An Efficient Preparation of 2-*C*-Methyl-D-Erythritol 4-Phosphoric Acid and Its Derivatives

Klaus Kis,[†] Juraithip Wungsintaweekul,[‡] Wolfgang Eisenreich,[†] Meinhart H. Zenk,[‡] and Adelbert Bacher*[,†]

Institut für Organische Chemie und Biochemie, Technische Universität München, Lichtenbergstr. 4, D-85747 Garching, Federal Republic of Germany, and Institut für Pharmazeutische Biologie, Ludwig-Maximilians-Universität München, Karlstr. 29, D-80333 München, Germany

Received March 23, 1999

Introduction

Isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) are the key intermediates in terpenoid biosynthesis. Classical studies by Bloch, Cornforth, Lynen, and their co-workers have established that IPP and DMAPP can be biosynthesized from acetyl-CoA via mevalonate.[1−4] More recently, an alternative pathway was shown to be operative in certain bacteria and in plant chloroplasts.[5−8] The initial step of the novel pathway involves the thiamine pyrophosphate dependent condensation of pyruvate (**1**) with glyceraldehyde 3-phosphate (**2**) affording 1-deoxy-D-xylulose 5-phosphate (**3**). The availability of compounds such as **3** is of great importance for the elucidation of the later steps of this novel pathway. Recently, Blagg and Poulter could improve the synthesis of **3** from 5% to 58% in a reaction sequence that allows the introduction of carbon or hydrogen isotopes.[9] Most recently, Thiel and Adam described the introduction of ^{2}H in position C-5 of **3**.[10] Recent evidence indicates that deoxyxylulose 5-phosphate can be converted to 2-*C*-methyl-D-erythritol 4-phosphate (**5**) by an enzyme from *Escherichia coli* that catalyzes a two-step reaction involving an intramolecular rearrangement via aldehyde **4** followed by reduction (Scheme 1).[11,12] This reduction step was shown to proceed stereospecifically in *Liriodendron tulipifera* and *Synechocystis sp. PCC6803*.[13,14]

We decided to synthesize 2-*C*-methyl-D-erythritol 4-phosphate to study its potential involvement in the deoxyxylulose pathway of terpenoid biosynthesis. The synthetic strategy was designed to permit the introduction of stable or radioactive isotopes in different steps, thus leading to a set of labeled compounds, necessary for mechanistical studies of the alternative terpenoid pathway.

Results and Discussion

Derivatives of 2-*C*-methyl-D-erythritol and racemic 2-*C*-methyl-threitol were prepared in 1980 by Anthonsen et al.[15] In 1982, Yoshimura reported the synthesis of derivatives of 2-*C*-methyl-erythritol and 2-*C*-methyl-erythrose.[16] The reaction sequence was hampered by the formation of numerous byproducts and low yields. Retrosynthetic analysis suggested 2-*C*-methyl-D-erythrono-1,4-lactone (**12**) as starting material for the preparation of the putative terpene precursor, 2-*C*-methyl-D-erythritol 4-phosphate. De Pascual Teresa[17] and Ford[18] had obtained **12** as a natural product from the plants *Astragalus lusitanicus Lam.* and *Cicer ariatinum*. The lactone was thought to be a plant growth regulator involved in feedback inhibition in the biosynthesis of valine. Mukaiyama et al. and Kobayashi have reported the synthesis of **12** and 2-*C*-methyl-D-threono-1,4-lactone (**13**), the latter compound with an enantiomeric excess of >98%.[19,20]

Our initial attempt to generate the carboxylic acid **11** directly from 3,4-dihydroxy-2-butanone by cyanohydrin formation failed because the starting material formed butane-2,3-dione by dehydration under the reaction conditions. We decided to synthesize **12** from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**6**) (Scheme 2). This approach facilitates the introduction of stable or radioactive isotopes.

