Synthesis of the Papulacandin C-Arylglucosyl Spiroketal Nucleus[1]

Stuart B. Rosenblum[2a] and Ron Bihovsky*[,2b]

Contribution from the Department of Chemistry, State University of New York, Stony Brook, New York 11794. *Received June 7, 1989*

Abstract: The enantiomerically pure tricyclic *C*-arylglucosyl spiroketal nucleus of papulacandin has been synthesized by reaction of an appropriately protected gluconolactone **4** with a metalated derivative of 5-(hydroxymethyl)resorcinol (**5**). In model studies, alkyllithium and aryllithium reagents reacted with δ-valerolactone (**6**) and tetra-*O*-benzylgluconolactone (**9**) to afford the expected lactols or hydroxy ketones. Furthermore, aryllithium reagent **14a** reacted with δ-valerolactone to afford spiroketal **15a**. Aryllithium reagent **14a** reacted with tetra-*O*-benzylgluconolactone (**9**) to give a mixture of epimeric spiroketals **16a** and **17**. More satisfactorily, aryllithium reagent **14b** reacted with **9** to provide hydroxy ketone **19a** which was deprotected and cyclized to afford **16c**, the *C*-arylglucosyl spiroketal nucleus of papulacandin. A procedure has been developed for acylation at O-3.

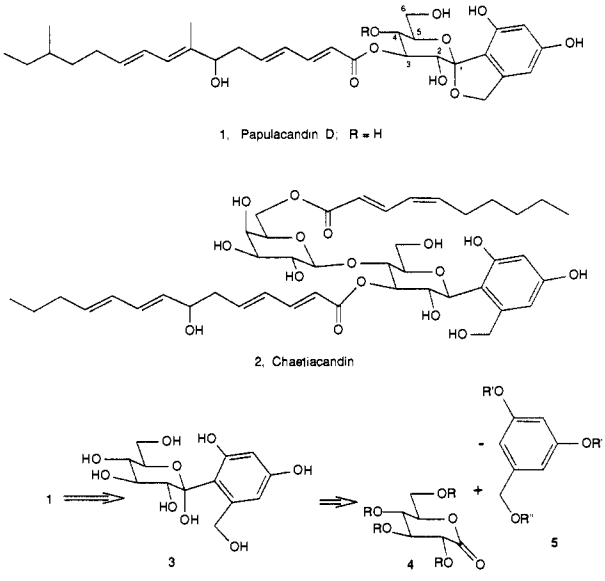
The papulacandins, a recently discovered class of antifungal antibiotics from the fungus *Papularia sphaerosperma*, were first reported in 1976.[3a,b] On the basis of ^1H and ^{13}C NMR characterization,[3c,d] chemical degradation,[3e] and X-ray crystallography,[3f] papulacandin D was assigned structure **1**. The unique tricyclic *C*-arylglucosyl spiroketal nucleus of papulacandin D is comprised of a β-*C*-glucoside and an α-*O*-glucoside both formally derived from 5-(hydroxymethyl)resorcinol. The O-3 of the glucose moiety in the papulacandins is esterified with an unusual 18-carbon branched unsaturated fatty acid. In papulacandins A, B, and C, O-4 is substituted as an *O*-(6-acyl-β-galactoside), but this moiety is not essential for biological activity. Chaetiacandin (**2**), isolated more recently from *Monochaetia dimorphospora*, bears considerable resemblance to the papulacandins but lacks the spiroketal moiety.[4]

Interest in the antibiotic, antifungal, and glucan synthesis inhibitory properties[3a,b] of these unique spiro C-alkylated glucosyl derivatives has prompted investigations toward synthesis. A total synthesis of the racemic *C*-arylglucosyl spiroketal nucleus of papulacandin, featuring a hetero Diels-Alder reaction to form the pyran ring of glucose, has been reported.[5] A synthesis of the optically pure arylglucosyl spiroketal from a protected glucose aldehyde and a protected gluconic ester has recently been reported.[6]

We envisioned that the tricyclic *C*-β-arylglucosyl spiroketal structural nucleus of the papulacandins (**1**) would form readily by dehydration of lactol **3**, which could be synthesized by reaction of a suitably protected D-gluconolactone (**4**) with a metalated derivative of 5-(hydroxymethyl)resorcinol (**5**, Scheme I).[1] In this concise synthetic scheme, the desired configuration at C-1 of the glucoside would be controlled by the anomeric effect.

