Lewis Acid Catalyzed Cyclocondensations of Formaldehyde with Activated Dienes. A Direct Route to Pyranosidal Pentoses

Samuel Danishefsky* and Robert R. Webb II[1]

Department of Chemistry, Yale University, New Haven, Connecticut 06511

Received September 26, 1983

Under the influence of zinc chloride, paraformaldehyde reacts with a variety of oxygenated butadienes. This provides a direct entry to functionalized pyrans, which are readily converted to pentose derivatives.

Background

In the last decade, carbohydrates have reemerged as a suitable terrain for explorations in organic synthesis. Most of this resurgence has involved partial synthesis, with a particular emphasis on preparing branched and deoxy versions of the common monosaccharides. These are encountered in a variety of antibiotics.[2] Furthermore, such manipulations have provided access to enantiomerically pure building blocks for the assembly of other natural products.[3,4]

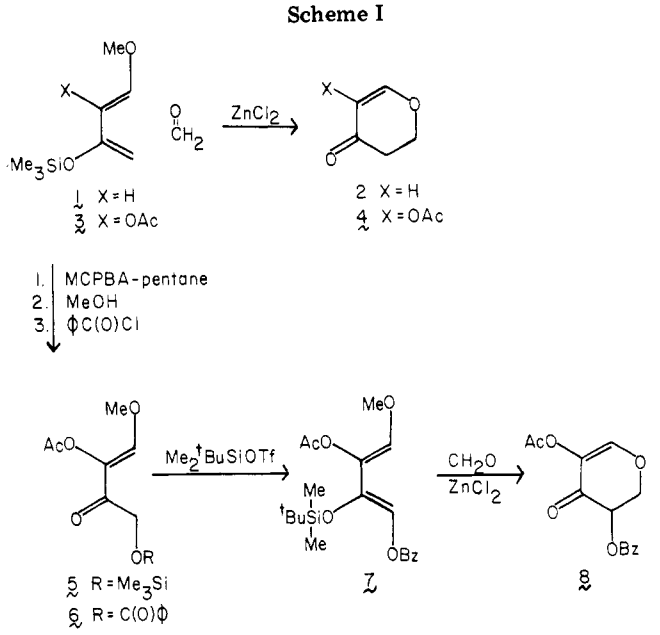
There has also been renewed activity in total synthesis of the well-known pentoses and hexoses.[5-7] These syntheses have been useful in their demonstration value with respect to the control of relative and even absolute stereochemistry.[8] Our interest in this area arose from a larger involvement in the development of the Lewis acid catalyzed cyclocondensation reaction of siloxy dienes with aldehydes.[9]

It has been demonstrated that a wide range of dienes and aldehydes function in this process.[9-11] However, we had not yet investigated the use of the simplest aldehyde, formaldehyde, in the cyclocondensation reaction.[12,13] Below we report that formaldehyde is indeed an effective heterodienophile[14] with a range of functionalized dienes and that this chemistry provides an exceedingly rapid entry to pentoses and functionalized pentoses.

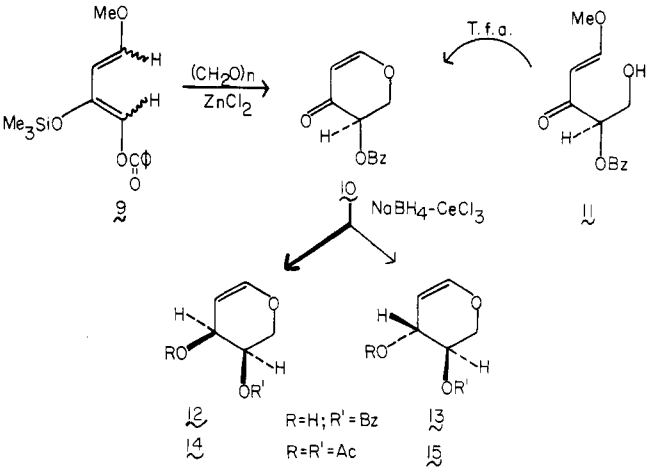
Results

Reaction of diene 1[15] with paraformaldehyde under the influence of zinc chloride was carried out in tetrahydrofuran under reflux.[16,17] Workup and chromatography over silica gel provided a 55% yield of the parent 2,3-dihydropyrone **2**. Remarkably, this simple compound had not previously been reported in the chemical literature.

Scheme I



Scheme II



(1) National Institutes of Health Postdoctoral Fellow, 1982–84.

