The reaction mixture was filtered to remove excess Zn and the filtrate diluted with 2000 mL of $CHCl_3$. This solution was extracted 4 times with 500 mL of distilled water and once with 200 mL of saturated NaCl solution. The organic phase was dried over Na_2SO_4 for 1 h, filtered to remove excess Zn, and flash evaporated. The residual solid was extracted with 1 L of 1:1 heptane–toluene. This mixture was filtered and the solid was dried to give 65 g (isolated yield 62%) of pure (>99%) dialdehyde.[69]

4,4′-Biphenol. A 500-mL, three-necked flask equipped with a 250-mL addition funnel, mechanical stirrer, and stopcock adapter was charged with 49 g (0.75 mol) of Zn, 35 g (0.13 mol) of TPP, 3.9 g (0.025 mol) of 2,2′-bipyridine, and 3.25 g (0.025 mol) of $NiCl_2$. After the flask was evacuated and filled with nitrogen several times, 250 mL of dry nitrogen-purged DMAc was added and the flask was placed in a 65 °C oil bath. After the dark-brown catalyst had formed, 85.3 g (0.50 mol) of neat *p*-chlorophenyl acetate was slowly added via the addition funnel. The reaction was heated at 70 °C for 4 h and then filtered. A solution of NaOH (100 g/L water) was added to the filtrate and the mixture was stirred overnight at room temperature. Diethyl ether (500 mL) was added, the mixture was vigorously mixed for $^1/_2$ h and filtered, and the filtrate was separated in a separatory funnel. The aqueous layer was acidified with concentrated HCl to pH ~1. The resulting precipitate was collected by filtration, washed with hot water, and dried to yield 35 g (75% isolated yield) of 4,4′-biphenol.

(69) Isolated yields are generally lower than those indicated by GC analysis because of the difficulty of separating excess triphenylphosphine from the reaction. We have found subsequently a convenient laboratory procedure which avoids this problem. After the excess zinc and solvent are removed, the crude reaction product is stirred in xylene with excess methyl iodide to form the insoluble Wittig salt which is removed by filtration. Pure product can be isolated after the solvent and methyl iodide are evaporated.

Acknowledgment. We are indebted to B. V. Watkins and F. N. Ferrara for their excellent technical assistance and to Dr. M. J. Youssefi for providing mass spectral data. We also thank Drs. G. T. Kwiatkowski, L. M. Maresca, J. W. Lynn, R. K. Barnes, and J. E. McKeon for their encouragement and support and Professors R. G. Bergman (University of California, Berkeley) and M. F. Semmelhack (Princeton University) for helpful suggestions and stimulating discussions.

Registry No. $Ni(PPh_3)_3$, 25136-46-3; Zn, 7440-66-6; chlorobenzene, 108-90-7; *p*-chlorophenol, 106-48-9; *p*-chlorophenyl acetate, 876-27-7; *p*-chloroaniline, 106-47-8; *p*-chloroanisole, 623-12-1; *p*-chlorotoluene, 106-43-4; *p*-chlorobenzaldehyde, 104-88-1; *p*-chloroacetophenone, 99-91-2; *p*-chlorobenzonitrile, 623-03-0; 2-chlorothiophene, 96-43-5; 2-chloropyridine, 109-09-1; biphenyl, 92-52-4; 4,4′-biphenol, 92-88-6; phenol, 108-95-2; 4,4′-diacetoxybiphenyl, 32604-29-8; phenyl acetate, 122-79-2; 4-acetoxybiphenyl, 148-86-7; 4,4′-diaminobiphenyl, 92-87-5; 4-aminobiphenyl, 92-67-1; 4,4′-dimethoxybiphenyl, 2132-80-1; anisole, 100-66-3; 4-methoxybiphenyl, 613-37-6; iodobenzene, 591-50-4; 4,4′-dimethylbiphenyl, 613-33-2; 4,4′-diformylbiphenyl, 66-98-8; 4,4″diacetylbiphenyl, 787-69-9; 4,4′-dicyanobiphenyl, 1591-30-6; 2,2′-bithienyl, 492-97-7; 2,2′-bipyridine, 366-18-7.

An Approach to Pseudomonic Acids from Acetylenic Precursors: Synthesis of 2-(Hydroxymethyl)-3-butyn-1-ol

Hans Aaron Bates,* James Farina, and Michael Tong

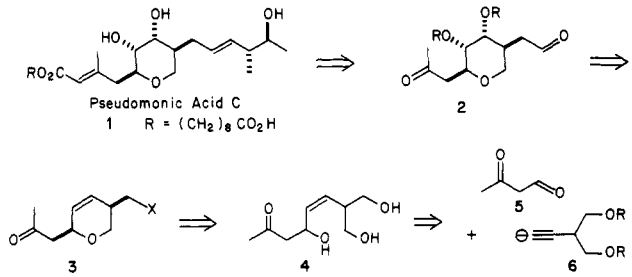
Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

Received October 22, 1985

The acetonide of 2-(hydroxymethyl)-3-butyn-1-ol (**17**) was prepared from bis(hydroxymethyl)malonate (**11**) or from 1,3-dihydroxypropanone (**22**). Alternative routes to **17** involving the intermediacy of highly unstable alkynal **21** or the corresponding acetate were unsuccessful. Condensation of the anion of **17** with aldehyde **30** followed by semihydrogenation and deprotection afforded keto triol **33**, which cyclized stereoselectively to dihydropyran **34**. Osmylation and functional group manipulation afforded **40** and **42**, precursors to pseudomonic acid C (**1**).

