Synthesis of 1-Deoxy-D-xylulose and 1-Deoxy-D-xylulose-5-phosphate

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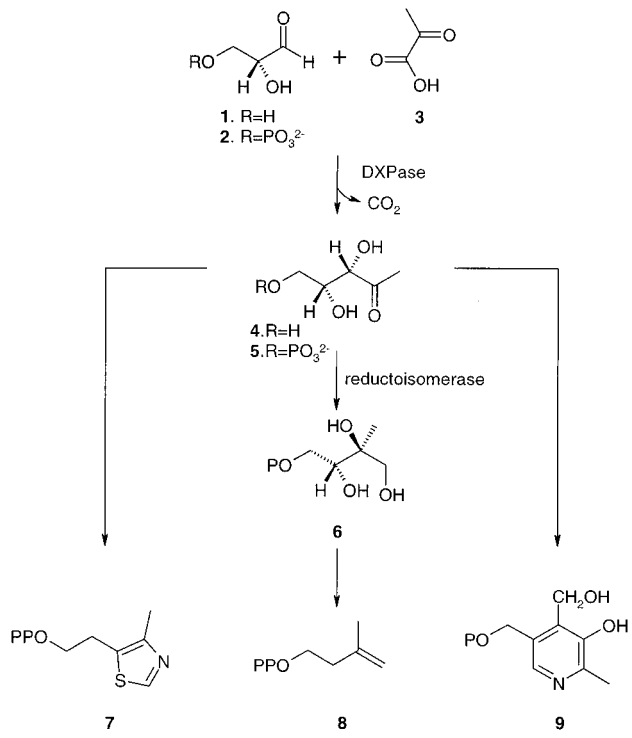
1-Deoxy-D-xylulose (**4**) and the corresponding 5-phosphate (**5**) are substrates for the first pathway-specific enzymes in the biosynthesis of thiamine diphosphate (vitamin B_1), pyridoxol phosphate (vitamin B_6), and the nonmevalonate family of isoprenoid compounds recently discovered in bacteria and plant chloroplasts. Both **4** and **5** were synthesized from commercially available (−)-2,3-*O*-isopropylidene-D-threitol (**10**). The protected tetraol was converted to (−)-3,4-*O*-isopropylidene-5-triisopropylsilyl-1-deoxy-D-xylulose (**14**) in four steps. Treatment of **14** with acetic acid gave **4** in an overall yield of 69%. The corresponding 5-phosphate was obtained by protection the carbonyl group in **14**, removal of the triisopropylsilyl moiety, and treatment of the resulting alcohol with trimethyl phosphite/$TeCl_4$, trimethylsilyl bromide, water, and HCl in successive steps to give **5** in 58% overall yield from **10**.

In most eukaryotic organisms and in archaebacteria, isoprenoid compounds are synthesized from acetyl CoA by the well-established mevalonate pathway.[1] However, recent isotopic labeling experiments have revealed a different pathway for the biosynthesis of isoprenoids in bacteria,[2−5] green algae,[6] and plants.[7−10] Although the exact sequence of the reactions in the nonmevalonate pathway has not been established, apparently the branch point to isoprenoids is at deoxy-D-xylulose phosphate (**5**)[11] along with vitamin B_1 (thiamine diphosphate, **7**) as illustrated in Scheme 1. The branch point to vitamin B_6 (pyridoxol phosphate, **9**) appears to be at deoxy-D-xylulose (**4**).[12] Genes for deoxyxylulose phosphate synthase (DXPase) have been isolated from *E. coli*[13,14] and *Mentha* x *piperita*.[15] Recombinant forms of DXPase synthesize phosphate **5** from D-glyceraldehyde 3-phosphate (**2**) and

Scheme 1



pyruvate (**3**). However, the recombinant enzymes also synthesize deoxy-D-xylulose from D-glyceraldehyde and **3**. At this point, it is not known if DXPase provides both deoxyketose **4** and phosphate **5** under normal metabolic conditions or if a second enzyme is present for synthesis of **4**.