Nucleophilic addition of organometallics to lactones is a well-known reaction.[7,8] However, applications to natural product synthesis have been limited by the tendency for 2 mol of organometallic to react with the lactone and by hydrogen abstraction α to the lactone. Tetra-*O*-benzylgluconolactone (**4**, R = Bn), for example, reacts readily with several simple aryllithium reagents but gives only low yields on reaction with lithiated protected 5-(hydroxymethyl)resorcinols[6] or with (2,6-dimethoxyphenyl)-lithium.[7c] Likewise, no product was isolated from the reaction between tetra-*O*-(trimethylsilyl)gluconolactone and aryllithium **5**.[5] Accordingly, the success of the synthetic approach depicted in Scheme I required detailed attention to conditions for additions to lactones as well as a careful consideration of appropriate hydroxyl protecting groups.

Scheme I



As a model, freshly distilled δ-valerolactone (**6**) reacted with methyllithium at −70 °C to afford a 1:4.5 mixture (by NMR in $CDCl_3$) of hemiketal **7a** and hydroxy ketone **8a**[9,10] in 60% yield

(1) This investigation was originally reported by Rosenblum, S. B.; Bates, H. A. at 194th National Meeting of the American Chemical Society, New Orleans, LA, Sept. 1987; American Chemical Society: Washington, DC, 1987; ORGN 188.

(2) (a) Current address: Pharmaceutical Research Division, Schering-Plough Corp., Bloomfield, NJ 07003. (b) Current Address: Berlex Laboratories, Inc., 110 East Hanover Ave., Cedar Knolls, NJ 07927. Previous publications of R.B. were published under the name Hans Aaron Bates.

(3) (a) Traxler, P.; Gruner, J.; Auden, J. A. L. *J. Antibiotics* **1977**, *30*, 289. (b) Traxler, P.; Gruner, J. Ger. Offen. 2,609,611, 1976. (c) Traxler, P.; Fritz, H.; Richter, W. J. *Helv. Chim. Acta* **1977**, *60*, 578. (d) Gruner, J.; Traxler, P. *Experientia* **1977**, *33*, 137. (e) Traxler, P.; Fritz, H.; Fuhrer, H.; Richter, W. J. *J. Antibiotics* **1980**, *33*, 967. (f) Rihs, G.; Traxler, P. *Helv. Chim. Acta* **1981**, *64*, 1533.

(4) (a) Komori, T.; Yamashita, M.; Tsurumi, Y.; Kohsaka, M. *J. Antibiotics*, **1985**, *38*, 455. (b) Komori, T.; Itoh, Y. *J. Antibiotics* **1985**, *38*, 544.

(5) Danishefsky, S.; Phillips, G.; Ciufolini, M. *Carbohydr. Res.* **1987**, *171*, 317. Phillips, G. Personal communication.

(6) Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163.

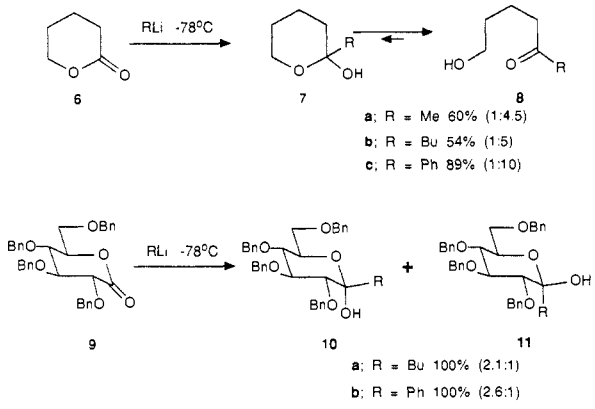
(7) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370. (c) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752. (d) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610. Stereochemistry was assigned to **10** and **11** on the basis of the anomeric effect and ^{13}C NMR chemical shifts.