The pseudomonic acids, a group of structurally related antibiotics produced by *Pseudomonas fluorescens*, possess potent antibiotic activity.[1] The pseudomonic acids display no cross resistance with other antibiotics due to their novel mechanism of action, interference with bacterial protein synthesis by inhibition of isoleucyl-tRNA synthetase. Recently considerable effort has been directed toward total synthesis of the pseudomonic acids.[2]

Scheme I



Our retrosynthetic analysis of pseudomonic acid C (**1**) is depicted in Scheme I. We envisaged that the unsaturated side chains could be elaborated from a protected derivative of keto aldehyde **2** and that the cis vicinal diol could be introduced by stereoselective osmylation of the double bond in 5,6-dihydro-2*H*-pyran **3**. Previous syntheses of pseudomonic acids have also employed derivatives of **3**.[2] Retrosynthetically, the aldehyde side chain in **2** can be degraded by one carbon in order to introduce a simplifying element of symmetry into **3**. We anticipated that dihydropyran **3** might be formed with a high degree

(1) (a) O'Hanlon, P. J.; Rogers, N. H.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 2655. (b) Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans 1* **1982**, 2827. (c) Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H. *Tetrahedron Lett.* **1980**, *21*, 881. (d) Alexander, R. G.; Clayton, J. P.; Luk, K.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans 1*, **1978**, 561. (e) Hughes, J.; Mellows, G. *J. Antibiot.* **1978**, *31*, 330. (f) Chain, E. B.; Mellows, G. *J. Chem. Soc., Perkin Trans 1* **1977**, 294. (g) Chain, E. B.; Mellows, G. *J. Chem. Soc., Chem. Commun.* **1974**, 847.

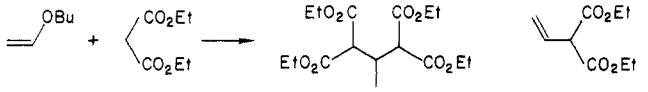
(2) (a) Curran, D. P.; Suh, Y.-G.; *Tetrahedron Lett.* **1984**, *25*, 4179. (b) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 4317. (c) Snider, B. B.; Phillips, G. B.; Cordova, R. *J. Org. Chem.* **1983**, *48*, 3003. (d) Beau, J.-M.; Aburaki, S.; Pougny, J.-R.; Sinaÿ, P. *J. Am. Chem. Soc.* **1983**, *105*, 621. (e) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3661. (f) Schönenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333. (g) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577.

0022-3263/86/1951-2637$01.50/0

of stereocontrol by cyclodehydration of cis-unsaturated keto triol **4**. Ultimately **4** would be prepared by semihydrogenation of the alkyne resulting from condensation of a protected form of 3-oxobutanal (**5**) with a derivative of 2-(hydroxymethyl)-3-butyn-1-ol (**6**). Because this deceptively simple five-carbon alkynediol and its derivatives were unknown, our initial goal was the development of an efficient synthesis of **6**.

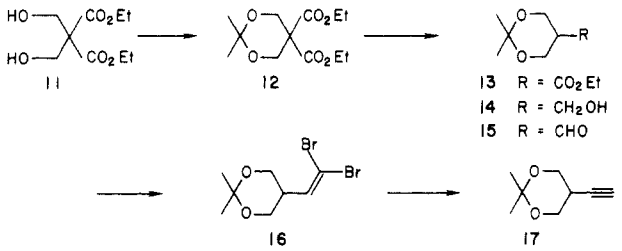
Results and Discussion

2-Vinylmalonate (**10**) appeared promising as a precursor of **6**. This compound was reported to result from the aluminum chloride catalyzed condensation of butyl vinyl ether (**7**) with diethyl malonate (**8**).[3] However, upon replication of this reaction, we found that the product was instead tetraester **9**[4] produced by conjugate addition of malonate to 2-ethylidenemalonate.



7 **8** **9** **10**

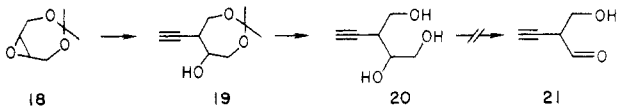
A well-precedented,[5] though lengthy, approach to **6** (i.e., **17**) was next pursued. Diethyl 2,2-bis(hydroxymethyl)malonate (**11**)[6] was protected as acetonide **12** and decarboxylated in refluxing wet Me_2SO to afford ester **13**. The ester was reduced to alcohol **14** with LAH and then oxidized with PCC[7] to afford aldehyde **15**. Direct reduction



11 **12** **13** R = CO_2Et; **14** R = CH_2OH; **15** R = CHO **16** **17**

of **13** with DIBAH afforded a lower yield of **15**, contaminated with **14**. Aldehyde **15** was treated with triphenylphosphonium dibromomethylide, prepared from triphenylphosphine, tetrabromomethane, and zinc,[8] to give dibromoalkene **16**. Finally, **16** was dehalogenated to the desired alkynediol derivative **17** with 2 equiv of butyllithium.[8] The overall yield of **17** was 12% from diethyl malonate.

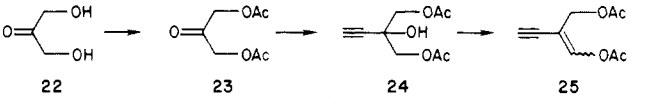
A potential alternative route to **17** commenced with epoxide **18**, which is easily prepared from *cis*-2-butene-1,4-diol.[9] Epoxide **18** was opened with lithium acetylide–ethylenediamine complex[10] to afford **19**. Hydrolysis



18 **19** **20** **21**

of the acetonide produced triol **20**, oxidation of which with buffered periodic acid apparently produced a small amount of extremely unstable **21**, which could be detected by NMR but could not be isolated. The instability of **21** is discussed below.

Conceptually, a very direct route to **17** would involve displacement of a protected 2-halo-1,3-propanediol by acetylene anion. In practice, however, displacements of secondary halides by acetylene anion proceed in abysmal yields.[11] Therefore we considered addition of acetylene anion to a protected derivative of 1,3-dihydroxypropanone (**22**). Because the isopropylidene and benzylidene acetals of 1,3-dihydroxypropanone are very susceptible to hydrolysis and difficult to prepare,[12] the diacetate **23**[13] was utilized instead. Treatment of **23** with lithium acetylide[14] afforded the expected tertiary alcohol **24**.