(2) (a) Hanessian, S.; Haskell, T. H. In "The Carbohydrates, Chemistry and Biochemistry"; Pigman, Horton Eds.; Academic Press: New York, 1970; Vol. 11A, pp 139–211. (b) For a recent review in this area, note: Umezawa, S. *J. Org. Synth. Chem. Jpn.* **1982**, *40*, 1051.

(3) Fraser-Reid, B. O.; Anderson, K. C. *Fortschr. Chem. Org. Naturst.* **1980**, *39*, 1–60.

(4) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159.

(5) Holland, D.; Stoddart, J. F. *Tetrahedron Lett.* **1982**, *23*, 5367.

(6) Holland, D.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1553.

(7) Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1.

(8) Ko, S. Y.; Lee, A. W. M.; Masamune, L. A.; Reed, K. B., III; Sharpless, K. B.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949.

(9) Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

(10) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 360.

(11) Danishefsky, S.; Harvey, D.; Quallich, G.; Uang, B. J. *J. Org. Chem.* **1984**, *49*, 392.

(12) For a thermal variation of this reaction under high pressure, see: Jurczak, J.; Chmielewski, M.; Filipek, S. *Synthesis* **1979**, 41.

(13) A Lewis acid catalyzed Diels–Alder reaction of formaldehyde has been used in the synthesis of pseudomonic acid C, note: Snider, B. B.; Phillips, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 1113.

(14) For a review, see: Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

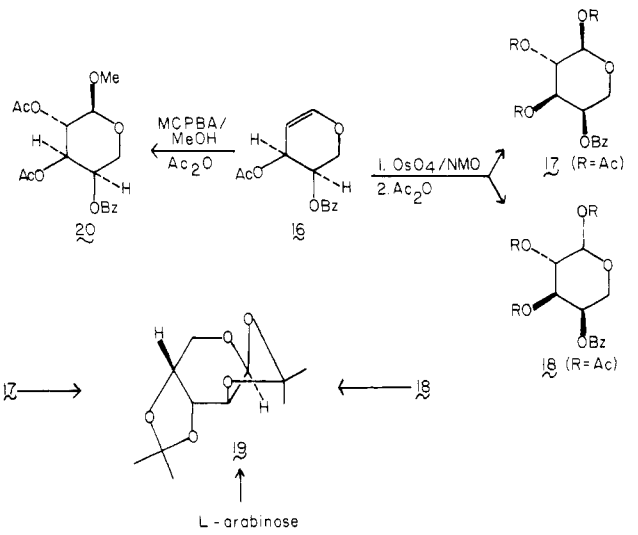
(15) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth.* **1983**, *61*, 147.

(16) Although it was found that the reaction proceeds at room temperature, refluxing the mixture dramatically accelerated the reaction to complete the process within a reasonable period. In addition, the yield is increased somewhat by heating, presumably because decomposition of the diene, found to occur over longer reaction periods, is precluded.

(17) Gaseous formaldehyde could be used in this reaction, but its use made the procedure somewhat tedious and gave no significant increase in yields.

0022-3263/84/1949-1955$01.50/0

Scheme III



In a similar vein, reaction of paraformaldehyde with diene **3**[18] afforded a 67% yield of the 5-acetoxy derivative **4**.[19] (See Scheme I.)

It was of interest to evaluate the preparation and use of dienes at still higher oxidation levels. Toward this end, diene **3** was subjected to a Rubottom-like reaction with *m*-chloroperoxybenzoic acid.[20] Desilylation of the resultant **5** followed by benzoylation afforded **6** in 50% overall yield from **3**.[21] Enol silylation of **6** following the precedent of Simchen[22] afforded diene **7**, as substantially a single isomer. It was expected that the synergistic directivity of the 2-siloxy and 4-methoxy groups would comfortably dominate over the combined directivities of the two acyloxy substituents at the 1- and 3-positions. This expectation has been clearly borne out. Thus, reaction of **7** with paraformaldehyde under the usual conditions afforded, in one step, a 75% yield of the pentose enolone[23] derivative **8**.

