmol) in 200 mL of CH_2Cl_2 was added BBr_3 (9.7 mL of a 1 M solution in CH_2Cl_2). A bright yellow precipitate appeared instantly. After 4 h the reaction mixture was a clear brown solution. The reaction mixture was then added dropwise to a solution of CH_3OH and water. The precipitate was collected by filtration to give 1.43 g (98%) of 4-bromo-8-(1-bromoethyl)-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one as a beige solid: mp 228–231 °C dec; ^1H NMR (DMSO) δ 2.07 (3 H, d, *J* = 6.9 Hz, CH_3), 5.74 (1 H, q, benzylic), 6.90 (1 H, d, $J_{2,3}$ = 8.3 Hz, H-2), 7.75 (1 H, d, H-3), 8.13 (1 H, dd, $J_{7,9}$ = 1.9 Hz, $J_{9,10}$ = 8.5 Hz, H-9), 8.16 (1 H, d, $J_{11,12}$ = 9.0 Hz), 8.36 (1 H, d, H-7), 8.37 (1 H, d, H-11,12), 8.53 (1 H, d, H-10); ^{13}C NMR (DMSO) δ 26.01, 49.06, 103.58, 111.21, 114.54, 119.22, 119.69, 120.36, 121.60, 124.08, 127.23, 127.33, 134.10, 134.48, 135.03, 144.41, 145.92, 153.09, 159.13. Anal. Calcd for $C_{19}H_{12}O_3Br_2$: C, 50.9; H, 2.70. Found: C, 51.2; H, 2.44.

4-Bromo-8-(1-bromoethyl)-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (16). To an ice-cooled mixture of 4-bromo-8-(1-bromoethyl)-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one in 150 mL of toluene was added trimethylacetyl chloride (1.47 g, 12.mmol) and 4-(dimethylamino)pyridine (12 g, 16 mmol). The reaction mixture was then brought to room temperature and stirred for 10 h. Volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and separated by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 3.81 g (88%) of **16** as off-white crystals: mp 187–189 °C; ^1H NMR ($CDCl_3$) δ 2.13 (3 H, d, *J* = 7.0 Hz, CH_3), 5.31 (1 H, q, benzylic), 7.10 (1 H, d, $J_{2,3}$ = 8.2 Hz, H-2), 7.80 (1 H, d, $J_{11,12}$ = 9.1 Hz), 7.89 (1 H, d, H-3), 7.96 (1 H, dd, $J_{7,9}$ = 2.1 Hz, $J_{9,10}$ = 8.4 Hz, H-9), 8.10 (1 H, d, H-11,12), 8.15 (1 H, d, H-10), 8.45 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 26.38, 27.29, 40.60, 47.30, 113.82, 114.54, 118.18, 120.45, 120.73, 121.04, 122.83, 123.04, 127.95, 129.99, 134.05, 134.36, 134.52, 144.60, 146.19, 146.96, 158.48, 176.49. Anal. Calcd for $C_{24}H_{20}O_4Br_2$: C, 54.2; H, 3.79. Found: C, 54.6; H, 3.70.

4-Bromo-8-ethyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one. To a stirred solution of 4-bromo-8-ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one[16] (14) (2.62 g, 6.8 mmol) in 100 mL of CH_2Cl_2 was added BBr_3 (20.5 mL of a 1 M solution in CH_2Cl_2). A bright yellow precipitate appeared instantly. After 2 h the reaction mixture was a clear brown solution. The reaction mixture was then added dropwise to a solution of CH_3OH and water. The precipitate was collected by filtration and was sufficiently pure to be used in the following step. To an ice-cooled mixture of the dried precipitate in 150 mL of toluene was added trimethylacetyl chloride (1.23 g, 10.26 mmol). 4-(Dimethylamino)pyridine (1.67 g, 13.68 mmol) was then added, and the reaction was brought to room temperature and stirred for 6 h. Volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and separated by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 2.63 g (85%) of 4-bromo-8-ethyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one as off-white crystals: mp 195–197 °C; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, CH_3), 1.48 (9 H, s, *t*-Bu), 2.79 (2 H, q, benzylic), 7.06 (1 H, d, $J_{2,3}$ = 8.3 Hz, H-2), 7.67 (1 H, dd, $J_{7,9}$ = 1.8 Hz, $J_{9,10}$ = 8.3 Hz, H-9), 7.76 (1 H, d, $J_{11,12}$ = 9.1 Hz), 7.88 (1 H, d, H-3), 8.05 (1 H, d, H-11,12), 8.22 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 15.16, 27.28, 28.62, 39.51, 113.65. 115.06, 117.85, 119.98, 120.76, 120.86, 122.28, 122.83, 128.92, 129.57, 132.28, 134.08, 135.15, 145.95, 146.14, 146.29, 160.03, 177.14. Anal. Calcd for $C_{24}H_{21}O_4Br$: C, 63.6, H, 4.67. Found: C, 63.2; H, 4.55.