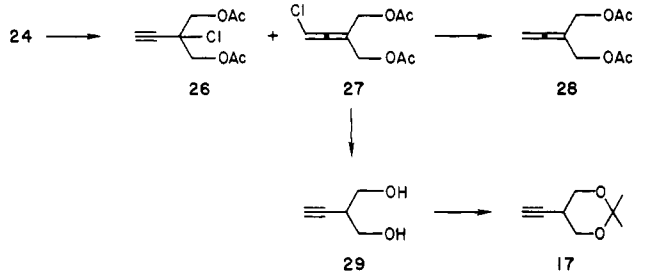


22 **23** **24** **25**

Deoxygenation of tertiary propargylic alcohol **24** and adjustment of the protecting group were now required to complete the preparation of **17**. Direct deoxygenation with triethylsilane–boron trifluoride[15] or bis(trifluoroacetoxy)borane[16] produced a mixture of unidentified products. Dehydration of **24** with phosphorus oxychloride in pyridine[17] afforded a mixture of somewhat unstable (*E*)- and (*Z*)-enynes **25**, accompanied by traces of propargylic chloride **26** and chloroallene **27**. Despite considerable effort, we were unable to hydrolyze **25** to aldehyde **21** or the corresponding acetate. Only complex mixtures of unidentified materials were obtained when **25** was treated with aqueous or methanolic potassium hydroxide, sodium methoxide, potassium carbonate, or potassium cyanide. We presumed that the acetylenic aldehyde **21** was unstable to the reaction conditions. Consistent with this assumption, the few 3-alkynals that have been prepared were reported to isomerize, hydrolyze, oxidize in air, and polymerize.[18] In order to avoid isolation of this unstable aldehyde intermediate, we attempted to reduce **21** (or the acetate thereof) formed in situ. However treatment of **25** with LAH[19] or with a mixture of sodium borohydride and weak base (sodium hydroxide, sodium acetate, sodium cyanide, or ammonium hydroxide) or even sodium borohydride alone[20] resulted only in decomposition.

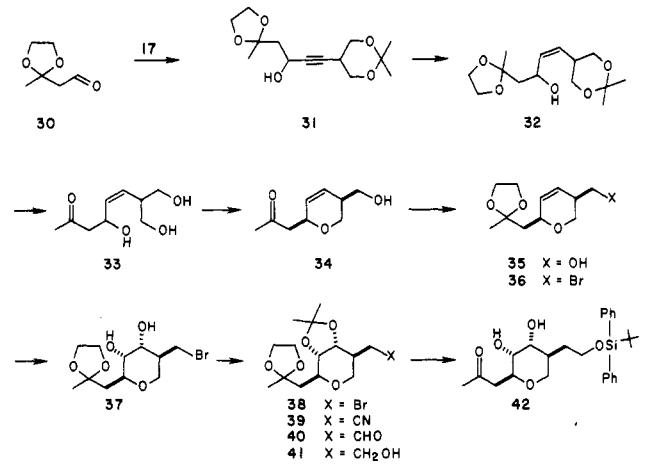
(3) Torgashina, Z. I.; Naumchuk, A. L. *J. Gen. Chem. USSR (Engl. Tranl.)* **1956**, *26*, 3731.
(4) Gaudemar-Bardone, F.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1968**, 3065.
(5) Dekmezian, A. H.; Kaloustian, M. K. *Synth. Commun.* **1979**, *9*, 431. Eliel, E. L.; Banks, H. D. *J. Am. Chem. Soc.* **1972**, *94*, 171. Eliel, E. L.; Banks, H. D. *J. Am. Chem. Soc.* **1970**, *92*, 4730.
(6) Block, P. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 381.
(7) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(8) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.
(9) Elliott, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469. Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 2643.
(10) Casadevall, E.; Jallageas, J.-C.; Mion, L.; Mion, M.; Moreau, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1967**, *265*, 839. Adams, M. A.; Duggan, A. J.; Smolanoff, J.; Meinwald, J. *J. Am. Chem. Soc.* **1979**, *101*, 5364.
(11) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1971. Bernadou, F.; Mesnard, D.; Miginiac, L. *J. Chem. Res., Synop.* **1978**, 106. Yurchenko, O. I.; Dybova, T. N.; Komarov, N. V. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 203.
(12) Marei, A. A.; Raphael, R. A. *J. Chem. Soc.* **1960**, 886. Collins, P. M.; Travis, A. S.; Tsiquaye, K. N.; Lindley, P. F.; Perratt, D. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1895. Araki, Y.; Nagasawa, J.; Ishido, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 12.
(13) Bentley, P. H.; McCrae, W. *J. Org. Chem.* **1970**, *35*, 2082.
(14) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.
(15) Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, 2955. Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758.
(16) Maryanoff, B. E.; McComsey, D. F.; Nortey, S. O. *J. Org. Chem.* **1981**, *46*, 355. Gribble, G. W.; Leese, R. M. *Synthesis* **1977**, 172.
(17) Eaton, P. E.; Srikrishna, A.; Uggeri, F. *J. Org. Chem.* **1984**, *49*, 1728. Jeganathan, S.; Johnston, A. D.; Kuenzel, E. A.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1984**, *49*, 2152.
(18) Winter, M.; *Helv. Chim. Acta* **1963**, *46*, 1749; 1754. Herbertz, T. *Chem. Ber.* **1952**, *85*, 477. Bogdanova, A. V.; Kugatova-Shemyakina, G. P.; Ushakova, T. M.; Kozub, G. I. *J. Org. Chem. USSR (Engl. Transl.)* **1967**, *3*, 644.
(19) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157. Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749.

Treatment of propargylic alcohol **24** with neat phosphorus oxychloride[21] afforded a 65:35 mixture of chloroallene **27** and propargylic chloride **26**. Reduction of this mixture with zinc–copper couple[22] furnished only a low yield of allene **28**. In welcome contrast, reduction of **26**



and **27** with LAH[23] concomitantly cleaved the acetate protecting groups to furnish the desired alkynediol **29**. Treatment with 2,2-dimethoxypropane, provided acetonide **17**, identical in all respects with that prepared from diethyl malonate. While the sequence from **22** affords a lower overall yield, it is shorter and more convenient than the route from diethyl malonate.