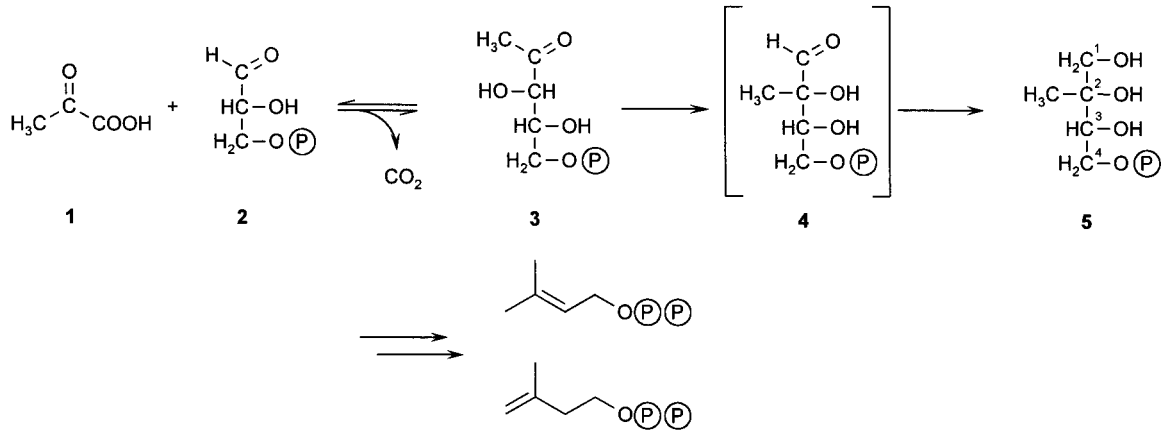
Cleavage of **6** with lead tetraacetate followed by subsequent treatment of the resulting isopropylidene glyceraldehyde (**7**) with methylmagnesium iodide and oxidation afforded (3*R*)-3,4-*O*-isopropylidene-2-butanone (**9**).[21] Reaction of **9** with trimethylcyanosilane under catalysis with KCN and 18-crown-6 quantitatively afforded (2*R*,3*RS*)-1,2-*O*-isopropylidene-3-*O*-trimethylsilyl-1,2,3-trihydroxy-3-cyano-butane (**10**). The ratio of the diastereomeric products 2*R*,3*R* and 2*R*,3*S* was 3:1, as determined by NOE experiments of isopropylidene derivative **14**. Hydrolysis of the diastereomeric mixture with 25% hydrochloric acid afforded a mixture of the erythronolactone **12**, threonolactone **13**, and the corresponding open chain carboxylic acids **11**. Small amounts of this reaction mixture could be purified by column

* Tel.+49-89-289-13360. Fax: +49-89-289-13363. E-mail: adelbert.bacher@ch.tum.de.
† Technische Universität München.
‡ Ludwig-Maximilians-Universität München.