A solution of 4-bromo-8-ethyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (1.2 g, 2.6 mmol), NBS (481 mg, 2.7 mmol), and benzoyl peroxide (150 mg) in 100 mL of CCl_4 was heated under reflux for 30 min. Volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and purified by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 1.24 g (88%) of **16** indistinguishable from that prepared by the previous method (see above).

4-Bromo-8-ethenyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (17). A solution of 4-bromo-8-(1-bromoethyl)-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (16) (600 mg, 1.13 mmol), tetrakis(triphenylphosphine)-palladium(0) (119 mg, 0.11 mmol), and $NaHCO_3$ (189 mg, 2.26 mmol) in 20 mL of DMF was stirred at room temperature for 24 h. Volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and separated by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 387 mg (76%) of **17** as off-white crystals: mp 203–205 °C; ^1H NMR ($CDCl_3$) δ 1.50 (9 H, s, *t*-Bu), 5.42 (1 H, d, J_{cis} = 11.0 Hz), 5.91 (1 H, d, J_{trans} = 17.6 Hz), 6.78 (1 H, dd, vinyl), 7.06 (1 H, d, $J_{2,3}$ = 8.3 Hz, H-2), 7.77 (1 H, d, $J_{11,12}$ = 9.0 Hz), 7.83 (1 H, dd, $J_{7,9}$ = 1.9 Hz, $J_{9,10}$ = 8.4 Hz, H-9), 7.85 (1 H, d, H-3), 8.06 (2 H, d, H-10, H-11,12), 8.32 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 27.14, 39.81, 113.92, 114.64, 116.82, 117.88, 120.80, 121.21. 122.78, 124.44, 127.64, 129.21, 132.32, 133.54, 135.00, 138.55, 142.25, 145.36, 147.24, 159.61, 176.41. Anal. Calcd for $C_{24}H_{19}O_4Br$: C, 63.9; H, 4.24. Found: C, 63.9; H, 4.31.

8-Ethenyl-4-iodo-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (18). From 16. A solution of 4-bromo-8-(1-bromoethyl)-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]-pyran-6-one (16) (3.14 g, 5.90 mmol), CuI (8 g, 41 mmol), and KI (29.4 g, 177 mmol) in 300 mL of DMF was heated under reflux for 4 h. Volatiles were removed in vacuo, and $CHCl_3$ (500 mL) was then added. The reaction mixture was then filtered, and the filtrate was washed with a saturated solution of sodium thiosulfate.

The organics were dried over Na_2SO_4, the volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and purified by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 1.82 g (62%) of **18** as off-white crystals: mp 228–230 °C; ^1H NMR ($CDCl_3$) δ 1.52 (9 H, s, *t*-Bu), 5.41 (1 H, d, J_{cis} = 10.7 Hz), 5.92 (1 H, d, J_{trans} = 17.5 Hz), 6.77 (1 H, dd, vinyl), 6.89 (1 H, d, $J_{2,3}$ = 7.9 Hz, H-2), 7.74 (1 H, d, $J_{11,12}$ = 9.0 Hz), 7.83 (1 H, dd, $J_{7,9}$ = 1.4 Hz, $J_{9,10}$ = 8.3 Hz, H-9), 8.04 (1 H, d, H-10), 8.05 (1 H, d, H-11,12), 8.28 (1 H, d, H-3), 8.30 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 27.29, 39.56, 81.72, 114.34, 116.64, 117.98, 120.42, 120.69, 121.13, 122.51, 124.24, 127.73, 129.27, 132.32, 133.66, 135.00, 138.59, 142.27, 145.48, 147.20, 159.52, 176.41. Anal. Calcd for $C_{24}H_{19}O_4I$: C, 57.8; H, 3.84. Found: C, 58.0; H, 3.73.