The first pathway-specific transformation in the nonmevalonate isoprenoid branch is a tandem pinacol rearrangement/reduction to produce 2-*C*-methyl-D-erythritol-4-phosphate (**6**) containing an intact isoprenoid carbon skeleton.[11,16] The steps between **6** and isopentenyl diphosphate (**8**) have not been established, but beyond that point, the mevalonate and nonmevalonate path-

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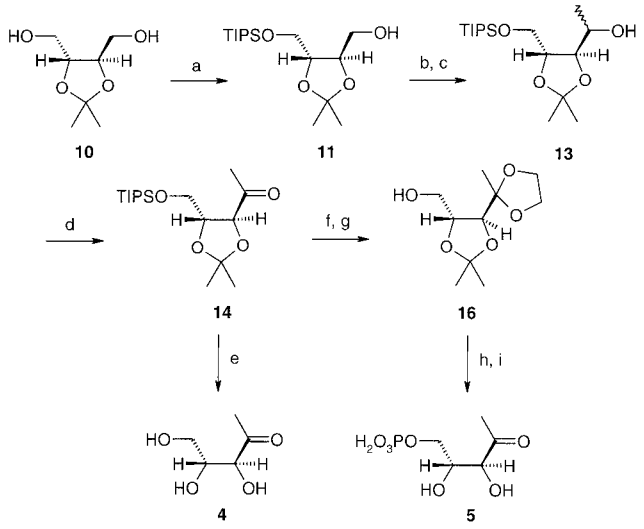
Scheme 2[a]



[a] Key: (a) NaH, TIPS-Cl, 96%; (b) Swern oxidation; (c) MeMgBr, 88% for b and c; (d) TPAP, NMO, 97%; (e) AcOH, THF, H_2O, 84%; (f) $HO(CH_2)_2OH$, TsOH, 88%; (g) TBAF, THF, 99%; (h) $P(OMe)_3$, $TeCl_4$, 91%; (i) TMSBr, H_2O, HCl, 90%.

ways converge to a common set of reactions.[17] Recently, Takahashi and co-workers[16] reported an activity in *E. coli* for the enzyme responsible for the pinacol-like rearrangement of **5** originally proposed by Rohmer.[5,18] They subsequently isolated the gene for the enzyme and discovered that the encoded protein catalyzes both the pinacol-like rearrangement and the subsequent NADPH-dependent reduction of the pinacol product.

Interest in the biosynthesis of thiamine diphosphate, pyridoxol phosphate, and more recently, isoprenoids has prompted several groups to develop syntheses of deoxyxylulose (**4**).[19−23] Recently, Taylor and co-workers reported both chemical and enzymatic routes to the 5-phosphate (**5**).[24] The chemical synthesis gave **5** in an overall yield of 5% from diethyl tartrate in seven steps. Although the enzymatic procedure produced **5** from fructose-1,6-bisphosphate and pyruvate in 47% yield, one of the necessary enzymes is not available commercially. We now describe syntheses of 1-deoxy-D-xylulose and 1-deoxy-D-xylulose-5-phosphate from (−)-2,3-*O*-isopropylidene-D-threitol (**10**) in overall yields of 69% and 58%, respectively.

Results and Discussion

The routes used to synthesize 1-deoxy-D-xylulose (**4**) and phosphate **5** are outlined in Scheme 2. The steps from (−)-2,3-*O*-isopropylidene-D-threitol (**10**) to triisopropylsilyl (TIPS)-protected deoxyxylulose **14** are similar to those reported by Kennedy et al.[20] for the corresponding *tert*-butyldimethylsilyl derivative. Monosilylation of the C_2-symmetric acetonide of D-threitol was accomplished by treatment with triisopropylsilyl chloride to afford **11** in high yield.[25,26]

Swern oxidation[27] of primary alcohol **11** followed by addition of methyl Grignard reagent to the resulting aldehyde gave a mixture of diastereomeric secondary alcohols (**13**). Oxidation with TPAP/NMO[28] produced protected deoxyxylulose **14** in good yield. Ketone **14** is an important intermediate. Both protecting groups can be removed under acidic conditions (3:1:1 $AcOH/H_2O$/THF)[29] to give deoxyxylulose in 84% yield, or **14** can be converted to phosphate **5** in four additional steps. In contrast, attempts to deprotect the corresponding *tert*-butyldimethylsilyl derivative with NaF in HCl gave **4** in a 25% yield.[20]