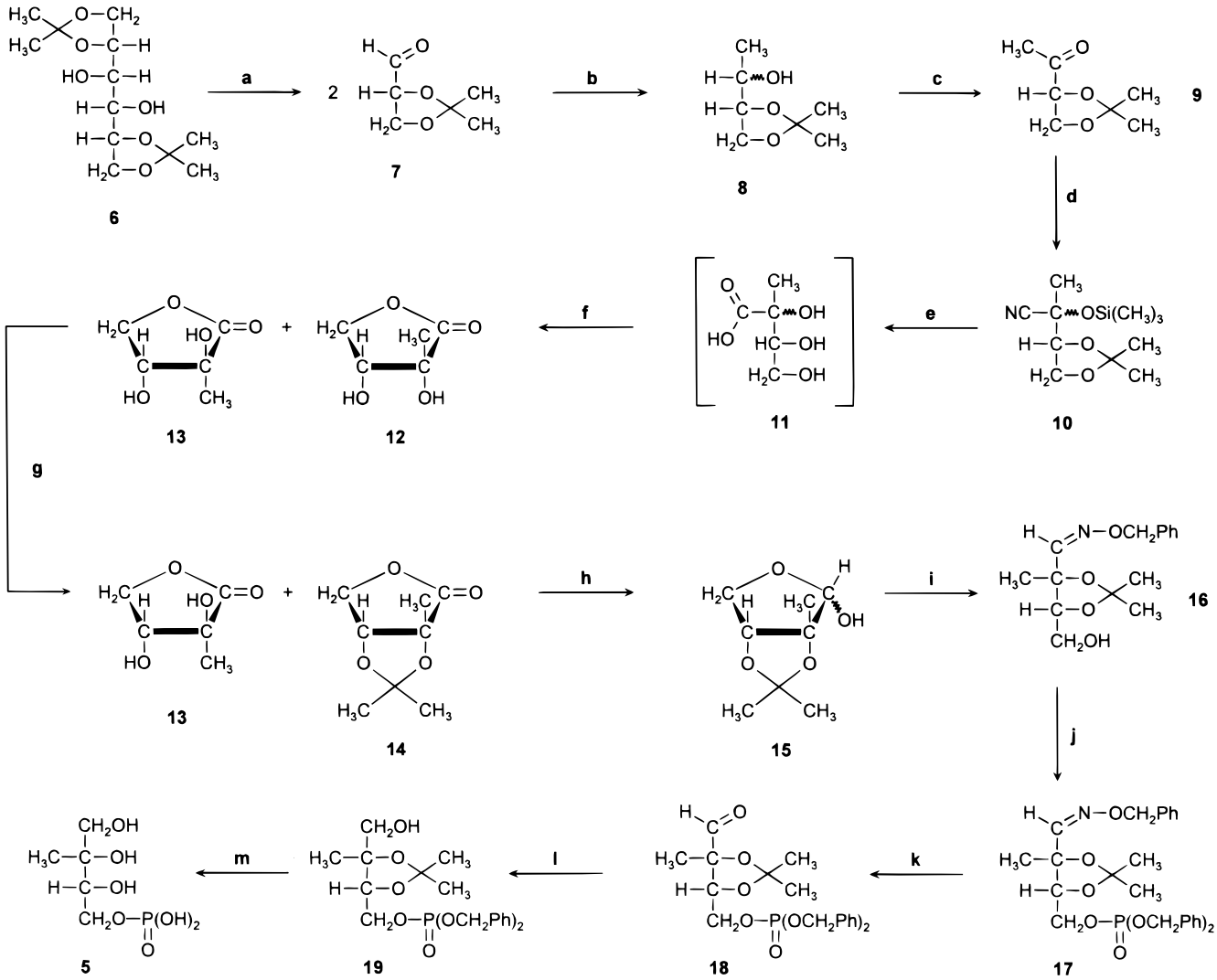
(1) Bloch, K. *Steroids* **1992**, *57*, 378−382.
(2) Qureshi, N.; Porter, J. W. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; John Wiley: New York, 1981; Vol. 1, pp 47−94.
(3) Banthorpe, D. V.; Charlwood, B. V.; Francis, M. J. O. *Chem. Rev.* **1972**, *72*, 115−155.
(4) Bach, T. J. *Lipids* **1995**, *30*, 191−202.
(5) Flesch, G.; Rohmer, M. *Eur. J. Biochem.* **1988**, *175*, 405−411.
(6) Rohmer, M.; Knani, M.; Simonin, P.; Sulter, B.; Sahm, H. *Biochem. J.* **1993**, *295*, 517−524.
(7) Lichtenthaler, H. K.; Schwender, J.; Disch, A.; Rohmer, H. *Biochem. J.* **1996**, *316*, 73−80.
(8) Seto, H.; Watanabe, H.; Furihata, K. *Tetrahedron Lett.* **1996**, *37*, 7979−7982.
(9) Blagg, B. S.; Poulter, C. D. *J. Org. Chem.* **1975**, *40*, 1508−1511.
(10) Thiel, R.; Adam, K. P. *Tetrahedron Lett.* **1999**, *40*, 5307−5308.
(11) Takahashi, S.; Kuzuyama, T.; Watanabe, H.; Seto, H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9879−9884.
(12) Kuzuyama, T.; Takahashi, S.; Watanabe, H.; Seto, H. *Tetrahedron Lett.* **1998**, *39*, 4509−4512.
(13) Arigoni, D.; Giner, J.-L.; Sagner, S.; Wungsintaweekul, J.; Zenk, M. H.; Kis, K.; Bacher, A.; Eisenreich, W. *Chem. Commun.* **1999**, 1127−1128.
(14) Proteau, P. J.; Woo, Y.-H.; Williamson, R. T.; Phaosiri, C. *Org. Lett.* **1999**, *1*, 921−923.
(15) Anthonsen, T.; Hagen, S.; Sallam, M. A. E. *Phytochemistry* **1980**, *19*, 2375−2377.
(16) Yoshimura, J.; Hara, K.; Yamaura, M.; Mikamin, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 933−937.
(17) De Pascual Teresa, J.; Hernándesz Aubanell, J. C.; San Feliciano, A.; Migel del Corral, J. M. *Tetrahedron Lett.* **1980**, *21*, 1359−1360.
(18) Ford, C. W. *Phytochemistry* **1981**, *20*, 2019−2020.
(19) Mukaiyama, T.; Hiina, I.; Izumi, J.; Kobayashi, S. *Heterocycles* **1996**, *35*, 719−724.
(20) Kobayashi, S.; Horibe, H.; Saito, Y. *Tetrahedron* **1994**, *50*, 9629−9642.
(21) Kis, K.; Volk, R.; Bacher, A. *Biochemistry* **1995**, *34*, 2883−2892.