From 17. A solution of 4-bromo-8-ethenyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**17**) (304 mg, .67 mmol), CuI (512 mg, 2.7 mmol), and KI (1.2 g, 6.7 mmol) in 30 mL of DMF was heated under reflux for 1.5 h. The volatiles were removed in vacuo, and $CHCl_3$ (100 mL) was then added. The reaction mixture was filtered, and the filtrate was washed with a saturated solution of sodium thiosulfate. The organics were dried over Na_2SO_4, the volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and purified by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 255 mg (76%) of **18**.

8-Ethyl-4-iodo-1-(trimethylacetoxy)benzo[*d*]naphtho-[1,2-*b*]pyran-6-one (19). A solution of 4-bromo-8-ethyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (2.4 g, 5.3 mmol), CuI (5 g, 26.6 mmol), and KI (17.7 g, 106.4 mmol) in 150 mL of DMF was heated under reflux for 1 h. Volatiles were removed in vacuo, and $CHCl_3$ (200 mL) was then added. The reaction mixture was then filtered, and the filtrate was washed with a saturated solution of sodium thiosulfate. The organics were dried over Na_2SO_4, the volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and separated by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 1.89 g (71%) of **19** as off-white crystals: mp 208–209 °C; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, J = 7.5 Hz, CH_3), 2.78 (2 H, q, benzylic), 6.95 (1 H, d, $J_{2,3}$ = 8.1 Hz, H-2), 7.63 (1 H, dd, $J_{7,9}$ = 1.9 Hz, $J_{9,10}$ = 8.3 Hz, H-9), 7.72 (1 H, d, $J_{11,12}$ = 9.1 Hz), 7.98 (1 H, d, H-10), 8.03 (1 H, d, H-11,12), 8.17 (1 H, d, H-7), 8.27 (1 H, d, H-3); ^{13}C NMR ($CDCl_3$) δ 15.12, 27.27, 28.57, 39.52, 81.63, 114.55, 117.76, 120.44, 120.84, 122.24, 124.21, 128.79, 129.02, 132.19, 135.09, 142.09, 145.13, 145.80, 147.16, 159.69, 176.41. Anal. Calcd for $C_{24}H_{21}O_4I$: C, 57.6; H, 4.23. Found: C, 57.6; H, 4.10.

8-Ethyl-4-(β-D-*glycero*-pentofuran-3′-ulos-1′-yl)-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (21). To a stirred solution of 8-ethyl-4-iodo-1-(trimethylacetoxy)benzo-[*d*]naphtho[1,2-*b*]pyran-6-one (**19**) (750 mg, 1.5 mmol), 1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol[25] (**20**) (637 mg, 1.8 mmol), sodium acetate (123 mg, 1.5 mmol), and tributylamine (71 μL, 0.3 mmol) in 25 mL of DMF was added palladium acetate (34 mg, 0.15 mmol). The reaction mixture was stirred for 6 h at which time acetic acid (2 mL) and a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (THF) (1 mL) were added. The volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$, filtered through Celite, and purified by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 644 mg (88%) of **21** as white needles: mp 208–210 °C; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, J = 7.6 Hz, CH_3), 2.27 (1 H, dd, OH), 2.37 (1 H, dd, $J_{1',2'\alpha}$ = 10.0 Hz, $J_{2'\alpha,2'\beta}$ = 18.6 Hz, H-2′α), 2.80 (2 H, q, benzylic), 3.63 (1 H, dd, $J_{1',2'\beta}$ = 6.2 Hz, H-2′β), 4.06 (2 H, m, H-5′,5″), 4.28 (1 H, dd, $J_{4',5'}$ = 3.8 Hz, $J_{4',5''}$ = 3.9 Hz, H-4′), 6.57 (1 H, dd, H-1′), 7.29 (1 H, d, $J_{2,3}$ = 8.2 Hz, H-2), 7.68 (1 H, dd, $J_{7,9}$ = 1.7 Hz, $J_{9,10}$ = 8.3 Hz, H-9), 7.78 (1 H, d, $J_{11,12}$ = 9.0 Hz), 8.04 (1 H, d, H-3), 8.17 (1 H, d, H-10), 8.19 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 15.13, 27.29, 28.59, 39.49, 46.20, 61.74, 75.90, 82.00, 114.78, 118.25, 119.57, 119.97, 120.22, 122.13, 122.37, 124.30, 128.49, 128.82, 132.59, 135.38, 135.40, 145.89, 146.32, 147.17, 160.33, 176.74, 214.31. Anal. Calcd for $C_{29}H_{28}O_7$; C, 71.3; H, 5.78. Found: C, 71.1; H, 5.68.