In preliminary experiments, we found that the 3,4-acetonide of deoxyxylulose rapidly cyclized to mixture of hemiketals upon removal of the silyl group in **14**, thus preventing a direct phosphorylation of the deprotected acetonide. Instead, we chose to mask the ketone as a 1,2-dioxolane by treatment with ethylene glycol under acidic conditions[30] before attempting the phosphorylation. The TIPS moiety was then removed with tetrabutylammonium fluoride to give primary alcohol **16**.[31] The primary alcohol was efficiently phosphorylated with trimethyl phosphite and $TeCl_4$ according to the procedure of Watanabe and co-workers.[32] The methyl groups in the resulting phosphotriester were selectively removed by treatment with trimethylsilyl bromide followed by aqueous hydrolysis.[33] The acetonide and dioxolane protecting groups were then removed in the same pot by addition of HCl to give **5**. Deoxyxylulose phosphate was unstable when the material was concentrated by lyophilization in the presence of ammonia or ammonium cations and gave a mixture of phosphate-containing products. We were, however, able to obtain **5** in good yield by neutralizing the HCl used to remove the dioxolane and acetonide protecting groups by careful addition of solid $NaHCO_3$ to pH 7 before the sample was frozen. The sample was lyophilized, and the resulting solid material was purified by cellulose chromatography[34] under acidic conditions, using dilute trifluoroacetic acid as a cosolvent, to give **5** in a 58% overall yield from isopropylidene-D-threitol.

The synthetic route presented in Scheme 2 is sufficiently versatile to permit one to incorporate isotopes of hydrogen or carbon into **4** and, in addition, phosphorus into **5** for biosynthetic experiments. Deoxyxylulose readily cyclizes to anomeric hemiketals. Thus, the open-chain ketone must be prepared freshly immediately prior to use.[12] Our route allows us to store deoxyxylulose as the

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protected TIPS-acetonide, which can be readily converted to the free sugar or 5-phosphate in good yields.

Experimental Section

General Methods and Materials. All nonaqueous reactions were run in dry solvents under a dry Ar atmosphere. "Dried and concentrated" refers to removal of residual amounts of water with anhydrous $MgSO_4$ followed by evaporation of solvent on a rotary evaporator. Flash chromatography[35] was conducted on Merck silica grade 60, 230−400 mesh, with the solvent system indicated. Cellulose flash chromatography[33] was performed on Whatman CF-11 fibrous cellulose and visualized with *p*-anisaldehyde. Thin-layer plates were developed with potassium permanganate or anisaldehyde. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded in $CDCl_3$ at 7.05 T, using residual $CHCl_3$ (^{1}H NMR, 7.26 ppm; ^{13}C NMR, 77.23 ppm, center line) signals as an internal standard, unless otherwise stated. The ^{13}C and ^{31}P spectra for compound **5** were calibrated against internal methanol (50.50 ppm) and external phosphoric acid (0 ppm), respectively. Optical rotations were determined at 20 °C (*c* in g per 100 mL solvent). High-resolution mass spectra (HRMS) were recorded using chemical ionization (CI), unless otherwise stated. (−)-2,3-*O*-Isopropylidene-D-threitol was purchased from Lancaster; all other reagents were purchased from Aldrich. All solvents and volatile reagents were distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone; CH_2Cl_2 and benzene were distilled from CaH_2.

(2*R*,3*R*)-4-[(Triisopropylsilyl)oxy]-2,3-(isopropylidenedioxy)butanol (11). To a solution of NaH (50% in mineral oil, 1.55 g, 32 mmol, 1.05 equiv) in 60 mL of THF at 0 °C was added a solution of (−)-2,3-*O*-isopropylidene-D-threitol (**10**, 5.0 g, 31 mmol) in 15 mL of THF over a 5 min period. The slurry was warmed to room temperature and stirred for 45 min before triisopropylsilyl chloride (6.60 mL, 31 mmol) was added over a 15 min period. After being stirred for 3 h, the reaction was poured into saturated $NaHCO_3$ and extracted with ether (3 × 50 mL). The combined organic layers were dried and concentrated. Purification by flash chromatography (1:9 (v/v) ethyl acetate in hexanes) gave 9.0 g (96%) of a colorless oil: $[\alpha]^{20}_D$ −9.2° (*c* 17.0, CH_2Cl_2); IR (thin film) 3500 (br), 2944, 2868, 1464, 1380, 1370, 1248 cm^{-1}; ^{1}H NMR δ 4.04 (dt, J = 7.5, 4.8 Hz, 1H), 3.98 (dd, J = 9.6, 3.9 Hz, 1H), 3.93−3.87 (m, 1H), 3.83−3.71 (m, 3H), 2.40 (br, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.16−1.02 (m, 21H); ^{13}C NMR δ 109.3, 80.7, 78.4, 64.4, 63.0, 27.2, 27.1, 18.1, 12.0; HRMS (CI) calcd for $C_{16}H_{35}SiO_4$ 319.2306, found 319.2307.