10.1021/jo9905118 CCC: $19.00
Published on Web 12/31/1999

Scheme 1. Biosynthesis of IPP and DMAPP via the Deoxyxylulose Pathway



Scheme 2[a]



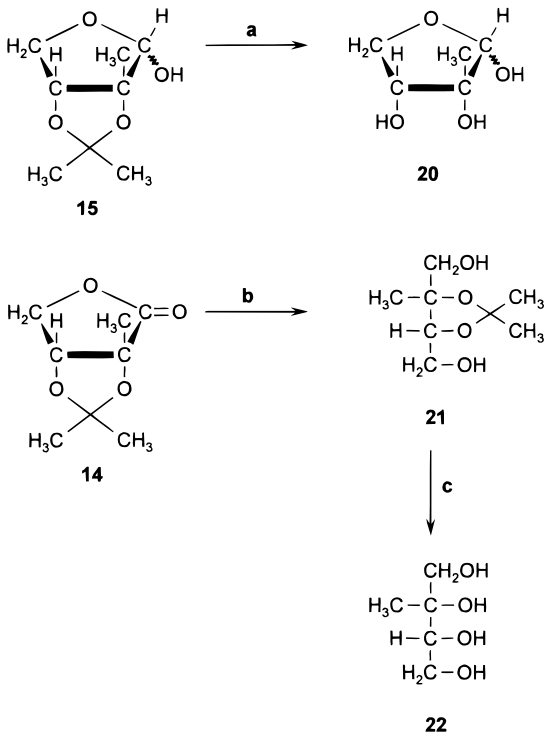
[a] Reagents and conditions: (a) $Pb(OOCCH_3)_4$, CH_2Cl_2, 0 °C (12 h); (b) (1) CH_3MgI, Et_2O, 0 → 25 °C (12 h), (2) H_2O, NH_4Cl; (c) RuO_2, $NaIO_4$, K_2CO_3, $CHCl_3/H_2O$, 25 °C (2 d); (d) $(CH_3)_3SiCN$, KCN, 18-crown-6, CH_2Cl_2, 0 → 25 °C (30 min); (e) HCl (25%), H_2O, EtOH, 40 → 80 °C (3 h); (f) HCOOH (60%), 80 °C (2 h); (g) CH_3COCH_3, $ZnCl_2$, 25 °C (12 h); (h) (1) DIBAH (1.4 equiv), THF, −78 → 25 °C (2 h), (2) H_2O, −78 °C (1 h); (i) $PhCH_2ONH_2$, pyridine, CH_2Cl_2, 25 °C (12 h); (j) (1) $(PhCH_2O)_3P$, I_2, CH_2Cl_2, −20 → 25 °C (30 min), (2) $(PhCH_2O)_2POI$, pyridine, CH_2Cl_2, −20 °C (2 h); (k) (1) O_3, pyridine, CH_2Cl_2, −78 °C (10 min), (2) CH_3SCH_3, −78 °C (1 h); (l) $NaBH_4$, MeOH, 0 → 25 °C (2 h); (m) (1) H_2, Pd/C, MeOH (50%), 25 °C (12 h), (2) 70 °C (60 min).