The reaction of paraformaldehyde with the diene mixture **9**[24] (see Scheme II) under zinc chloride catalysis afforded, in 65–75% yield, the 5-(benzoyloxy)pyrone **10**. Small amounts of acyclic aldol product **11** which were occasionally obtained in this reaction were converted to **10** upon exposure to trifluoroacetic acid. Reduction of **10** under the conditions of Luche[25] affords a 95% yield of an 8.5:1 mixture of the (±)-arabinal and (±)-xylal derivatives **12** and **13**. These were converted to the diacetate analogues **14** and **15** (respectively), which were compared with authentic samples.[26,27]

In addition, acetylation of the major compound **12** afforded the differentiated glycal derivative **16** (see Scheme III). Hydroxylation of **16** according to Van Rheenen[28] followed by acetylation afforded a separable 1:1 anomeric mixture of the arabinopyranosides **17** and **18**. Their structures could be readily assigned by analysis of their high-field NMR spectra in conjunction with known data.[29] Deacylation of either **17** or **18** followed by reaction of the resultant arabinose with acetone afforded (±)-diacetone arabinose **19** whose spectral properties were identical with those of an authentic sample.[30] In another elaboration **16** was treated with MCPBA (*m*-chloroperoxybenzoic acid) in methanol.[31] Upon acetylation there was thus obtained a 65% yield of the crystalline (±)-methyl arabinoside **20** whose stereochemistry was determined by spectral means (see Experimental Section).

In summary, the feasibility of incorporating formaldehyde into our cyclocondensation process is a useful advance *since it allows the 2-position of the 2,3-dihydropyrone to emerge in unsubstituted form.* This could be helpful in the synthesis of a variety of important natural products. Already it is seen to lead to an expeditious route to pentose systems in defined pyranosidal form.

Experimental Section

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were obtained on a Varian EM390 spectrometer for protons at 90 MHz and a Bruker WM500 spectrometer for protons at 500 MHz and carbon at 125 MHz; chemical shifts are reported in parts per million downfield from internal Me_4Si. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet, o, octet; m, multiplet; dd, doublet of doublets, etc. Mass spectra were obtained on a Hewlett Packard 5985 GC/MS spectrometer in the electron-impact mode. Yields reported are for material judged homogeneous by NMR, TLC, and HPLC (for liquids) and melting point for solids. Thin-layer chromatography was performed on Merck 0.25-mm glass silica gel plates; visualization of the developed plates was by fluorescence quenching and staining with phosphomolybdic acid. Column chromatography was performed with Merck silica gel 60 (230–400 mesh) by using the procedure of Still.[32] HPLC analyses were performed on a Waters Model 6000A chromatography system. Analyses were performed by Mic Anal, Tucson, AZ.

All solvents were distilled prior to use. THF was distilled from Na/benzophenone under argon.

Zinc chloride[33] was heated to melting point under vacuum (0.8 mm) followed by cooling under argon. The solid was stored in a dessicator and crushed just prior to use.

2,3-Dihydro-4*H*-pyran-4-one (2). To a solution of 1-methoxy-3-((trimethylsilyl)oxy)buta-1,3-diene (2.17 g, .012 mol) in THF (50 mL) were added $ZnCl_2$ (1.71 g, .013 mol) and paraformaldehyde (4 g). The resulting suspension was heated at reflux for 3 h. Ice-cold saturated aqueous $NaHCO_3$ was then added. The resulting mixture was extracted with ether, and the combined ether layers were dried (K_2CO_3) and concentrated in vacuo, leaving a dark yellow oil. Chromatography[32] (SiO_2, 30% EtOAc/hexanes) yielded 680 mg (55%) of a volatile, unstable yellow oil: ^1H NMR ($CDCl_3$, Me_4Si, 90 MHz) δ 7.28 (d, J = 6 Hz, 1 H), 5.40 (d, J =

(18) Danishefsky, S.; Craig, T. A. *Tetrahedron* **1981**, *37*, 4081.
(19) This compound was previously reported, but without experimental details: Goshima, K.; Maezono, N.; Tokuyama, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*(3), 3692.
(20) Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.
(21) This compound had been previously prepared in these laboratories by Mr. Clarence J. Maring.
(22) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H.; Hotmann, F.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.
(23) For previous work in the area of sugar enolones, note: Lichtenthaler, F. W.; Sakakibara, T.; Egert, E. *Ber.* **1980**, *113*, 471, 489.
(24) The preparation and use of these dienes was accomplished by Clarence Maring of these laboratories, see: Danishefsky, S.; Maring, C. J.; *J. Am. Chem. Soc.*, manuscript submitted for publication.
(25) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
(26) L-Arabinal: Hummoler, F. L. *Methods Carbohydr. Chem.* **1962**, *1*, 83.
(27) D-Xylal: Weygand, F. *Methods Carbohydr. Chem.* **1962**, *1*, 182.
(28) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(29) Durette, P. L.; Horton, D. *J. Org. Chem.* **1971**, *36*, 2658.
(30) (a) Freundenberg, K.; Svanberg, O. *Ber.* **1922**, *55*, 3239. (b) Schmidt, O. T. *Methods Carbohydr. Chem.* **1966**, *2*, 318. (c) Singh, P. O.; Gharia, M. M.; Dasgupta, F.; Srivastava, H. C. *Tetrahedron Lett.* **1977**, 439.
(31) Frimer, A. *Synthesis* **1977**, 578. Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571.
(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(33) It has been pointed out by a referee that this method of "drying" the zinc chloride may in fact lead to the incorporation of Zn(OH)Cl in the catalyst. The literature procedure for anhydrous $ZnCl_2$ through refluxing thionyl chloride was not followed in these cases. The advantages of the two methods of pretreatment will be evaluated in further experiments.