(2*R*,3*R*)-4-[(Triisopropylsilyl)oxy]-2,3-(isopropylidenedioxy)butanal (12). A solution of DMSO (3.95 mL, 55 mmol, 2.6 equiv) in 16 mL of CH_2Cl_2 was added to a solution of oxalyl chloride (2.41 mL, 28 mmol, 1.3 equiv) in 60 mL of CH_2Cl_2 at − 78 °C. After the solution was stirred for 5 min, a solution of 6.80 g (21 mmol) of alcohol **11** in 30 mL of CH_2Cl_2 was added via cannula. The reaction was stirred for 15 min at −78 °C, and 14.9 mL of Et_3N (107 mmol, 5 equiv) was added. The reaction was warmed to room temperature and stirred for 1 h, before 50 mL of water was added. The organic layer was removed and concentrated. The residue was redissolved in 100 mL of 50% (v/v) ether/hexanes and washed with water and then brine. The combined aqueous layers were extracted with ether, and the combined organic fractions were dried and concentrated. The residue was poured onto a 70 g plug of silica, eluted with 300 mL of 50% (v/v) ethyl acetate in hexanes, and concentrated to give 6.20 g of oil. A small amount was purified (1:9 (v/v) ethyl acetate in hexanes) for analysis, and the remainder was used without further purification: $[\alpha]^{20}_D$ −4.8° (*c* 24.0, CH_2Cl_2); IR (thin film) 2944, 2866, 1735, 1463, 1371 cm^{-1}; ^{1}H NMR δ 9.8 (d, J = 1.5 Hz, 1H), 4.43 (dd, J = 7.2, 1.5 Hz, 1H), 4.15 (dt, J = 6.9, 4.5 Hz, 1H), 3.91 (d, J = 4.5 Hz, 2H), 1.49 (s, 3H), 1.43 (s, 3H), 1.19−1.02 (m, 21H); ^{13}C NMR δ 201.0, 111.7, 82.4, 77.9, 63.6, 27.0, 26.5, 18.1, 12.1; HRMS (CI) calcd for $C_{16}H_{33}SiO_4$ 317.2149, found 317.2138.

(3*R*,4*R*)-5-[(Triisopropylsilyl)oxy]-3,4-(isopropylidenedioxy)pentan-2-ol (13). To a solution of 6.2 g (20 mmol) of aldehyde **12** in 200 mL of THF was added 20 mL of methylmagnesium bromide (3 M in hexanes, 60 mmol, 3 equiv) at −78 °C. The reaction was stirred at −78 °C for 2 h, warmed to room temperature, and stirred overnight. The reaction was quenched with 50 mL of saturated NH_4Cl. The aqueous layer was washed with ether, and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (1:9 (v/v) ethyl acetate in hexanes) to give 6.20 g (88% for both steps) of **13** as a mixture of diastereomers: IR (thin film) 3500 (br), 2939, 2867, 1463, 1380, 1249, 1145, 1082 cm^{-1}; ^{1}H NMR δ 4.02−3.64 (m, 5H), 1.42, 1.40, and 1.39 (3s, total of 6H), 1.27 and 1.24 (2d, J = 6.6, 6.3 Hz, 4:1 ratio, respectively, total of 3H), 1.20−1.02 (m, 21H); ^{13}C NMR δ 109.4, 108.9, 84.6, 83.2, 79.8, 77.8, 68.4, 67.6, 64.7, 64.5, 27.6, 27.5, 27.1, 27.0, 20.0, 19.6, 18.2, 18.1, 12.1, 12.0; HRMS (CI) calcd for $C_{17}H_{37}SiO_4$ 333.2462, found 333.2463.