4-[2′-Deoxy-β-D-ribo(=arabino)furanosyl]-8-ethyl-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (22). To a solution of 8-ethyl-4-(β-D-*glycero*-pentofuran-3′-ulos-1′-yl)-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**21**) (78 mg, 0.16 mmol) in 5 mL of DMF and 2 mL of acetic acid was added sodium triacetoxyborohydride (47 mg, 0.22 mmol). After 10 min, volatiles were removed in vacuo and the residue was dissolved in 5 mL of $CHCl_3$. The solution was then passed through a short column of silica gel, the volatiles were removed in vacuo, and methanol (20 mL) was added. A small piece of metallic sodium (ca. 1 mg) was added to the white suspension. The reaction mixture was a clear yellow solution after 15 min, at which time the reaction was complete based on TLC. Acetic acid (1 mL) and water (15 mL) were added, and the resulting precipitate was collected to afford 59 mg (91%) of **22** as an off white powder: mp 216–218 °C dec; ^1H NMR (DMSO-d_6) δ 1.25 (3 H, t, J = 7.6 Hz, CH_3), 1.90 (1 H, ddd, $J_{1',2'\beta}$ = 6.9 Hz, $J_{2'\alpha,2'\beta}$ = 13.0 Hz, H-2′β), 2.72 (1 H, ddd, $J_{1',2'\alpha}$ = 7.0 Hz, H-2′α), 2.79 (2 H, q, benzylic), 3.64 (1 H, dd, $J_{4',5'}$ = 5.4 Hz, $J_{5',5''}$ = 11.5 Hz, H-5′), 3.69 (1 H, dd, $J_{4',5''}$ = 3.7 Hz, H-5″), 3.80 (1 H, m, H-4′), 4.03 (1 H, m, H-3′), 6.28 (1 H, dd, H-1′), 6.97 (1 H, d, $J_{2,3}$ = 8.2 Hz, H-2), 7.85 (1 H, dd, $J_{7,9}$ = 1.3 Hz, $J_{9,10}$ = 8.3 Hz, H-9), 7.94 (1 H, d, H-3), 8.12 (1 H, br s, H-7), 8.16 (1 H, d, $J_{11,12}$ = 9.0 Hz), 8.29 (1 H, d, H-11,12), 8.44 (1 H, d, H-10); ^{13}C NMR (DMSO-d_6) δ 16.00, 28.50, 44.50, 62.49, 71.09, 77.75, 86.80, 110.27, 114.84, 119.10, 119.92, 120.51, 122.14, 124.03, 125.83, 126.51, 128.44, 131.59, 133.56, 136.22, 145.95, 147.86, 152.64, 160.65. Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.9; H, 5.46. Found: C, 70.5; H, 5.36.