6 Hz, 1 H), 4.50 (t, J = 7 Hz, 2 H), 2.56 (t, J = 7 Hz, 2 H); IR ($CHCl_3$) 1706 (s), 1602 (s), 1200 cm^{-1}; MS(EI), m/e (relative intensity) 99.1 (0.1), 98.1 (0.6).

5-Acetoxy-2,3-dihydro-4*H*-pyran-4-one (4). To a solution of 1-methoxy-2-acetoxy-3-((trimethylsilyl)oxy)-buta-1,3-diene[18] (350 mg, 1.73 mmol) in THF (20 mL) were added $ZnCl_2$ (260 mg, 2.90 mmol) and paraformaldehyde (300 mg). The resulting suspension was heated at reflux for 2 h. The light yellow mixture was then cooled, poured into saturated aqueous $NaHCO_3$, and extracted with Et_2O. The combined ether extracts were dried ($MgSO_4$) and concentrated in vacuo to give a dark yellow oil. Chromatography (SiO_2, 30% EtOAc/hexanes as eluent) yielded 100 mg (67%) of the pyrone as a colorless syrup: ^1H NMR ($CDCl_3$, 90 MHz, Me_4Si) δ 7.42 (s, 1 H), 4.50 (t, J = 7 Hz, 2 H), 2.67 (t, J = 7 Hz, 2 H), 2.30 (s, 3 H); IR ($CHCl_3$) 3005, 1780, 1710 (s), 1630, 1190 (vs) cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) δ 184.31, 168.53, 155.82, 131.79, 68.49, 35.68, 19.97; MS(EI), m/e (relative intensity) 157.1 (1.0), 156.0 (8.2), 115.1 (7.7), 114.1 (100), 86.0 (12.2), 85.1 (20.0), 58.1 (27.6), 43.2 (26.2).

Anal. Calcd for $C_7H_8O_4$: C, 53.83; H, 5.16. Found: C, 53.67; H, 5.27.

1-(Benzoyloxy)-3-acetoxy-4-methoxybut-3-en-2-one (6). To a suspension of m-chloroperbenzoic acid (Aldrich, 4.97 g, 0.028 mol) in pentane at −78 °C was added, rapidly dropwise, 1-methoxy-2-acetoxy-3-((trimethylsilyl)oxy)buta-1,3-diene[3] (**3**, 6.05 g, 0.026 mol). After addition was complete, the solution was stirred for 1 h at −78 °C and then allowed to warm to room temperature, and the suspension was filtered, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated in vacuo to an oil, which was treated with MeOH (10 mL) and allowed to stand for 1 h. The MeOH was removed, and the white solid dissolved in pyridine (20 mL) and CH_2Cl_2 (20 mL), cooled to 0 °C, and treated with (dimethylamino)pyridine (100 mg) followed by benzoyl chloride (4.22 mL, 0.036 mol). The solution was stirred for 2 h at 0 °C, then warmed to room temperature, poured over ice-cold saturated aqueous $NaHCO_3$, and extracted with Et_2O. The combined Et_2O layers were dried ($MgSO_4$) and concentrated in vacuo to a dark yellow oil. Chromatography (SiO_2, 25% EtOAc/hexanes) afforded 5.09 g (50%) of the enone **6** as colorless crystals: mp 107–108.5 °C; ^1H NMR ($CDCl_3$, Me_4Si, 90 MHz) δ 8.05 (m, 2 H), 7.45 (m, 3 H), 7.30 (s, 1 H), 5.00 (s, 2 H), 3.91 (s, 3 H), 2.15 (s, 3 H); IR ($CHCl_3$) 1780, 1725(s), 1702, 1602, 1270(s), 1190 (vs) cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) δ 186.66, 167.85, 165.83, 150.83, 133.50, 133.29, 129.88, 129.72, 129.30, 128.65, 128.38, 65.04, 62.66, 20.12.