(3*S*,4*R*)-5-[(Triisopropylsilyl)oxy]-3,4-(isopropylidenedioxy)pentan-2-one (14). To a solution of **13** (3.10 g, 9.3 mmol) in 30 mL of CH_2Cl_2 were added NMO (1.53 g, 13 mmol, 1.4 equiv), 3 g of finely crushed and activated 4 Å molecular sieves, and TPAP (164 mg, 0.47 mmol, 0.05 equiv). The reaction was stirred for 1.5 h, concentrated, and purified by flash chromatography (1:19 (v/v) ethyl acetate in hexanes) to give 2.99 g (97%) of a colorless oil: $[\alpha]^{20}_D$ −12.1° (*c* 10.9, CH_2Cl_2); IR (thin film) 2940 (s), 1720, 1464, 1379, 1248, 1217, 1148, 1095 cm^{-1}; ^{1}H NMR δ 4.39 (d, J = 7.5 Hz, 1H), 4.09 (dt, J = 7.5, 3.9 Hz, 1H), 3.95 (dd, J = 10.8, 3.9 Hz, 1H), 3.85 (dd, J = 3.9, 10.8 Hz, 1H), 2.28 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.16−1.02 (m, 21H); ^{13}C NMR δ 208.7, 110.9, 81.7, 79.1, 63.4, 27.1, 26.7, 26.6, 18.1, 12.1; HRMS (CI) calcd for $C_{17}H_{35}SiO_4$ 331.2305, found 331.2296.

1-Deoxy-D-xylulose (4). To 3 mL of glacial actetic acid, 1 mL of water, and 1 mL of THF was added 52 mg (0.16 mmol) of ketone **14**. The solution was stirred overnight at 90 °C, solvent was removed by a stream of nitrogen, and the residue was purified by flash chromatography (1:5 (v/v), methanol in chloroform) to give 18 mg (84%) of a colorless oil: $[\alpha]^{20}_D$ −1.7° (*c* 1.8, MeOH); IR (thin film) 3500 (br), 3003, 2932, 2890, 1782, 1714, 1540, 1422, 1364 cm^{-1}; ^{1}H NMR (CD_3OD) δ 4.16−3.41 (mm, 4H), 2.15, 1.34, and 1.29 (3 s in a ratio of 4:1:1, total of 3H); ^{13}C NMR (CD_3OD) δ107.5, 103.8, 83.1, 82.8, 78.5, 78.4, 77.4, 73.6, 73.3, 71.4, 63.7, 26.5, 25.0, 21.8; HRMS (CI) calcd for $C_5H_{11}O_4$ 135.0657, found 135.0649.

(3*S*,4*R*)-5-[(Triisopropylsilyl)oxy]-3,4-(isopropylidenedioxy)penta-2-(1,3-dioxolane) (15). To a solution of ketone **14** (2.81 g, 8.5 mmol) in 90 mL of benzene was added 3.2 g (51 mmol, 6 equiv) of ethylene glycol and 81 mg (0.42 mmol, 0.05 equiv) of *p*-toluenesulfonic acid monohydrate. The reaction was heated to reflux using a Dean−Starke trap to remove water. After 8 h, the reaction was cooled and concentrated. Purification by flash chromatography (1:19 (v/v), ethyl acetate in hexanes) gave 2.7 g (84%) of a colorless oil: $[\alpha]^{20}_D$ +10.3° (*c* 4.9, CH_2Cl_2); ^{1}H NMR δ 4.12 (d, J = 8.1 Hz, 1H), 4.06 (dd, J = 3.6, 2.7 Hz, 1H), 4.03−3.97 (m, 4H), 3.96 (dd, J = 10.8, 2.7 Hz, 1H), 3.79 (dd, J = 11.0 Hz, 3.9 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.12−1.04 (m, 21H); ^{13}C NMR δ 134.9, 110.0, 109.2, 79.4, 79.3, 65.6, 65.4, 64.2, 27.6, 27.2, 20.7, 18.2, 12.2; IR (thin film) 2946, 2871, 1465, 1375, 1251, 1170, 1077, 882 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{39}SiO_5$ 375.2567, found 375.2560.