chromatography on silica with EtOAc/2-propanol/H_2O (65:24:12; v/v/v) as solvent system. The compound eluted first was identified as **13**. The specific rotation $[\alpha]_D$ −35.9° was about two times larger than the value reported by Mukaiyama et al. ($[\alpha]_D$ −18°).[19] The possibility of racemization of this compound was pointed out by De Pascual Teresa et al.[17] Elemental analysis, IR absorption at 1770 cm^{-1} (γ-lactone), and the impossibility to convert the

compound into a cyclic acetal with acetone established the threono-1,4-lactone structure **13**. The second (main) fraction could be identified as the erythronolactone **12**, which could easily be transformed into a cyclic acetal with acetone/$ZnCl_2$. Compound **12** had a specific rotation of $[\alpha]_D$ −60.9°. This value is consistent with reported values (−58.6° and −61.2°).[17,20] The third fraction was very likely a mixture of both diastereomeric open chain carboxylic acids **11** as shown by NMR spectroscopy. The NMR spectra of all three fractions agreed well with published data.[18,20] Lactonization of this reaction mixture was performed to completeness with 60% formic acid at 80 °C. During this procedure the spot on TLC corresponding to compound **11** completely disappeared. The mixture of both lactones was then treated with acetone/$ZnCl_2$. The cyclic acetal **14** could be separated from unreacted **13** by extraction with chloroform after dilution with water. The unchanged 2-*C*-methyl-D-threono-1,4-lactone (**13**) remained in the water phase and could be isolated and purified. In addition to the specific rotation of **12** that demonstrates the 2*R*,3*R* configuration of 2-*C*-methyl-D-erythrono-1,4-lactone, further evidence for this configuration was obtained from NOESY spectroscopy of its isopropylidene derivative **14**. The proton at 4.41 ppm showed strong NOEs to two methyl groups located at 1.33 and 1.48 ppm. The proton at 4.24 ppm showed a strong NOE to the methyl group at 1.48 ppm. Thus, the protons at 1.48, 4.24, and 4.41 ppm are located on the same side of the lactone ring plane. Finally, the proton at 4.34 ppm did not show NOEs to the methyl groups at 1.33 and 1.48 ppm. In contrast, only a weak NOE to the methyl group located at 1.37 ppm could be observed. Because the configuration of carbon atom C-3 should remain *R* (as in the starting material), during the synthesis the configuration of C-2 should also be *R*. The ^{1}H NMR signals at 1.48, 4.24, 4.34, and 4.41 ppm can now be assigned to the C-2 methyl group, C-4 H_{pro-R}, C-4 H_{pro-S}, and C-3 H_R, respectively. The protons C-4 H_{pro-S} and C-3 H_R have a small coupling constant (≈ 0 Hz), suggesting a bond angle near 90°, which is reasonable for such a rigid structure in **14**. The configuration of **12** and **14** is further corroborated by the observed specific rotation of **14**. This compound showed a large specific rotation $[\alpha]_D$ −82.5° in acetone. Ishizu et al. reported a value of $[\alpha]_D$ −40° for **14**.[22] Also here a partial racemization may have occured during their preparation procedure. All these data suggest that the configuration of **12** is 2*R*,3*R*, which is the desired configuration of the final product **5**.