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.41; H, 5.07. Found: C, 60.28; H, 4.90.

1-(Benzoyloxy)-2-(((1,1-dimethylethyl)dimethylsilyl)-oxy)-3-acetoxy-4-methoxybuta-1,3-diene (7). A suspension of 1-(benzoyloxy)-3-acetoxy-4-methoxybut-3-en-2-one (**6**; 385 mg, 1.38 mmol) in CCl_4 (10 mL) and NEt_3 (2 mL) was cooled to 0 °C and treated with (*tert*-butyldimethylsilyl)trifluoromethanesulfonate (Aldrich, 0.35 mL, 1.52 mmol) via syringe. After stirring for 1 h at 0 °C, an aliquot was removed and examined by NMR, indicating the absence of the starting enone and presence of the diene. The solution was then diluted with Et_2O-pentane, and the dark bottom layer was separated and discarded. The organic phase was washed with ice-cold saturated aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated in vacuo to yield 514 mg (95%) of a dark yellow oil of sufficient purity for use. Column chromatography over silica gel (30% EtOAc–hexanes) deactivated with 1% NEt_3 gave an analytical sample as an unstable yellow oil with the following spectral properties: ^1H NMR ($CDCl_3$, no Me_4Si, 90 MHz) δ 8.00 (m, 2 H), 7.45 (m, 3 H), 7.00 (s, 1 H), 6.28 (s, 1 H), 3.63 (s, 3 H), 2.01 (s, 3 H), 0.90 (s, 9 H), 0.00 (s, 6 H); IR ($CHCl_3$) 1780 (s), 1735 (vs), 1650, 1270 cm^{-1}; ^{13}C NMR ($CDCl_3$, no Me_4Si) δ 167.56, 163.31, 138.46, 133.88, 133.38, 129.95, 129.13, 128.44, 127.00, 119.20, 119.16, 60.84, 25.71, 20.47, 18.25; MS(EI), m/e (relative intensity) 394.1 (1.4), 393.1 (5.0), 392.1 (18.2), 246.2 (10.8), 245.2 (64.1), 229.1 (24.7), 172.1 (10.7), 171.1 (65.9), 105.1 (100).

3-(Benzoyloxy)-5-acetoxy-2,3-dihydro-4*H*-pyran-4-one (8). To a solution of 1-(benzoyloxy)-2(((1,1-dimethylethyl)dimethylsilyl)oxy)-3-acetoxy-4-methoxybuta-1,3-diene (**7**, 514 mg, 1.31 mmol) in THF (20 mL) was added $ZnCl_2$ (196 mg, 1.44 mmol) and paraformaldehyde (500 mg), and the resulting suspension was heated at reflux for 3 h. Saturated aqueous $NaHCO_3$ was then added, and the mixture was extracted with Et_2O. The combined Et_2O layers were dried ($MgSO_4$) and concentrated in vacuo to leave a yellow oil, which upon chromatography (SiO_2, 30% EtOAc/hexanes) yielded 271 mg (75%) of pyrone **8** as a colorless oil: ^1H NMR ($CDCl_3$, Me_4Si, 90 MHz) δ 8.05 (m, 2 H), 7.56 (m, 3 H), 7.48 (s, 1 H), 5.66 (t, J = 6 Hz, 1 H), 4.60 (d, J = 6 Hz, 2 H), 2.30 (s, 3 H); IR ($CHCl_3$) 3050, 1778, 1735 (s), 1711, 1630 (s), 1260, 1185 (s), 910 cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) δ 180.37, 168.35, 164.94, 156.36, 133.56, 130.90, 129.94, 128.66, 128.37, 70.22, 68.55, 19.98; MS(EI), m/e (relative intensity) 277.0 (0.1), 276.0 (0.6), 234.1 (15.5), 112.1 (10.2), 106.2 (7.1), 105.1 (100).

Anal. Calcd for $C_7H_8O_4$: C, 53.83; H, 5.16. Found: C, 53.67; H, 5.27.