(3*S*,4*R*)-Isopropylidenedioxy-2-(1,3-dioxolane)-5-pentanol (16). To a solution of **15** (356 mg, 0.96 mmol) in 40 mL of THF was added tetrabutylammonium fluoride (1.0 M in THF, 1.44 mL, 1.5 equiv). The reaction stirred at room temperature for 1 h and concentrated to a thick orange oil. Purification by flash chromatography (1:3 (v/v), hexanes in ethyl acetate) gave 206 mg (99%) of a colorless oil: $[\alpha]^{20}_D$ + 7.4° (*c* 15.1, CH_2Cl_2); IR (thin film) 3500 (br), 2950 (s), 1458, 1377, 1253, 1218, 1168, 1076, 1044; ^{1}H NMR δ 4.06−94 (m, 5H), 3.83 (d, J = 8.4 Hz, 1H), 3.77 (dd, J = 11.7 Hz, 3.9 Hz, 1H), 3.66 (dd, J = 11.7, 3.9 Hz, 1H), 2.45 (s(br), 1H), 1.40 (s,

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3H), 1.39 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 109.9, 108.6, 80.6, 78.2, 65.5, 65.2, 63.3, 27.4, 26.9, 20.5; HRMS (CI) calcd for $C_{10}H_{19}O_5$ 219.1233, found 219.1231.

Dimethyl (3*S*,4*R*)-3,4-Isopropylidenedioxy-2-(1,3-dioxolane)-5-oxopentyl Phosphate (17). To a stirred solution of alcohol **16** (206 mg, 0.94 mmol), 2,6-lutidine (142 mg, 1.3 mmol, 1.4 equiv), and trimethyl phosphite (141 mg, 1.1 mmol, 1.2 equiv) in 5 mL of CH_2Cl_2 was added at once $TeCl_4$ (203 mg, 0.75 mmol, 0.8 equiv). After 1 h, the resulting suspension was filtered, concentrated, and purified by flash chromatography (100% ethyl acetate) to give 279 mg (91%) of a colorless oil: $[\alpha]^{20}_D$ +12.7° (*c* 14.7, CH_2Cl_2); IR (thin film) 3109 (s), 2825, 1378, 1284, 1218, 1172, 1067; ^{1}H NMR δ 4.31 (ddd, J = 6.1, 6.0, 2.1 Hz, 1H), 4.22−4.16 (m, 1H), 4.1 (ddd, J = 5.4, 7.2, 11.0 Hz, 1H) 4.03−3.98 (m, 4H), 3.89 (d, J = 7.8 Hz, 1H), 3.81 (d, J = 11 Hz, 6H), 1.46 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 110.7, 108.6, 79.7, 76.7, 68.2 (d, J = 5.5 Hz), 65.7, 65.2, 54.6 (d, J = 5.5 Hz), 27.3, 27.0, 20.5; ^{31}P NMR δ −1.15; HRMS (CI) calcd for $C_{12}H_{24}PO_8$ 327.1209, found 327.1211.

1-Deoxy-D-xylulose-5-phosphate (5). To a solution of phosphotriester **17** (279 mg, 0.86 mmol) in 0.5 mL of CH_2Cl_2 was added trimethylsilyl bromide (341 μL, 2.57 mmol, 3 equiv). The reaction was stirred for 2 h at room temperature and then concentrated. Water (2 mL) was added to the flask, and the reaction was stirred for 2 h before concentrated HCl (200 μL) was added. The reaction was stirred for an additional 1 h, and solid $NaHCO_3$ was added to a pH = 7. The mixture was frozen and lyophilized to give a yellow solid. The residue was purified by cellulose chromatography (15−50% (v/v) 0.1% trifluoroacetic acid and THF) to give 194 mg (90%) of a white solid: [α] −1.2° (*c* 4.2, H_2O); ^{1}H NMR δ 4.38 (s, 1H), 4.21 (t, J = 6.6 Hz, 1H), 3.73 (t, J = 6.6 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR δ 214.8, 78.6, 72.3 (d, J = 7.1 Hz), 66.0 (d, J = 5 Hz) 27.5; ^{31}P NMR δ 2.23; HRMS (−FAB) calcd for $C_5H_{10}PO_7$ 213.0164, found 213.0173.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **4**, **5**, **11**−**17** and ^{31}P NMR spectra for compounds **5** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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