Ring opening of **14** with methoxide in methanol afforded a complex product mixture. However, **14** could be reduced with diisobutylaluminum hydride (DIBAH) yielding the cyclic hemiacetals **15** in both anomeric forms (α/β). The open chain aldehyde was not present in significant amounts according to NMR spectra. Deprotection of **15** with 60% acetic acid at 60 °C afforded 2-*C*-methyl-D-erythrose (**20**) as cyclic acetals in 89% yield (Scheme 3). Again, no open chain aldehyde was present in this anomeric mixture. Reduction of **14** with a 2.5-fold excess of DIBAH resulted in quantitative reduction of the lactone yielding 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (**21**). NMR data of this compound correspond to those reported by Anthonsen.[15] However, the specific rotation of **21** determined by us ($[\alpha]_D$ −26.0°) and the value

Scheme 3[a]



[a] Reagents and conditions: (a) CH_3COOH (60%), 60 °C (1 h); (b) (1) DIBAH (2.5 equiv), THF, −78 → 25 °C (2 h), (2) H_2O, −78 °C (1 h); (c) CH_3COOH (12%), 60 °C (3 h).

reported by Anthonsen ($[\alpha]_{578}$ +7.92) differ significantly. This may be due to the different wavelength used. Deprotection of **21** with 12% acetic acid at 60 °C afforded 2-*C*-methyl-D-erythritol (**22**) which had the same spectroscopic properties as an authentic sample. However, $[\alpha]_D$ of compound 22 was 50% smaller than reported.[23,24]

Ring opening of the protected hemiacetal **15** could easily be achieved by oxime ether formation using *O*-benzylhydroxylamine hydrochloride in pyridine. This reaction proceeded smoothly at room temperature in high yield, and the product could easily be extracted with chloroform. Benzyloxime ether **16** was then phosphorylated using tribenzyl phosphite[25] and iodine in dichloromethane, affording **17** in 71% yield. Removal of the benzyloxime ether group by boiling with benzaldehyde under acid catalysis was not successful. Ozone cleavage was considered as an alternative. Little is known about ozonization of oximes. Erikson et al. reported that ozonization of the carbon−nitrogen double bond may give complex reaction mixtures, but carbonyl formation was also observed.[26] Recently, acyclic sugar aldehydes were successfully prepared by ozonization of oximes by Weitz and Bednarski.[27] Although it was mentioned by Erikson et al. that aldoximes may undergo further oxidation upon treatment with ozone, we attempted the ozonization of benzyloxime ether **17**. Initially, a complex reaction

(22) Ishizu, A.; Lindberg, B.; Theander, O. *Acta Chem. Scand.* **1967**, *21*, 424−432.

(23) Anthonsen, T.; Hagen, S.; Kazi, M.; Shah, S.; Tager, S. *Acta Chem. Scand. Ser. B* **1976**, *30*, 91−93.

(24) Ostrovsky, D.; Shashkov, A.; Sviridov, A. *Biochem. J.* **1993**, *295*, 901−902.

(25) Gefflaut, T.; Lemaire, M.; Valentin, M.-L.; Bolte, J. *J. Org. Chem.* **1997**, *62*, 5920−5922.

(26) Erikson, R. E.; Andrulis, P. J.; Collins, J. C.; Lungle, M. C., Mercer, G. D. *J. Org. Chem.* **1969**, *34*, 2961−2966.

(27) Weitz, D. J.; Bednarski, M. D. *J. Org. Chem.* **1989**, *54*, 4957−4959.