4-(Benzoyloxy)-2*H*-pyran-3-one (10). To a mixture of 1-methoxy-3-((*tert*-butyldimethylsilyl)oxy)-4-(benzoyloxy)-1,3-butadienes **9** (500 mg, 1.49 mmol) in THF (10 mL) was added anhydrous $ZnCl_2$ (200 mg, 1.49 mmol). The resulting mixture was stirred for 10 min at room temperature. Excess paraformaldehyde (500 mg) was then added, and the mixture was heated at reflux for 3 h. The suspension is then cooled, poured into ice-cold $NaHCO_3$, and extracted exhaustively with ether. The combined ether layers layers are dried (K_2CO_3) and concentrated in vacuo to give a yellow oil. Chromatography (SiO_2, 35% EtOAc/hexane as eluent) afforded 211 mg (65%) of colorless crystals ($CHCl_3$–pentane): mp 85–85.5 °C; ^1H NMR ($CDCl_3$, Me_4Si, 500 MHz) δ 8.05 (m, complex, 2 H), 7.60 (m, 2 H), 7.49 (m, 2 H), 7.45 (d, J = 6 Hz, 1 H), 5.66 (dd, J = 5, 10 Hz, 1 H), 5.55 (d, J = 6 Hz, 1 H), 4.66 (dd, J = 5, 12 Hz, 1 H), 4.54 (dd, J = 10, 12 Hz, 1 H); IR ($CHCl_3$) 3000, 1740 (s), 1703 (s), 1602 (vs), 1460, 1405, 1270 (s), 940, 708 cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si, 125 MHz) δ 186.98, 165.11, 163.36, 133.51, 129.94, 128.93, 128.40, 105.84, 69.48, 68.55; MS(EI), m/e (relative intensity) 218.1 (.7), 175.1 (43.2), 105.1 (100), 77.0 (67.9), 69.1 (10.0), 51.1 (21.5).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.03; H, 4.62. Found: C, 65.96; H, 4.75.

4-*O*-Benzoylarabinal (12). The prrocedure of Luche[25] was employed. A solution of pyrone **10** (1.50 g, 6.87 mmol) in anhydrous MeOH (30 mL) was treated with $CeCl_3 \cdot 7H_2O$ (Aldrich, 2.85 g, 7.56 mmol) and the mixture stirred for 10 min and then cooled to −78 °C (dry ice/*i*-PrOH). To this was added $NaBH_4$ (Alfa, 0.19 g, 7.56 mmol) in EtOH (10 mL), *taking care to ensure that the temperature of the reaction mixture did not exceed −70 °C.*[34] After addition was complete, the resulting mixture was stirred for 2 h while warming to room temperature. Saturated aqueous potassium acetate (10 mL) was then added, and the resulting suspension was stirred for 10 min and then partitioned between ether and brine. The combined ether layers were dried and concentrated in vacuo, giving a colorless oil. chromatography (SiO_2, 20% EtOAc/hexane as eluent) gave 1.28 g (89%) of 4-*O*-benzoylarabinal (**12**) as a colorless syrup: ^1H NMR ($CDCl_3$, Me_4Si, 500 MHz) δ 8.04 (d, J = 6 Hz, 2 H), 7.55 (t, J = 6 Hz, 1 H), 7.42 (t, J = 6 Hz, 2 H), 6.50 (d, J = 6 Hz, 1 H), 5.50 (t, J = 4 Hz, 1 H), 4.95 (dd, J = 4, 6 Hz, 1 H), 4.19 (dt, J = 4, 10 Hz, 1 H), 4.06 (ddd, J = 2, 4, 10 Hz, 1 H), 3.93 (t, J = 10 Hz, 1 H), 2.70 (br s, 1 H, disappears w/D_2O); IR ($CHCl_3$) 3005 (w), 1720 (s), 1650, 1466, 1280 (s), 1220 (vs), 1118, 725 (s, br) cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) δ 166.70, 148.13, 133.17, 129.85, 129.61, 128.35, 97.21, 66.23, 65.32, 65.20; MS(EI), m/e (relative intensity) 220.2 (0.1), 202.1 (28.1), 105.1 (100), 77.1 (4.9), 69.1 (9.4).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.43; H, 5.49. Found: C, 65.14; H, 5.60.