(8) (a) Bonner, W. A. *Adv. Carbohydr. Chem.* **1951**, *6*, 251. (b) Ogura, H.; Takahashi, H. *J. Org. Chem.* **1974**, *39*, 1374. (c) Sanchez, E. L.; Arzeno, H. *Rev. Latinoam. Quim.* **1976**, *7*, 143. (d) Horton, D.; Priebe, W. *Carbohydr. Res.* **1981**, *94*, 27. (e) Plaumann, D. E.; Fitzsimmons, B. J.; Ritchie, B. M.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 941. (f) Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246. (g) Jacobson, R.; Taylor, R. J.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1982**, *47*, 3140. (h) Isobe, M.; Ichikawa, Y.; Masaki, H.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 3607. (i) de Perez, R. M. B.; Fuentes, L. M.; Larson, G. L.; Barnes, C. L.; Heeg, M. J. *J. Org. Chem.* **1986**, *51*, 2039. (j) Danishefsky, S. J.; DeNinno, M. P.; Audia, J. E.; Schulte, G. *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; ACS Symposium Series 386; American Chemical Society: Washington, DC, 1989; pp 160-175.

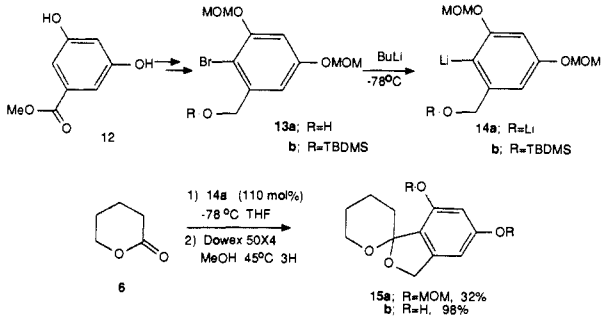
(9) Weber, G. F.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 364. LaMontagne, M. P.; Markovac, A.; Khan, M. S. *J. Med. Chem.* **1982**, *25*, 964.

0002-7863/90/1512-2746$02.50/0

Scheme II



Scheme III



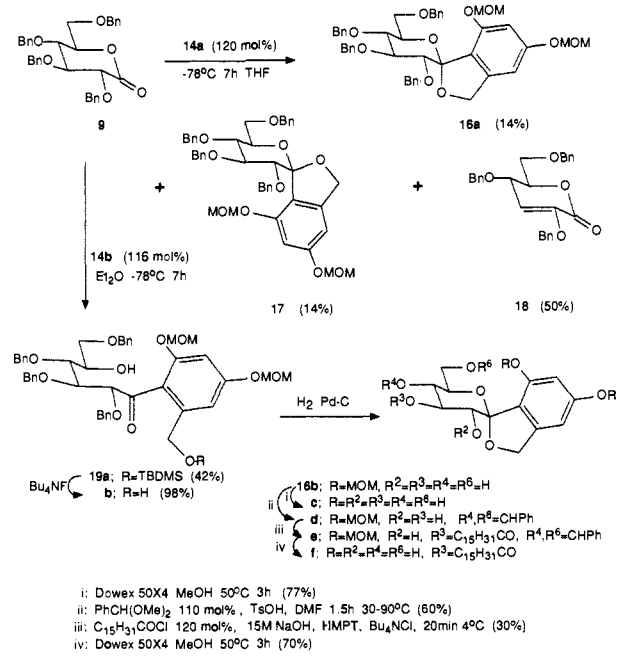
(Scheme II). Similarly, δ-valerolactone reacted with *n*-butyllithium to give a 1:5 mixture of **7b** and **8b**[8c] in 54% yield and with phenyllithium to give a 1:10 mixture of **7c** and **8c** in 89% yield. The tautomerization of hydroxy ketones has been discussed previously.[10] Tetra-*O*-benzylgluconolactone (**9**)[11] reacted with *n*-butyllithium and phenyllithium to provide a 2.1:1 mixture of epimeric hemiketals **10a** and **11a** and a 2.6:1 mixture of hemiketals **10b** and **11b**,[7d] respectively, in nearly quantitative yield. None of the tautomeric hydroxy ketones derived from hemiketals **10** and **11** were detected, suggesting that the benzyloxy groups are more favorably accommodated as equatorial substituents on the six-membered ring.