With **17** in hand, construction of the dihydropyran proceeded according to plan. Aldehyde **30**[24] was coupled with the magnesium salt of **17** to give alcohol **31**. Semihydrogenation of the triple bond was accomplished over Lindlar catalyst. Inclusion of quinoline as a catalyst poison was unnecessary. Treatment of **32** with dilute HCl resulted in complete deprotection to **33**, which cyclized upon distillation to afford the desired cis dihydropyran **34**, in 70% yield, accompanied by 15% of the corresponding trans isomer, which was readily removed by chromatography.



The stereochemistry was assigned on the basis of the analysis of the ^1H NMR and ^{13}C NMR spectra of **34** and verified by subsequent transformations. Formation of **34** presumably involves the intermediacy of a dienone. Preferential formation of the cis isomer was anticipated because favorable hydrogen bonding between the pseudoaxial hydroxymethyl group and the oxygen of the developing ether is possible only in the half-chair transition state leading to the cis isomer. Analogous hydrogen bonding in 3-(hydroxymethyl)tetrahydropyrans is well established.[5]

We were now in a position to further elaborate dihydropyran **34** by osmylation and homologation. Hydroxy ketone **34** was protected as the ethylene ketal **35** and then treated with triphenylphosphine–*N*-bromosuccinimide to produce the corresponding bromide **36**. Cis hydroxylation from the less hindered face with catalytic osmium tetraoxide[25] afforded the vicinal diol **37**, which was protected as acetonide **38**. Treatment of **38** with 1,3-dithiane anion was unfruitful; however, reaction with sodium cyanide in Me_2SO provided the corresponding nitrile **39**, which was reduced to aldehyde **40** with diisobutylaluminum hydride. Transformation of **40** into pseudomonic acid C can be readily accomplished by Wittig and Emmons–Wadsworth olefinations in accord with established procedures.[2] The stereochemistry of **40** was verified by reduction of the aldehyde to alcohol **41** with sodium borohydride. Protection of the primary alcohol as the *tert*-butyldiphenylsilyl ether followed by liberation of the ketone and secondary alcohol groups afforded **42**, the spectra of which were identical with those of an authentic sample.[2c,2e,26]

Experimental Section

NMR spectra were obtained with a Varian HFT-80 (^1H NMR, 80 MHz), a Varian CFT-20 (^{13}C NMR, 20 MHz), and a Nicolet NT-300NB (^1H NMR, 300 MHz; ^{13}C NMR, 75 MHz) spectrometer. Low-resolution mass spectra were obtained on a Hewlett-Packard 5980A spectrometer with 70-eV electron impact ionization, and high-resolution mass spectra were recorded on a Kratos MS-30 spectrometer. Infrared spectra were recorded on a Unicam SP1000 spectrophotometer. Tetrahydrofuran was distilled from sodium and benzophenone. All reactions were carried out under nitrogen and stirred magnetically unless otherwise stated. Organic phases were dried over anhydrous $MgSO_4$. Solvents were evaporated in vacuo on a rotary evaporator.

Diethyl 2,2-Dimethyl-1,3-dioxane-5,5-dicarboxylate (12). Diethyl 2,2-bis(hydroxymethyl)malonate (**11**)[6] (220 g, 1.00 mol), acetone (220 mL, 3.0 mol), 2,2-dimethoxypropane (220 mL, 1.8 mol), and concentrated sulfuric acid (0.5 mL, 9.0 mmol) were stirred for 18 h. The mixture was slowly poured into saturated aqueous sodium carbonate (50 mL). The organic supernatant was decanted, evaporated, dissolved in ether, rinsed with saturated aqueous sodium carbonate and NaCl, and then dried. Evaporation of the ether afforded crude **12** (263 g, 100% yield): bp 115–135 °C (1 torr); ^1H NMR ($CDCl_3$) δ 1.23 (6 H, t), 1.37 (6 H, s), 4.12 (4 H, q), 4.18 (4 H, s).

Ethyl 2,2-dimethyl-1,3-dioxane-5-carboxylate (13) was prepared by decarboxylation of crude **12** in refluxing Me_2SO containing water and NaCl:[5] yield, 70%; bp 90–120 °C (5 torr) (Kugelrohr); ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t), 1.39 (3 H, s), 1.41 (3 H, s), 2.75 (1 H, pentet), 4.15 (4 H, q), 3.9–4.4 (4 H, m). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.67; H, 8.52.

2,2-Dimethyl-1,3-dioxane-5-methanol (14). Reduction of **13** with lithium aluminum hydride (70 mol %) in ether at 20 °C for 2 h afforded **14**:[5] yield, 85%; bp 120–130 °C (4 torr) (Kugelrohr); ^1H NMR ($CDCl_3$) δ 1.39 (3 H, s), 1.42 (3 H, s), 1.82 (1 H, m), 2.3 (1 H, s, OH), 3.6–4.2 (6 H, m). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.45; H, 9.72.

2,2-Dimethyl-1,3-dioxane-5-methanal (15). Pyridinium chlorochromate[7] (64 g, 297 mmol, 140 mol %) was added in portions over 1 h to a stirred refluxing mixture of **14** (30.7 g, 210 mmol) and sodium acetate (28 g, 340 mmol, 160 mol %, dried at 70 °C) in dry dichloromethane (500 mL, distilled from P_2O_5). After 0.5 h, ether (1500 mL) was added, and the precipitate was removed by decantation and filtration through Florisil. Kugelrohr distillation [80–95 °C (5 torr)] afforded **15** (17.0 g, 56% yield): ^1H NMR ($CDCl_3$) δ 1.35 (3 H, s), 1.43 (3 H, s), 2.32 (1 H, pentet),

(20) Marshall, J. A.; Greene, A. E. *J. Org. Chem.* **1972**, *37*, 982. Dauben, W. G.; Eastham, J. F. *J. Am. Chem. Soc.* **1951**, *73*, 4463.
(21) Crandall, J. K.; Keyton, D. J.; Kohne, J. *J. Org. Chem.* **1968**, *33*, 3655.
(22) Schuster, H. F.; Cappola, G. M. In *Allenes in Organic Synthesis*; Wiley: New York, 1984; pp 270–271. Jacobs, T. L.; Teach, E. G.; Weiss, D. *J. Am. Chem. Soc.* **1955**, *77*, 6254.
(23) Jacobs, T. L.; Petty, W. L. *J. Org. Chem.* **1963**, *28*, 1360.
(24) Meyer, H. H. *Justus Liebigs Ann. Chem.* **1977**, 732. Salmi, E. J. *Chem. Ber.* **1938**, *71*, 1803. Zoretic, P. A.; Branchaud, B.; Maestrone, T. *Org. Prep. Proced. Int.* **1975**, *7*, 51.
(25) Schröder, M. *Chem. Rev.* **1980**, *80*, 187. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(26) We are grateful to Professor Barry B. Snider for providing spectra of authentic **42**.