Continued elution afforded 143 mg (10%) of epimer **13**, which was identified by conversion (K_2CO_3/MeOH then Ac_2O/py) to di-*O*-acetylxylal (**15**), which was identical with an authentic sample prepared from *d*-xylose (Pfanstiehl) by using the procedure of Weygand.[27]

***dl*-Di-*O*-acetylarabinal (14).** A solution of 4-*O*-benzoylarabinal (**12**, 90 mg, 0.40 mmol) in anhydrous MeOH (2 mL) was cooled to 0 °C and treated with anhydrous methanol (5 mL) that had been saturated with ammonia. After stirring for 2 h at 0 °C, the MeOH was removed in vacuo. The residue was dissolved in

(34) In cases where the temperature was allowed to exceed −70 °C, the ratio of **12** to **13** was found to drop substantially.

pyridine (2 mL) and treated with acetic anhydride (0.5 mL). After 1 h, the volatiles were evaporated. The residue was subjected to chromatography (SiO_2, 35% EtOAc/hexane as eluent) to yield 75 mg (90%) *dl*-di-*O*-acetylarabinal. The material thus obtained was spectroscopically (^1H NMR, IR) as well as chromatographically (TLC, HPLC) identical with a sample of *l*-di-*O*-acetylarabinal, prepared from *l*-arabinose (Pfanstiehl) by using the procedure of Humoller.[26]

4-*O*-Benzoyl-3-*O*-acetylarabinal (16). 4-*O*-Benzoylarabinal (**12**, 0.30 g, 1.36 mmol) was dissolved in pyridine (5 mL) and treated with acetic anhydride (1 mL). After 1 h, TLC analysis showed the absence of the starting monoprotected arabinal and the presence of a higher R_f spot (0.65 vs. 0.4 for **12** in 50% EtOAc/hexanes). The pyridine and acetic anhydride were removed in vacuo to give 0.34 g (96%) of essentially pure 4-*O*-benzoyl-3-*O*-acetylarabinal as a syrup: ^1H NMR ($CDCl_3$, Me_4Si, 500 MHz) δ 8.05 (d, J = 5 Hz, 2 H), 7.56 (t, J = 5 Hz, 1 H), 7.44 (t, J = 5 Hz, 2 H), 6.56 (d, J = 6 Hz, 1 H), 5.69 (t, J = 3 Hz, 1 H), 5.28 (m, complex (eight lines), 1 H), 4.99 (t, J = 6 Hz, 1 H), 4.09 (d, J = 6 Hz, 2 H), 2.01 (s, 3 H); IR ($CHCl_3$) 2990, 1720 (s), 1710 (s), 1640, 1270, 1210 (s), 1103, 1090, 900, 700 cm^{-1}; ^{13}C NMR ($CDCl_3$; Me_4Si) δ 169.63, 165.81, 147.97, 132.97, 130.08, 129.53, 128.31, 97.48, 66.23, 66.33, 62.78, 10.58; MS, *m/e* (relative intensity) 262.1 (0.3).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.10; H, 5.38. Found: C, 64.07; H, 5.65.

α- and β-4-*O*-Benzoyl-1,2,3-tri-*O*-acetylarabinose (17 and 18). A solution of 4-*O*-benzoyl-3-*O*-acetylarabinal (500 mg, 1.90 mmol) in 10 mL THF/H_2O (5:1) was treated with *N*-methylmorpholine *N*-oxide (250 mg, 2.09 mmol) and OsO_4 (0.10 mL, 4 M in THF), and the resulting mixture was stirred for 12 h at room temperature. The mixture was diluted with saturated aqueous $NaHSO_3$ (2 mL) and partitioned between Et_2O and H_2O. The combined Et_2O layers were washed with H_2O and brine and dried, and the solvent removed was in vacuo, yielding a colorless oil which was acetylated by exposure to acetic anhydride (1 mL) in pyridine (5 mL) at room temperature for 1 h. The volatiles were removed in vacuo, leaving 610 mg (85%) 4-*O*-benzoyl-1,2,3-tri-*O*-acetylarabinose as colorless rosettes ($CHCl_3$/pentane): mp 93–93.5 °C; the solid was determined to be a 1:1 mixture of anomers separated by HPLC (μ-porasil, 20% EtOAc/hexane, 4 mL/min isocratic) and characterized as follows.

α-Anomer: ^1H NMR ($CDCl_3$) δ 8.02 (d, J = 6 Hz, 2 H), 7.61 (t, J = 6 Hz, 1 H), 7.45 (t, J = 6 Hz, 2 H), 5.80 (d, J = 6 Hz, 1 H), 5.43 (m, complex, 2 H), 5.37 (dd, J = 2, 6 Hz, 1 H), 4.14 (B part, AB qd, J = 4, 12 Hz, 1 H), 3.85 (A part, AB qd, J = 1, 12 Hz, 1 H), 2.12 (s, 3 H), 2.08 (s, 3 H), 2.04 (s, 3 H).