Aryllithium reagents **14a** and **14b**, appropriate for the synthesis of papulacandin, were generated regiospecifically by metal–halogen exchange on 2-bromo-3,5-bis(methoxymethoxy)benzyl alcohol (**13a**)[12] and the corresponding *tert*-butyldimethylsilyl ether (**13b**) with *n*-butyllithium, as shown in Scheme III.

Slow addition of δ-valerolactone (**6**) to anion **14a** at −78 °C, followed by treatment with Dowex 50 resin, afforded the anticipated spiroketal **15a** in 32% yield (Scheme III). 3,5-Bis(methoxymethoxy)benzyl alcohol was recovered in 68% yield, and no deuterium was incorporated into its aromatic ring when the reaction was quenched with D_2O. Therefore deprotonation of the lactone is a troublesome side reaction in this case. The methoxymethyl protecting groups of **15a** were removed with Dowex 50 to give **15b** in excellent yield.

Aryllithium reagent **14a** reacted with tetra-*O*-benzylgluconolactone (**9**) to afford 14% of desired tricyclic spiroketal papulacandin nucleus, **16a**, as shown in Scheme IV. Hydrogenolysis of the benzyl protecting groups provided **16b**, thus confirming the structure of **16a** (see below). Side products from reaction of lactone **9** with **14a** included 14% of epimeric spiroketal **17** and 50% of conjugated lactone **18**,[13] which arises from enolate formation followed by β-elimination. Attempted equilibration of the epimeric mixture of **16a** and **17** with camphorsulfonic acid (8 h, 45 °C) or Dowex 50 resin (3 days, 22 °C) did not affect the ratio. Presumably the spiroketal does not open to the corresponding oxonium ion under these conditions.

Scheme IV



The presence of the basic alkoxide moiety in **14a** was perceived to be responsible for the predominance of elimination to **18** and for formation of the undesired diastereomer **17**. In order to overcome these problems, aryllithium reagent **14b**, in which the benzylic alcohol is protected as a *tert*-butyldimethylsilyl ether, was employed. Tetra-*O*-benzylgluconolactone (**9**) reacted with **14b** to give acyclic hydroxy ketone **19a** in 42% yield (Scheme IV). Only 20% of unsaturated lactone **18** was formed. The silyl ether was readily cleaved with tetrabutylammonium fluoride to afford **19b**. Surprisingly, **19b** did not dehydrate to **16a** spontaneously or under a variety of acidic conditions. The stability of related acyclic hydroxy ketones, relative to the corresponding lactols, has previously been reported.[8j] As expected, however, hydrogenolysis of the *O*-benzyl protecting groups induced spontaneous cyclization of two hydroxyl groups with the ketone, affording tricyclic spiroketal **16b** as the *only* diastereomer. Removal of the MOM protecting groups with Dowex 50 resin afforded the tricyclic *C*-arylglucosyl spiroketal papulacandin nucleus, **16c**, the ^1H and ^{13}C NMR spectra of which were identical with those reported for **16c** prepared by degradation of papulacandin.[3c,d]

Completion of the synthesis of papulacandin D, the simplest congener, requires regioselective esterification of the unique 18-carbon fatty acid residue to O-3 of the tricyclic *C*-arylglucosyl spiroketal nucleus. Accordingly, O-4 and O-6 of **16b** were protected as a benzylidine acetal to give **16d**. Treatment of **16d** with palmitoyl chloride and sodium hydroxide under phase-transfer conditions[14] gave predominantly **16e** esterified at O-3. Deprotection of the hydroxyl and phenol groups afforded the papulacandin D analogue **16f**.