4.18 (4 H, d), 9.82 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.1, 46.4, 58.9, 98.4, 202.2. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.30; H, 8.21.

5-(2,2-Dibromoethenyl)-2,2-dimethyl-1,3-dioxane (16). Tetrabromomethane (56.1 g, 168 mmol, 200 mol %) in dichloromethane (60 mL) was slowly added to zinc (11 g, 169 mmol, 200 mol %), which had been activated by washing with 0.5 M HCl, water, methanol, and ether and dried, and triphenylphosphine (44.3 g, 168 mmol, 200 mol %) dissolved in dichloromethane (400 mL, dry).[8] After 24 h, **15** (12.1 g, 84 mmol) was added, and 0.5 h later, the mixture was rapidly poured into mechanically stirred hexane (4 volumes). The supernatant was evaporated, and the volatile materials were removed (60 °C, 30 torr). Distillation [80–84 °C (1 torr)] afforded **16** (14.4 g, 57% yield), which tended to decompose after several weeks: ^1H NMR ($CDCl_3$) δ 1.41 (6 H, s), 2.7 (1 H, m), 3.60 (4 H, 8 lines), 6.50 (1 H, d); ^{13}C NMR ($CDCl_3$) δ 23.1, 24.4, 39.6, 62.0, 90.9, 97.8, 135.9; MS, *m/e* (relative intensity) 287 (6, M – 15), 285 (15, M – 15), 283 (7, M – 15), 214 (46), 212 (100), 210 (54). Anal. Calcd for $C_8H_{12}O_2Br_2$: C, 32.03; H, 4.03. Found: C, 31.71; H, 3.78.

5-Ethynyl-2,2-dimethyl-1,3-dioxane (17). A hexane solution of butyllithium (35 mL, 1.65 M, 57.7 mmol, 206 mol %) was added to a solution of **16** (8.44 g, 28.1 mmol) in THF at –78 °C. After 1 h at –78 °C and 1 h at 0 °C water (12 mL) was added to the yellow solution. The organic layer was rinsed with saturated NaCl and dried. The solvents were removed by distillation at 1 atm. Short-path distillation furnished a forerun of bromobutane followed by **17** (2.95 g, 75% yield): bp 85–95 °C (30 torr); ^1H NMR ($CDCl_3$) δ 1.38 (3 H, s, CH_3), 1.46 (3 H, s, CH_3), 2.10 (1 H, d, CH), 2.75 (1 H, d–pentet, $CH(CH_2)_2$), 3.6–4.1 (4 H, m, OCH_2); ^{13}C NMR ($CDCl_3$) δ 19.3, 27.6, 28.3, 63.4, 71.5, 80.6, 97.9; MS, *m/e* (relative intensity) 125 (M – 15, 79), 110 (34), 82 (32), 52 (82), 43 (100). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.52, H, 8.59.

2-Oxo-1,3-propanediol 1,3-Diacetate (23) was prepared directly from 1,3-dihydroxypropanone dimer and acetic anhydride:[13] ^1H NMR ($CDCl_3$) δ 2.25 (6 H, s, OAc), 4.73 (4 H, s, CH_2); ^{13}C NMR ($CDCl_3$) δ 20.2, 67.8, 169.9, 197.9.

2-Ethynyl-1,2,3-propanetriol 1,3-Diacetate (24). Acetylene (passed through two dry ice traps to remove acetone) was rapidly bubbled into tetrahydrofuran (150 mL) cooled in a liquid nitrogen–ether slush bath (–85 °C external) for 1 h. Butyllithium (36.0 mL, 2.6 M in hexane, 93.6 mmol, 108 mol %) was added dropwise.[14] After 1 h at –78 °C, **23** (15.06 g, 86.55 mmol) dissolved in tetrahydrofuran (45 mL) was added. The reaction was stirred 1 h more at –78 °C, warmed to 0 °C, and quenched slowly with 1 M HCl (105 mL). The organic phase was separated, and the aqueous phase was extracted three times with ether. The combined organic extracts were rinsed with saturated NaCl and dried over $MgSO_4$, and the solvent was evaporated to give crude product (14.0 g), which was purified by Kugelrohr distillation [50–120 °C (0.1 torr)] to afford a yellow oil (9.8 g, 56 %): IR (neat) 3400, 3010, 1750, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (6 H, s, OAc), 2.56 (1 H, s, CH), 3.6 (1 H, s, OH), 4.22 (4 H, s, CH_2); ^{13}C NMR ($CDCl_3$) δ 20.8, 66.4, 68.5, 75.5, 81.3, 170.8; MS, *m/e* (relative intensity) 127 (18, M – $AcOCH_2$), 110 (22), 43 (100). Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 53.63; H, 6.18.