8-Ethenyl-4-(β-D-*glycero*-pentofuran-3′-ulos-1′-yl)-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (24). To a stirred solution of 8-ethenyl-4-iodo-1-(trimethylacetoxy)-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**18**) (350 mg, 0.7 mmol), 1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol[25] (**20**) (299 mg, 0.84 mmol), sodium acetate (58 mg, 0.7 mmol), and tributylamine (33 μL, 0.14 mmol) in 8 mL of DMF was added palladium acetate (16 mg, 0.07 mmol). The reaction mixture was stirred for 10 h, at which time acetic acid (1 mL) and a 1 M solution of tetrabutylammonium fluoride in THF (0.5 mL) were then added. The volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$, filtered through Celite, and purified by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 191 mg (56%) of **24** as yellow needles: mp 232–234 °C; ^1H NMR ($CDCl_3$) δ 1.50 (9 H, s, *t*-Bu), 2.40 (1 H, dd, $J_{1',2'\alpha}$ = 10.0 Hz, $J_{2'\alpha,2'\beta}$ = 18.6 Hz, H-2′α), 3.65 (1 H, dd, $J_{1',2'\beta}$ = 6.2 Hz, H-2′β), 4.08 (2 H, br, H-5′,5″), 4.29 (1 H, dd, $J_{4',5'}$ = 3.8 Hz, $J_{4',5''}$ = 3.9 Hz, H-4′), 5.43 (1 H, d, J_{cis} = 10.9 Hz), 5.94 (1 H, d, J_{trans} = 17.6 Hz), 6.60 (1 H, dd, H-1′), 6.82 (1 H, dd, vinyl), 7.33 (1 H, d, $J_{2,3}$ = 8.2 Hz, H-2), 7.82 (1 H, d, $J_{11,12}$ = 9.0 Hz), 7.91 (1 H, dd, $J_{7,9}$ = 1.9 Hz, $J_{9,10}$ = 8.4 Hz, H-9), 8.08 (1 H, d, H-11,12), 8.12 (1 H, d, H-10), 8.20 (1 H, d, H-3), 8.37 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 27.32, 39.61, 46.23, 61.78, 75.94, 81.97, 114.63, 116.78, 118.49, 119.86, 120.02, 120.54, 122.19, 122.68, 124.48, 127.76, 128.76, 132.63, 134.06, 134.96, 135.51, 138.68, 146.40, 147.53, 160.16, 176.75, 214.25. Anal. Calcd for $C_{29}H_{26}O_7 \cdot 0.5H_2O$: C, 70.3; H, 5.49. Found: C, 70.2; H, 5.14.

4-[2′-Deoxy-3′,5′-diacetyl-β-D-ribo(=arabino)furanosyl]-8-ethenyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]-pyran-6-one (25). To a solution of 8-ethenyl-4-(β-D-*glycero*-pentofuran-3′-ulos-1′-yl)-1-(trimethylacetoxy)benzo[*d*]naphtho-[1,2-*b*]pyran-6-one (**24**) (140 mg, 0.29 mmol) in 5 mL of DMF and 2 mL of acetic acid was added sodium triacetoxyborohydride (122 mg, 0.58 mmol). After 10 min, acetaldehyde (1 mL) was added, and the reaction was stirred for an additional 5 min. The volatiles were removed in vacuo, and the residue was dissolved in pyridine (50 mL). Acetic anhydride (4 mL) was added, and the reaction was stirred overnight. The volatiles were removed in vacuo, and the residue was dissolved in $CHCl_3$ and purified by column chromatography followed by recrystallization from $CHCl_3$–ethanol to give 152 mg (92%) of **25** as off-white crystals: mp 162–163 °C; ^1H NMR ($CDCl_3$) δ 1.52 (9 H, s, *t*-Bu), 2.01 (1 H, ddd, $J_{1',2'\alpha}$ = 9.8 Hz, $J_{2'\alpha,2'\beta}$ = 13.7 Hz, $J_{2'\alpha,3'}$ = 5.9 Hz, H-2′α), 2.12 (3 H, s, OAc), 2.30 (3 H, s, OAc), 3.11 (1 H, ddd, $J_{1',2'\beta}$ = 5.3 Hz, $J_{2'\beta,3'}$ = 1.9 Hz, H-2′β), 4.36 (1 H, dd, $J_{4',5'}$ = 4.1 Hz, $J_{5',5''}$ = 11.1 Hz, H-5′), 4.47 (1 H, m, H-4′), 4.50 (1 H, dd, $J_{4',5''}$ = 4.1 Hz, H-5″), 5.28 (1 H, m, H-3′), 5.46 (1 H, d, J_{cis} = 11.0 Hz), 5.97 (1 H, d, J_{trans} = 17.6 Hz), 6.54 (1 H, dd, H-1′), 6.85 (1 H, dd, vinyl), 7.32 (1 H, d, $J_{2,3}$ = 8.2 Hz, H-2), 7.82 (1 H, d, $J_{11,12}$ = 9.0 Hz), 7.91 (1 H, dd, $J_{7,9}$ = 1.9 Hz, $J_{9,10}$ = 8.4 Hz, H-9), 8.09 (1 H, d, H-11,12), 8.11 (1 H, d, H-3), 8.16 (1 H, d, H-10), 8.40 (1 H, d, H-7); ^{13}C NMR ($CDCl_3$) δ 20.94, 21.26, 27.32, 39.51, 41.80, 64.35, 76.47, 79.14, 81.27, 114.44, 116.58, 118.38, 119.83, 119.84, 120.66, 122.19, 122.64, 124.15, 127.71, 128.73, 132.49, 134.21, 135.06, 136.42. 138.50, 146.05, 147.86, 160.06, 170.86,