Experimental Section

2-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3,5-bis(methoxymethoxy)benzene (13b). 2-Bromo-3,5-bis(methoxymethoxy)benzyl alcohol (**13a**)[12] (0.967 g, 3.16 mmol), *tert*-butyldimethylsilyl chloride (0.571 g, 3.79 mmol, 120 mol %), and imidazole (0.538 g, 7.9 mmol, 250 mol %) were dissolved in DMF (10 mL). After 5 h, the DMF was removed under vacuum (60 °C, 0.2 mmHg) to afford a semicrystalline solid. Chromatography on silica gel 60 with hexane–ethyl acetate (2:1) eluent afforded **13b** (1.12 g, 84% yield): ^1H NMR (80 MHz, $CDCl_3$) δ 6.95 (2

(10) Whiting, J. E.; Edward, J. T. *Can. J. Chem.* **1971**, *49*, 3799. Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Plenum: New York, 1985; pp 98–113.
(11) Kuzuhara, H.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531.
(12) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885.
(13) Hall, R. H.; Bischofberger, K.; Eitelman, S. J.; Jordaan, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2236. Tsuda, Y.; Nunozawa, T.; Yoshimoto, K. *Chem. Pharm. Bull.* **1980**, *28*, 3223.
(14) Szeja, W. *Synthesis* **1979**, 821.

H, d, J = 3), 6.70 (2 H, d, J = 3), 5.16 (2 H, s), 5.10 (2 H, s), 4.72 (2 H, s), 3.48 (3 H, s), 3.42 (3 H, s), 0.95 (9 H, s), 0.11 (6 H, s); ^{13}C NMR (20 MHz, $CDCl_3$) δ 157.4, 153.9, 142.6, 108.5, 103.5, 103.2, 95.2, 94.6, 64.7, 56.3, 55.9, 25.8, 18.3, -5.4.

Anal. Calcd for $C_{17}H_{29}O_5SiBr$: C, 48.45; H, 6.94. Found: C, 48.29; H, 6.85.

3′,4′,5′,6′-Tetrahydro-5,7-bis(methoxymethoxy)spiro[isobenzofuran-1(3*H*),2′-[2*H*]pyran] (15a). Butyllithium (2.45 M, 1.01 mL, 2.48 mmol, 243 mol %) was added dropwise to a suspension of aryl bromide **13a** (371 mg, 1.21 mmol, 119 mol %) in 15 mL THF at -78 °C. After 30 min of stirring, freshly distilled δ-valerolactone (102 mg, 1.02 mmol) in 2 mL of THF was added dropwise. After 14 h at -70 °C the reaction was quenched with water and extracted three times with diethyl ether, and the organic layers were dried over potassium carbonate. Chromatography of the crude product on silica gel 60 with hexane–ethyl acetate (50:50) eluent afforded **15a** (101 mg, 32% yield): MS m/e (relative intensity) 310 (50, M^+), 265 (94), 251 (95), 221 (100), 192 (97); IR (neat) 2940, 2860, 1610, 1100, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (1 H, d, J = 1.7), 6.58 (1 H, d, J = 1.7), 5.31 (1 H, m), 5.18 (1 H, m), 5.15 (2 H, s), 5.10 (2 H, s), 4.07 (1 H, m), 3.80 (1 H, m), 3.52 (3 H, s), 3.47 (3 H, s), 2.65 (2 H, m), 2.0–1.8 (4 H, m); ^{13}C NMR (20 MHz, $CDCl_3$) δ 159.5, 152.9, 143.5, 123.5, 108.4, 102.9, 101.5, 94.6, 94.2, 71.0, 63.1, 56.2, 55.9, 32.7, 25.1, 19.5.