1-Acetoxy-2-(acetoxymethyl)-1-buten-3-yne (25). Phosphorus oxychloride (6.26 mL, 68.0 mmol, 950 mol %) was added dropwise to **24** (1.432 g, 7.16 mmol) dissolved in pyridine (25.6 mL) in an ice bath.[17] After 19 h at 20 °C, the dark heterogeneous reaction mixture was slowly added to a mixture of ice and water (250 mL). The product was extracted with six portions of EtOAc, and the combined organic phase was rinsed with water, 1 M HCl, saturated $NaHCO_3$, water, and saturated NaCl and dried. Evaporation of the solvent afforded crude product (760 mg). Kugelrohr distillation [40–85 °C (0.2 torr)] provided a mixture (677 mg, 52% yield) consisting of (*E*)- and (*Z*)-**25** (90%), chloroallene **27** (5%), and propargyl chloride **26** (5%). A sample of **25** was purified by preparative GC (5% SE-30, 170 °C): IR (neat) 3310, 3130, 3000, 2160, 1770, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (*E* and *Z* mixture) δ 2.10 (3 H, s, OAc), 2.20, 2.23 (3 H, s, OAc), 2.85, 3.25 (1 H, s, CH), 4.57, 4.75 (1 H, s, CH_2), 7.65 (1 H, t, =CH); ^{13}C NMR ($CDCl_3$) δ 20.6, 20.8, 59.2, 63.2, 66.3, 84.7, 102.5, 103.9, 143.5, 144.1, 166.0, 166.9, 170.1, 170.6; MS, *m/e* (relative intensity) 182.0579 (13 M^+, calcd 182.0579), 140 (87), 80 (80), 61 (34), 43 (100).

4-Acetoxy-3-(acetoxymethyl)-1-chloro-1,2-butadiene (27) and 2-Chloro-2-(hydroxymethyl)-3-butyn-1-ol Diacetate (26). Distilled phosphorus oxychloride (0.230 mL, 2.5 mmol, 100 mol %) was added to dry **24** (500 mg, 2.5 mmol). After 30 min at 25 °C and 8 h at 40 °C, the reaction mixture was cooled to 0 °C, and saturated $NaHCO_3$ was slowly added to bring the pH to 7. The mixture was extracted with ether (5 × 10 mL). The organic layer was washed with saturated $NaHCO_3$ and H_2O and then dried. Evaporation of the solvent gave a dark oil (350 mg). Kugelrohr distillation [40–120 °C (0.15 torr)] gave a light yellow oil (300 mg, 55% yield), a 65:35 mixture of **27** and **26**. Anal. Calcd for $C_9H_{11}O_4Cl$: C, 49.44; H, 5.07. Found: C, 49.05, H, 5.31.

A sample of **27** was purified by preparative GC: IR (neat) 3310, 3090, 2970, 1975, 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (6 H, s, OAc), 4.70 (4 H, d, J = 1.9 Hz, CH_2), 6.30 (1 H, p, J = 1.9 Hz, =CHCl); ^{13}C NMR ($CDCl_3$) δ 20.6, 61.1, 92.0, 107.1, 170.7, 200.7. MS, *m/e* (relative intensity) 183 (8, M – Cl), 176 (32), 145 (28), 43 (100).

26: ^1H NMR ($CDCl_3$, 300 MHz), δ 2.10 (6 H, s, OAc), 2.61 (1 H, s, CH) 4.51 (4 H, AB q, J = 11.8 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 20.3, 60.6, 66.7, 91.9, 170.0.

2-(Hydroxymethyl)-3-butyn-1-ol (29). The mixture of **27** and **26** (700 mg, 3.25 mmol) was added dropwise to a stirred mixture of 1 M LAH in ether (4 mL, 4 mmol, 125 mol %) at 0 °C.[23] After 1 h at 0 °C the reaction was quenched with water (0.15 mL), 15% NaOH (0.15 mL), and water (0.45 mL). The precipitate was extracted three times with ether, and the combined filtrate was dried over Na_2SO_4 and concentrated. The residue was dissolved in chloroform (10 mL) and extracted three times with water (0.2 mL). Evaporation of the water gave **29** (120 mg, 43% yield): IR (neat) 3350, 2960, 2900, 2120, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (1 H, d, J = 2 Hz), 2.72 (1 H, m), 3.6 (2 H, s, OH), 3.73 (4 H, d, J = 6 Hz, CH_2); MS, *m/e* (relative intensity) 82 (5, M – H_2O), 69 (9), 53 (10), 52 (100), 39 (16).

4-Ethynyl-2,2-dimethyl-1,3-dioxane (17). Diol **29** (180 mg, 1.8 mmol) was added to a mixture of acetone (0.40 mL, 5.45 mmol, 300 mol %), 2,2-dimethoxypropane (0.67 mL, 6.77 mmol, 380 mol %), and H_2SO_4 (1.5 μL). After 30 min, the reaction was quenched with saturated Na_2CO_3 (0.70 mL) and dried over Na_2SO_4. The solvent was evaporated at 1 atm to give crude **17** (280 mg, 100%). Kugelrohr distillation from K_2CO_3 [40–130 C (25 torr)] gave **17** (180 mg, 71%). Some loss occurred during distillation. For spectra, see above.

5-[3-Hydroxy-4-(2-methyl-1,3-dioxolan-2-yl)-1-butyn-1-yl]-2,2-dimethyl-1,3-dioxane (31). A THF solution of ethylmagnesium bromide (2.07 M, 4.5 mL, 9.35 mmol, 107 mol %) was added to alkyne **17** (1.32 g, 8.72 mmol) in THF (10 mL). After 1 h at 20 °C, aldehyde **30**[24] (1.36 g, 1.04 mmol, 120 mol %) was added. After 1 h, the yellow reaction mixture was quenched with saturated aqueous NH_4Cl. Extraction with ether afforded the crude product (2.33 g). Kugelrohr distillation [140–165 °C (1 torr)] afforded **31** (1.69 g, 72% yield): ^1H NMR ($CDCl_3$) δ 1.34 (6 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.10 (2 H, d, CH_2COH), 2.08 (1 H, m, $CH(CH_2)_2$), 3.9 (8 H, 7, CH_2O), 4.6 (1 H, t, CHOH); MS, *m/e* (relative intensity) 270 (1.6, M^+), 269 (10), 255 (29), 253 (17), 182 (33), 167 (33), 153 (33), 87 (100), 88 (100). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.92; H, 8.08.