171.23, 176.82. Anal. Calcd for $C_{33}H_{32}O_9$: C, 69.2; H, 5.63. Found: C, 69.3; H, 5.59.

4-[2′-Deoxy-B-D-ribo(=arabino)furanosyl]-8-ethenyl-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (2). To a solution of 4-[2′-deoxy-3′,5′-diacetyl-β-D-ribo(=arabino)furanosyl]-8-ethenyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**25**) (80 mg, 0.14 mmol) in 10 mL of methanol was added metallic sodium (3 mg). The suspension was then stirred for 3 h, at which time the reaction mixture was a clear yellow solution. Acetic acid (1 mL) and water (15 mL) was then added, and the resulting precipitate was collected to afford 52 mg (92%) of **2** as a light yellow powder: mp 258–260 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.91 (1 H, ddd, $J_{1',2'\alpha}$ = 7.0 Hz, $J_{2'\alpha,2'\beta}$ = 12.9 Hz, $J_{2'\alpha,3'}$ = 5.8 Hz, H-2′α), 2.70 (1 H, ddd, $J_{1',2'\beta}$ = 7.0 Hz, H-2′β), 3.60 (1 H, dd, $J_{4',5'}$ = 5.3 Hz, $J_{5',5''}$ = 11.6 Hz, H-5′), 3.66 (1 H, dd, $J_{4',5''}$ = 3.8 Hz, H-5″), 3.80 (1 H, m, H-4′), 4.03 (1 H, m, H-3′), 5.46 (1 H, d, J_{cis} = 11.0 Hz), 6.08 (1 H, d, J_{trans} = 17.6 Hz), 6.27 (1 H, dd, H-1′), 6.90 (1 H, dd, vinyl), 6.97 (1 H, d, $J_{2,3}$ = 8.2 Hz, H-2), 7.91 (1 H, d, H-3), 8.06 (1 H, br d, $J_{9,10}$ = 8.3 Hz, H-9), 8.12 (1 H, d, $J_{11,12}$ = 9.0 Hz), 8.22 (2 H, br, H-7, H-11,12), 8.40 (1 H,d, H-10); ^{13}C NMR (DMSO-d_6) δ 44.15, 62.21, 71.05, 77.73, 86.39, 110.27, 114.53, 117.45, 118.94, 119.97, 120.47, 121.84, 124.08, 125.72, 126.40, 127.27, 131.27, 133.05, 134.73, 135.51, 138.47, 147.81, 152.27, 160.61. Anal. Calcd for $C_{24}H_{20}O_6 \cdot 0.5H_2O$: C, 69.7; H, 5.12. Found: C, 69.8; H, 5.09.

Acknowledgment. We thank the American Cancer Society for financial support. Appreciation is expressed to William R. Anderson, Jr., for help with mass and nuclear magnetic resonance spectra and to Terry D. Lee, Beckman Research Institute of the City of Hope, Duarte, CA, for FAB mass spectra.