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.93; H, 7.14. Found: C, 61.38; H, 7.36.

3′,4′,5′,6′-Tetrahydrospiro[isobenzofuran-1(3*H*),2′-[2*H*]pyran]-5,7-diol (15b). Dowex 50X4 resin (13 mg) was added to a solution of **15a** (50 mg, 0.161 mmol) in methanol (2 mL). After 3 h at 55 °C, the mixture was filtered, and the filtrate was concentrated to afford **15a** as an oil (35 mg, 98% yield): ^{1}H NMR (80 MHz, D_2O) δ 6.6 (1 H, d), 6.35 (1 H, d), 5.25 (2 H, m), 4.05 (1 H, m), 3.70 (1 H, m), 2.65 (2 H, m), 2.20–1.85 (4 H, m); MS m/e (relative intensity) 222 (M^+, 11).

Anal. Calcd for $C_{12}H_{14}O_4 \cdot H_2O$: C, 59.99; H, 6.71. Found: C, 60.35; H, 6.55.

1,1^6-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-bis(methoxymethoxy)-phenyl]-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (16a). Butyllithium (2.45 M, 0.62 mL, 1.52 mmol, 262 mol %) was added dropwise to a solution of aryl bromide **13a** (225 mg, 0.734 mmol, 126 mol %) in THF at -78 °C. After 30 min at -78 °C, gluconolactone **9** (312 mg, 0.581 mmol) in THF was added. After 7 h at -78 °C the reaction was slowly warmed to -55 °C and stirred for a total of 19 h. Quenching and isolation as above, followed by chromatography (hexane–EtOAc 1:1) afforded pure diastereomeric hemiketals **16a** (14% yield), **17** (14%), and elimination product **18** (50% yield).

16a: IR ($CHCl_3$) 2920, 1600, 1150, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (20 H, m), 6.7 (2 H, dd), 5.15 (2 H, dd), 5.0–4.6 (8 H, m), 4.68 (2 H, s), 4.55–4.38 (3 H, m), 4.27 (1 H, dd), 4.0 (1 H, m), 3.78 (1 H, d), 3.48 (3 H, s), 3.06 (3 H, s); ^{13}C NMR (20 MHz, $CDCl_3$) δ 159.8, 155.0, 143.3, 139.3, 139.0, 138.9, 138.7, 129.0, 128.8, 128.5, 128.2, 128.0, 127.5, 127.4, 127.0, 110.9, 105.1, 101.3, 95.3, 94.5, 81.7, 79.2, 74.5, 74.3, 74.0, 73.9, 73.6, 72.6, 72.4, 71.7, 65.3, 56.1, 55.7.

Anal. Calcd for $C_{45}H_{48}O_{10}$: C, 72.17; H, 6.46. Found: C, 71.69; H, 5.95.

1,1^6-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-bis(methoxymethoxy)-phenyl]-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (17): IR ($CHCl_3$) 2920, 1600, 1150, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (20 H, m), 6.8 (2 H, dd), 5.2 (2 H, dd), 5.1–4.2 (8 H, m), 4.1–3.8 (4 H, m), 3.75 (1 H, dd), 3.46 (3 H, s, OCH_3), 3.08 (3 H, s, OCH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 160.2, 153.3, 143.9, 138.9, 138.6, 138.5, 128.7, 128.4, 128.2, 128.0, 127.8, 127.7, 127.5, 127.4, 110.0, 103.2, 101.4, 94.6, 94.5, 83.7, 81.4, 78.2, 75.8, 74.9, 74.8, 73.1, 73.1, 68.9, 56.3, 56.1.