***cis*-5-[3-Hydroxy-4-(2-methyl-1,3-dioxolan-2-yl)-1-buten-1-yl]-2,2-dimethyl-1,3-dioxane (32).** A stirred solution of **31** (326 mg) in methanol (3.3 mL) was hydrogenated at 1 atm over Lindlar catalyst[27] (100 mg) for 1 H. Removal of the catalyst and solvent afforded **32** (316 mg, 96% yield): ^1H NMR ($CDCl_3$) δ 1.34 (6 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.8 (2 H, m, CH_2COH), 2.9 (1 H, m, $CH(CH_2)_2$), 3.6 (4 H, m, CH_2O), 3.96 (4 H, s, CH_2O), 4.6 (1 H, dt, CHOH), 5.10 (1 H, dd, J = 8, 10 Hz, =CH), 5.50 (1 H, dd, J = 6, 10 Hz, =CH); MS, *m/e* (relative intensity) 272 (0.2), 271 (1.4), 257 (12), 184 (25), 155 (33), 95 (100). Anal. Calcd for $C_{14}H_{24}O_5$; C, 61.74; H, 8.88. Found; C, 61.70; H, 8.95.

***cis*-[5,6-Dihydro-5-(hydroxymethyl)-2*H*-pyran-2-yl]-2-propanone (34).** Ketal **32** (3.37 g, 12.4 mmol) was hydrolyzed in 0.1 M HCl (30 mL) for 1 h and then neutralized (pH 6) with saturated sodium carbonate. The water was evaporated, the residue was extracted into ethanol, and the ethanol was evaporated

(27) Lindlar, H.; Dubuis, R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 880.

to afford crude **33**: ^{1}H NMR (D_2O) δ 2.24 (3 H, s, CH_3), 2.79 (2 H, d, CH_2C=O), 3.5 (4 H, m, CH_2OH), 4.7 (1 H, m, CHOH), 5.30 (1 H, dd), 5.68 (1 H, dd).

Crude **33** was slowly Kugelrohr distilled [80–150 °C (1 torr)] to afford crude product contaminated with ethylene glycol. The crude product was dissolved in ethyl acetate, washed with saturated NaCl, dried, and concentrated to afford **34** (1.78 g, 85% yield). A sample was purified by chromatography on silica gel with chloroform–methanol (90:10) eluent: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (3 H, s, CH_3), 2.44 (1 H, dd, J = 5, 16 Hz, CH_2C=O), 2.72 (1 H, dd, J = 7.5, 16 Hz, CH_2C=O), 2.97 (1 H, m, CH), 3.7 (3 H, m, CH_2O), 3.99 (1 H, d, J = 13 Hz, CH_2O), 4.58 (1 H, m, =CCHO), 5.76 (2 H, m, =CH); ^{13}C NMR ($CDCl_3$) δ 30.3, 37.3, 48.8, 64.1, 65.5, 70.8, 126.1, 131.1, 206.7; MS, m/e (relative intensity) 170 (0.2, M^+), 155 (2.6), 153 (1.9), 152 (2), 139 (9), 113 (18), 97 (19), 90 (42), 44 (98), 43 (100). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.57; H, 8.34.

***cis*-[5,6-Dihydro-5-(hydroxymethyl)-2*H*-pyran-2-yl]-2-propanone Ethylene Ketal (35).** Ketone **34** (403 mg, 2.36 mmol), benzene (8 mL), ethylene glycol (200 mg, 3.2 mmol, 137 mol %), and toluenesulfonic acid monohydrate (2 mg) were refluxed beneath 3-Å molecular sieves for 1 h. The cooled organic layer was washed with saturated sodium carbonate, dried, and concentrated to afford **35** (428 mg, 85% yield): bp 80–120 °C (0.5 torr) (Kugelrohr); ^{1}H NMR ($CDCl_3$) δ 1.36 (3 H, s, CH_3), 1.85 (2 H, dd, CH_2), 2.5 (1 H, m, CH), 3.0 (1 H, s, OH), 3.58 (4 H, m, CH_2O), 3.92 (4 H, s, $(CH_2O)_2$), 4.25 (1 H, m, =CCHO), 5.72 (2 H, m, =CH). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.67; H, 8.51.

***cis*-[5-(Bromomethyl)-5,6-dihydro-2*H*-pyran-2-yl]-2-propanone Ethylene Ketal (36).** *N*-Bromosuccinimide (505 mg, 2.84 mmol, 200 mol %) was slowly added to a solution of alcohol **35** (305 mg, 1.42 mmol) and triphenylphosphine (745 mg, 2.84 mmol, 200 mol %) in DMF (3 mL). The reaction was warmed to 50 °C for 15 min and then cooled to 20 °C. Methanol (0.5 mL) was added to destroy the excess reagent. After 5 min, ether was added, and the ether layer was washed with water, saturated sodium carbonate, and saturated NaCl and then evaporated to a solid under high vacuum. The product was extracted twice into hexane, leaving a residue of triphenylphosphine oxide. After evaporation of the solvent, the residue was again triturated with hexane to afford somewhat unstable **36** (320 mg, 81% yield): ^{1}H NMR ($CDCl_3$) δ 1.38 (3 H, s, CH_3), 1.88 (2 H, t, CH_2), 2.3 (1 H, m, CH), 3.2–3.8 (4 H, m, CH_2O and CH_2Br), 3.90 (4 H, s, $(CH_2O)_2$), 4.23 (1 H, m, =CCHO), 5.78 (2 H, m, =CH).

[5-(Bromomethyl)-2α,3β,4β,5α-tetrahydro-3,4-dihydroxy-2*H*-pyran-2-yl]-2-propanone Ethylene Ketal (37). *N*-Methylmorpholine *N*-oxide dihydrate (154 mg, 1.01 mmol, 121 mol %) and osmium tetraoxide (15 mg, 0.06 mmol, 7 mol %) were added *in a hood* to a solution of **36** (231 mg, 0.83 mmol) in acetone (2 mL). The initially heterogeneous mixture became homogeneous and light brown. After 4 h, sodium dithionite (45 mg, 0.26 mmol, 31 mol %) and Florisil were added. The black precipitate was removed by filtration, and the solvent was evaporated. The residue was dissolved in ether containing a small amount of actone and filtered with Florisil, and then the solvent was evaporated to afford **37** as a clear oil (231 mg, 89% yield): ^{1}H NMR ($CDCl_3$) δ 1.39 (3 H, s, CH_3), 2.00 (2 H, m, CH_2), 2.14 (1 H, m, CH), 3.2–4.1 (9 H, m), 3.96 (4 H, s, $(CH_2O)_2$). Anal. Calcd for $C_{11}H_{19}O_5Br$: C, 42.46; H, 6.15. Found: C, 42.40; H, 6.09.