Convenient Syntheses of Stereoisomeric 1,2-Epoxyestr-4-en-3-ones, Putative Intermediates in Estradiol Metabolism

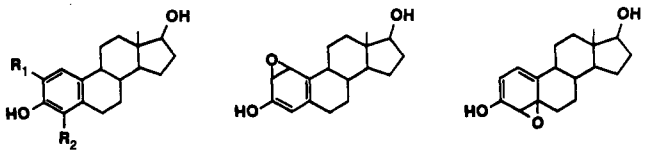
Dirshaye Menberu, Phuoc Van Nguyen, Kay D. Onan,* and Philip W. Le Quesne*

Department of Chemistry, Northeastern University, Boston, Massachusetts 02115-5096

Received August 9, 1991 (Revised Manuscript Received January 3, 1992)

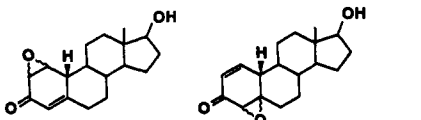
New synthetic sequences are described for 17β-hydroxy-1β,2β- and -1α,2α-epoxyestr-4-en-3-one, which are putative intermediates in the metabolism of estradiol to the 2,3- and 3,4-catecholestrogens, as well as the synthetic precursors of choice for these catechols.

The potent activity of estradiol (**1**) as a female hormone has been known for nearly 60 years. Its use in estrogen replacement therapy in menopausal women has been accompanied by reports of increased risk of cancer,[1] and despite intensive research especially in recent years, no firm connection between the biosynthesis, molecular structure, or catabolism of estradiol and carcinogenic events at the molecular level has yet been established. In 1980 we suggested[2,3] that phenolic arene oxides such as **2** and **3** (or their enone tautomers) might be intermediates in the well-known catabolism of estradiol to the catechols 2-hydroxyestradiol (**4**) and 4-hydroxyestradiol (**5**). Such



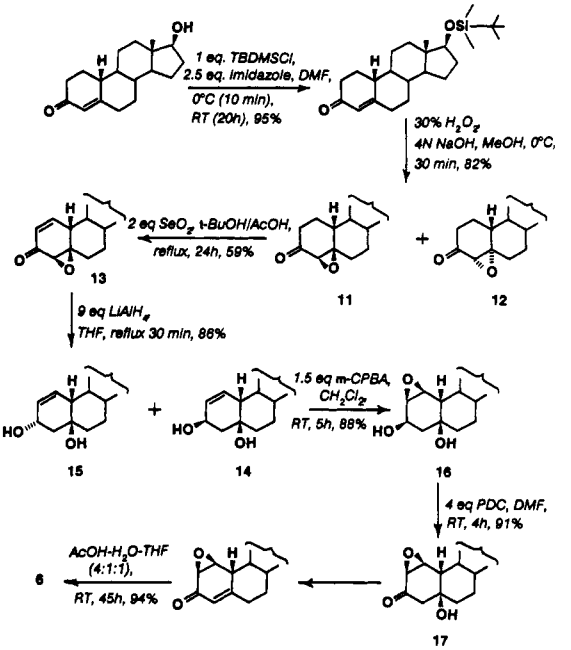
1 $R_1 = R_2 = H$ **2** **3**
4 R_1 = -OH, R_2 = H
5 $R_1 = H$, R_2 = -OH

phenolic arene oxides might also serve as carcinogenic electrophiles in analogy with the dihydrodiol epoxides derived from polycyclic aromatic hydrocarbons. During investigations designed to test this hypothesis, we developed syntheses of four epoxy enones **6–9**,[4] which are



6 1β, 2β-epoxy **8** 4β, 5β-epoxy
7 1α, 2α-epoxy **9** 4α, 5α-epoxy

Scheme I. First Synthesis of Epoxy Enone 6



stereoisomeric tautomers of dienol epoxides **2** and **3**. Recently, our attention has focused on epoxy enones **6** and **7**, because **6** was found to accumulate in estradiol-metabolizing MCF-7 cell cultures under conditions where epoxide hydrolysis is inhibited.[4] In this paper we report improved new syntheses of **6** and **7**. The ease with which such epoxy enones can be aromatized to catechols makes these routes also the pathways of choice for synthesis of estrogen-free catechol estrogens **4** and **5**.

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0022-3263/92/1957-2100$03.00/0