Anal. Calcd for $C_{45}H_{48}O_{10}$: C, 72.17 H, 6.46. Found: C, 71.92; H, 6.60.

2,4,6-Tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enonolactone (18): ^{1}H NMR and IR spectra are consistent with the literature;[13] ^{13}C NMR (20 MHz, $CDCl_3$, SFORD) δ 159.4 (s), 144.1 (s), 137.5 (s), 137.3 (s), 135.2 (s), 128.6 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.4 (d), 110.3 (d), 79.8 (t), 73.6 (t), 71.1 (t), 70.4 (t), 69.4 (d), 68.3 (d).

1-*C*-[6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,4-bis(methoxymethoxy)phenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucose (19a). Butyllithium (2.20 M, 0.39 mL, 0.858 mmol, 156 mol %) was added slowly to a solution of aryl bromide **13b** (347 mg, 0.825 mmol, 150 mol %) in ethyl ether at -80 °C. After 30 min at this temperature, gluconolactone **9** (296 mg, 0.550 mmol) in ether was added dropwise. After 1 h at -80 °C the reaction was allowed to warm to 15 °C over 3 h. The reaction was quenched with water and processed as usual to afford **19a** (204 mg, 42% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.2 (20 H, m), 6.82 (1 H, d), 6.78 (1 H, d), 5.3–4.4 (12 H, m), 4.2–3.9 (4 H, m), 3.70 (1 H, dd), 3.58 (1 H, dd), 3.45 (3 H, s), 3.23 (3 H, s), 0.95 (9 H, s), 0.05 (3 H, s), 0.01 (3 H, s); ^{13}C NMR (20 MHz, $CDCl_3$) δ 192.0, 160.2, 156.5, 138.9, 136.1, 128.3, 127.7, 126.7, 107.4, 101.5, 95.2, 94.3, 75.1, 73.3, 71.4, 70.8, 69.9, 62.5, 56.1, 25.9, 18.7, -5.6.

Anal. Calcd for $C_{51}H_{64}O_{11}Si$: C, 69.52; H, 7.32. Found: C, 69.80; H, 7.07.

1-*C*-[6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,4-dihydroxyphenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucose (19b). $Bu_4NF \cdot 3H_2O$ (145.6 mg, 0.461 mmol) was added to a solution of **19a** (336 mg, 0.381 mmol) in THF (5 mL). After 30 min at 22 °C, the solvent was evaporated and the residue chromatographed on silica gel (EtOAc) to afford **19b** (286 mg, 98% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.2 (20 H, m), 6.83 (1 H, d), 6.80 (1 H, d), 5.2–4.5 (14 H, m), 4.45 (2 H, br s), 4.1–3.9 (4 H, m), 3.52 (2 H, m), 3.50 (3 H, s), 3.35 (3 H, s); MS m/e (relative intensity) 748 (2, M^+).

1,1^6-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-bis(methoxymethoxy)-phenyl]-α-D-glucopyranose (16b). (a) A stirred solution of **19b** (55.5 mg) in ethanol (5 mL) was hydrogenated at atmospheric pressure over 10% Pd–C (55 mg) for 5.5 h at 45 °C. Removal of the catalyst and evaporation of the solvent afforded **16b** (23.4 mg, 82% yield).

(b) A solution of **16a** (45 mg) in ethanol (5 mL) was hydrogenated as above to afford **16b** (21 mg, 90% yield): ^{1}H NMR (200 MHz, D_2O) δ 6.62 (1 H, d), 6.44 (1 H, d), 5.2–4.9 (2 H, m), 5.15 (2 H, s), 4.95 (2 H, s), 4.80 (2 H, m), 4.15 (1 H, m) 4.0 (1 H, dd), 3.81 (2 H, m), 3.55 (3 H, s), 3.20 (3 H, s); MS m/e (relative intensity) 388 (M^+, 8).