[5-(Bromomethyl)-2α,3β,4β,5α-tetrahydro-3,4-dihydroxy-2*H*-pyran-2-yl]-2-propanone Acetonide Ethylene Ketal (38). Crude **37** (231 mg, 0.74 mmol) was dissolved in 2,2-dimethoxypropane (3.8 mL) and treated with toluenesulfonic acid monohydrate (5 mg) until the solution was acidic. After 0.5 h, saturated aqueous sodium carbonate (2 mL) was added, and the solution was extracted with ether. The extracted was washed with saturated NaCl solution, dried, concentrated, then dissolved in pentane, and filtered to afford **38** (221 mg, 85% yield): ^{1}H NMR ($CDCl_3$) δ 1.35 (6 H, s, CH_3), 1.50 (3 H, CH_3), 1.92 (2 H, m, CH_2), 2.31 (1 H, m, CH), 3.1–4.4 (7 H, m), 3.92 (4 H, s, $(CH_2O)_2$).

[5-(Cyanomethyl)-2α,3β,4β,5α-tetrahydro-3,4-dihydroxy-2*H*-pyran-2-yl]-2-propanone Acetonide Ethylene Ketal (39). Sodium cyanide (80 mg, 160 mmol, 170 mol %) which had been dried at 110 °C was added to bromide **38** (7335 mg, 0.95 mmol) dissolved in dry Me_2SO (3.5 mL) and heated to 65 °C for 2 h. Ether was added, and the Me_2SO was extracted into saturated aqueous sodium chloride. The ether layer was dried and evaporated to afford **39** (245 mg, 86% yield); ^{1}H NMR ($CDCl_3$) δ 1.39 (6 H, s, CH_3), 1.50 (3 H, CH_3), 1.85 (2 H, m, CH_2), 2.10 (1 H, m, CH), 2.50 (2 H, m, CH_2CN), 3.1–4.2 (5 H, m), 3.92 (4 H, s, $(CH_2O)_2$); MS, m/e (relative intensity) 282 (2, M – 15), 210 (4), 87 (100), 43 (15). Anal. Calcd for $C_{15}H_{23}O_5N$: C, 60.59; H, 7.80. Found, C, 60.67; H, 7.78.

[2α,3β,4β,5α-Tetrahydro-3,4-dihydroxy-5-(2-oxoethyl)-2*H*-pyran-2-yl]-2-propanone Acetonide Ethylene Ketal (40). A 25% solution of diisobutylaluminum hydride (0.040 mL, 1.54 M, 0.062 mmol, 135 mol %) in toluene was added over 2 min to a solution of **39** (13.5 mg, 0.0455 mmol) in dry toluene (2 mL) at 0 °C. After 30 min, methanol (0.15 mL) was added, and the mixture was stirred at 20 °C for 10 min. The product was extracted into ether and washed with water, saturated aqueous sodium carbonate, and saturated NaCl, dried, and concentrated to afford **40** (13 mg, 95% yield): ^{1}H NMR ($CDCl_3$) δ 1.33 (3 H, s, CH_3), 1.37 (3 H, s, CH_3), 1.50 (3 H, CH_3), 1.85 (2 H, m, CH_2), 2.10 (1 H, m, CH), 2.64 (2 H, m, CH_2C=O), 3.1–4.0 (5 H, m), 3.92 (4 H, s, $(CH_2O)_2$), 9.80 (1 H, t, J = 1.2 Hz, HC=O); HRMS calcd for $C_{15}H_{24}O_6$ m/e 300.1573, found m/e 300.1578.

[2α,3β,4β,5α-Tetrahydro-3,4-dihydroxy-5-(2-hydroxyethyl)-2*H*-pyran-2-yl]-2-propanone Acetonide Ethylene Ketal (41). Sodium borohydride (3 mg, 0.078 mmol, 144 mol %) was added to aldehyde **40** (16.4 mg, 0.055 mmol) dissolved in ethanol (0.17 mL) at 0 °C. After 15 min at 0 °C, the solvent was evaporated, water was added, and the product was extracted into ether. The organic phase was rinsed with saturated NaCl, dried, and concentrated to afford **41** (16 mg, 97% yield): ^{1}H NMR ($CDCl_3$) δ 1.35 (6 H, s, CH_3), 1.50 (3 H, s, CH_3), 1.64 (2 H, m, CH_2), 1.9 (1 H, m, CH), 3.2–3.9 (7 H, m), 3.92 (4 H, s, $(CH_2O)_2$).

[5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2α,3β,4β,5α-tetrahydro-3,4-dihydroxy-2*H*-pyran-2-yl]-2-propanone (42). Alcohol **41** (15.4 mg, 0.051 mmol) and imidazole (4.5 mg, 0.066 mmol, 130 mol %) were added to a solution of *tert*-butyldiphenylsilyl chloride (18 mg, 0.065 mmol, 128 mol %) dissolved in dry DMF (0.20 mL). After 4 h, ether was added. The organic layer was rinsed with water, 0.1 M HCl, and saturated sodium carbonate and then dried. Evaporation of the solvent afforded the crude silyl ether (25.3 mg). This was hydrolyzed with ethanol (0.20 mL) and 3 M HCl (0.10 mL). After 2 h, saturated sodium carbonate was added to pH 6. The solvent was evaporated, water was added, and the product was extracted into ethyl acetate. The organic phase was rinsed with saturated sodium chloride, dried, and evaporated to afford **42** (17.2 mg, 74% yield), spectrally identical with an authentic sample.[2c,2e,26]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health, and the Center for Biotechnology, SUNY at Stony Brook, sponsored by the New York State Science and Technology Foundation, for support of this research. We thank Dr. C. J. Sih for stimulating discussions.