β-Anomer: ^1H NMR ($CDCl_3$) δ 7.97 (d, J = 6 Hz, 2 H), 7.46 (t, J = 6 Hz, 1 H), 7.44 (t, J = 6 Hz, 2 H), 6.40 (d, J = 3 Hz, 1 H), 5.60 (AB qd, J = 3, 8 Hz, 2 H), 5.51 (br s, 1 H), 4.14 (B part AB q, J = 12 Hz, 1 H), 3.92 (A part, AB qd, J = 1, 12 Hz, 1 H), 2.18 (s, 3 H), 2.12 (s, 3 H), 1.97 (s, 3 H); IR ($CHCl_3$) 3010 (w), 1720–1730 (br s), 1465, 720 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_9$: C, 56.82; H, 5.30. Found: C, 56.97; H, 5.29.

1,2,3,4-Di-*O*-isopropylidenearabinopyranose. A solution of 4-*O*-benzoyl-1,2,3-tri-*O*-acetylarabinose (90 mg, 0.236 mmol) in MeOH (10 mL) was treated with solid K_2CO_3 (40 mg, 0.289 mmol) and stirred for 3 h at room temperature and then filtered and the methanol evaporated. The crude arabinose was then dissolved in acetone (5 mL) and treated with H_2SO_4 (2 drops), and the solution was stirred for 2 h at room temperature. The yellow mixture was neutralized with solid Na_2CO_3 and filtered, and the acetone was evaporated, giving 47 mg (87%) 1,2,3,4-di-*O*-isopropylidenearabinopyranose as colorless crystals ($CHCl_3$/pentane): mp 41–42 °C (lit.[30a] mp 41.5–43 °C). The 90- and 500-MHz proton NMR spectra and chromatographic behavior of the racemate thus obtained were identical with an authentic sample prepared from l-arabinose.[30b]

α-*O*-Methyl-2,3-di-*O*-acetyl-4-*O*-benzoylarabinopyranoside (20). A solution of 3-*O*-acetyl-4-*O*-benzoylarabinal (**14**, 250 mg, 0.95 mmol) in 10 mL of Et_2O–MeOH (4:1) was cooled to 0 °C (ice bath) and treated with *m*-chloroperbenzoic acid (250 mg, 1.14 mmol), and the resulting homogeneous mixture was stirred for 2 h at 0 °C, then warmed to room temperature, and allowed to stand for 2 days. The solution was then diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, dried, and concentrated in vacuo to give a crystalline solid. Recrystallization (CH_2Cl_2–pentane) yielded 217 mg (65%) of the methylarabinopyranoside as colorless needles: mp 115 °C; ^1H NMR ($CDCl_3$, Me_4Si) δ 8.00 (d, J = 6 Hz, 2 H), 7.57 (d, J = 6 Hz, 1 H), 7.43 (t, J = 6 Hz, 2 H), 5.39 (m, complex, 1 H), 5.35 (dd, J = 6, 9 Hz, 1 H), 5.28 (dd, J = 3, 9 Hz, 1 H), 4.45 (d, J = 6 Hz, 1 H), 4.11 (B part, AB qd, J = 3, 13 Hz, 1 H), 3.72 (A part, AB qd, J = 2, 13 Hz, 1 H), 3.53 (s, 3 H), 2.08 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 170.09, 169.51, 165.51, 133.40, 129.77, 129.26, 128.50, 101.56, 70.63, 69.23, 67.71, 62.58, 56.64, 20.78, 20.76.

Anal. Calcd for $C_{17}H_{20}O_8$: C, 57.93; H, 5.72. Found: C, 57.60; H, 5.74.

Acknowledgment. This work was supported by PHS Grant AI 49841. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University which was supported by NSF Chemistry Divison Grant CHE 7916210.

Registry No. 1, 59414-23-2; **2**, 84302-42-1; **3**, 82217-50-3; **4**, 33245-15-7; **5**, 89890-49-3; **6**, 89890-50-6; **7**, 89890-51-7; **8**, 89890-52-8; **9**, 87461-94-7; **10**, 89890-53-9; **11**, 89890-54-0; **12**, 89890-55-1; **13**, 89890-56-2; **14**, 89921-34-6; **15**, 89921-35-7; **16**, 89890-57-3; **17**, 89890-58-4; **18**, 89890-59-5; **19**, 89921-36-8; **20**, 89890-60-8; formaldehyde, 50-00-0; paraformaldehyde, 30525-89-4; $ZnCl_2$, 7646-85-7.