1,1^6-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-dihydroxyphenyl]-α-D-glucopyranose (16c). Dowex 50X4 resin (75 mg) was added to a solution of **16a** (480 mg, 1.23 mmol) in methanol (25 mL). After 3 h at 50 °C, the mixture was filtered, and the filtrate was concentrated to afford **16c** as an oil (284 mg, 77% yield): ^{1}H NMR (200 MHz, D_2O) δ 6.60 (1 H, d), 6.34 (1 H, d), 5.18 (1 H, m), 4.95 (1 H, d), 4.72 (2 H, m), 4.1 (1 H, m), 3.75 (1 H, m), 3.42 (2 H, m); FAB MS m/e (relative intensity) 301 (2, M + 1); ^{13}C NMR identical with the literature spectrum.[3c,d]

Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 52.09; H, 5.68.

1,1^6-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-dihydroxyphenyl]-α-D-glucopyranose 3-Hexadecanoate (16f). *p*-Toluenesulfonic acid (2 mg, 3 mol %) was added to a solution of **16b** (150 mg, 0.387 mmol) and benzaldehyde dimethyl acetal (65 mg, 0.428 mmol, 110 mol %) in DMF (2 mL). The reaction was heated from 22 °C to 90 °C over 1.5 h in vacuo (14 mmHg). The residue was washed with saturated aqueous $NaHCO_3$ and water and then dried to afford **16d** in 60% yield.

Crude **16d** (92 mg, 0.193 mmol) was dissolved in HMPA (5 mL). Benzene (1 mL), 40% aqueous NaOH (1 mL), and Bu_4NCl (27 mg, 0.096 mmol, 50 mol %) were added, and the mixture was cooled to 4 °C. Palmitoyl chloride (64 mg, 0.233 mmol, 120 mol %) in benzene (1 mL) was added dropwise. After 10 min at 4 °C, the reaction was filtered. The organic layer was rinsed with water and dried. Chromatography on silica gel (1:1 hexane–ethyl acetate) afforded 3-palmitate **16e** (41 mg, 30% yield) as well as the 2-palmitate (20%), and the 2,3-dipalmitate (20%). Treatment of **16e** with Dowex 50X4 resin in methanol, as above, gave **16f** (21 mg, 70% yield): ^{1}H NMR (D_2O, 200 MHz) δ 6.60 (1 H, d), 6.34 (1 H, d), 5.72 (1 H, d), 5.65 (1 H, m), 4.9 (1 H, dd), 4.15 (2 H, m), 3.65 (1 H, m), 2.55 (2 H, m), 1.45 (20 H, m), 0.95 (3 H, br t); FAB MS m/e (relative intensity) 539 (6, M + 1).

Anal. Calcd for $C_{29}H_{46}O_9$: C, 64.66; H, 8.01. Found: C, 65.00; H, 7.82.

Acknowledgment. We gratefully acknowledge support of this research by the National Institutes of Health (A123281), and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No. 1, 61036-49-5; 6, 542-28-9; **9**, 13096-62-3; **12**, 2150-44-9; **13a**, 79834-15-4; **13b**, 125568-62-9; **14a**, 125568-69-6; **14b**, 125568-70-9; **15a**, 125568-57-2; **15b**, 125568-63-0; **16a**, 125568-58-3; **16b**, 125568-64-1; **16c**, 88526-78-7; **16d**, 125568-61-8; **16e**, 125568-65-2; **16e** (R^2 = $C_{15}H_{31}CO$), 125568-68-5; **16e** (R^2 = $C_{15}H_{31}O$; R^3 = H), 125568-60-7; **16f**, 125568-66-3; **17**, 125639-32-9; **18**, 62641-00-9; **19a**, 125568-59-4; **19b**, 125568-67-4.

Supplementary Material Available: Synthetic procedures and spectroscopic and analytical data for **6**, **7a**, **7b**, **8a**, **8b**, **8c**, **9**, **10a**, **10b**, **11a**, and **11b** (3 pages). Ordering information is given on any current masthead page.