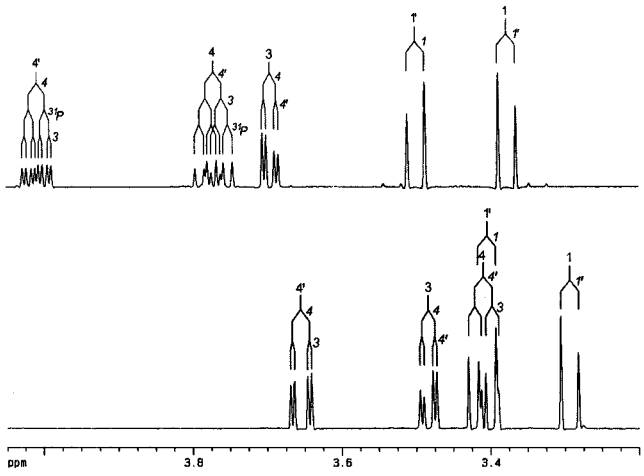


Figure 1. ^{1}H NMR spectrum of (top) 2-*C*-methyl-D-erythritol 4-phosphoric acid (**5**) and (bottom) 2-*C*-methyl-D-erythritol (**22**) (500 MHz D_2O, pH 1). The 2-*C*-methyl groups are not shown. Assignments are given according to the notation of **5** in Scheme 1 (primes denote diastereotopic protons).

mixture was obtained, probably as a result of a pH decrease of the solution. However, ozonization in the presence of pyridine was successful, and the aldehyde phosphate **18** could be isolated in 91% yield. This aldehyde compound **18** is very unstable and polymerizes even at −20 °C. The product **18** was then reduced with an excess of sodium borohydride in methanol, affording the 4-dibenzyl phosphate of 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (**19**). Hydrogenation and subsequent acidic hydrolysis of the isopropylidene group yielded 2-*C*-methyl-D-erythritol 4-phosphoric acid (**5**) in 9% overall yield after 14 steps (for ^{1}H NMR, see Figure 1). Isotopic labels can be introduced during the reaction steps **7** → **8**, **9** → **10**, **14** → **15**, and **18** → **19**, which would afford labels (^{2}H, ^{3}H, ^{13}C, or ^{14}C) in the positions C_2' or C_1 of **5**.

Experimental Section

Materials. Chemicals were obtained from Aldrich Chemicals (Steinheim, Germany) and were used without further purification. Solvents were dried prior to use. Potassium carbonate and magnesium sulfate were dried under reduced pressure at 120 °C. Silica gel was activated by drying at 120 °C for 2 days. TLC was performed on silica plates, and the compounds were visualized by fluorescence quenching, 2,4-dinitrophenylhydrazine (2% in ethanol containing 13% H_2SO_4), or lead tetraacetate (1% in toluene). All compounds gave only one single spot. NMR spectra were recorded at room temperature.

(2*R*,3*RS*)-1,2-*O*-Isopropylidene-1,2,3-butanetriol (8). 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**6**) (14.0 g, 53.0 mmol) was dissolved in 200 mL of dry chloroform. Anhydrous potassium carbonate (50.5 g, 366 mmol) was added, and the suspension was cooled to 0 °C. Lead tetraacetate (27.1 g, 61.1 mmol) was added in small portions under vigorous stirring. The orange suspension was allowed to stand at room temperature overnight. Potassium carbonate was filtered off by suction, and the filter cake was washed repeatedly with ether. The combined filtrate and washings were dried with magnesium sulfate, and the solvent was removed under reduced pressure. The oily residue was quickly distilled (60 °C at 30 mbar), affording 10.5 g (80.7 mmol, 76%) isopropylidene glyceraldehyde **7**. The product was immediately dissolved in 35 mL of dry ether to avoid polymerization. The solution was added to a cooled solution of methylmagnesium iodide prepared from 5.1 g (0.22 mol) of magnesium and 13 mL (0.21 mol) of methyl iodide in 140 mL of ether. After the aldehyde was added completely, the solution was stirred at room temperature overnight. The solution was then slowly poured onto crushed ice, and precipitated magnesium hydroxide was dissolved by the addition of saturated ammonium chloride (50 mL). The organic layer was removed, and the water phase was saturated with sodium chloride and extracted with chloroform (3 × 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was removed under reduced pressure, affording 9.9 g (68 mmol, 84%) of (2*R*,3*RS*)-1,2-*O*-isopropylidene-1,2,3-butanetriol as colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 0.96 (d, ^3J = 6.5 Hz), 1.07 (d, ^3J = 6.5 Hz), 1.24 (s), 1.25 (s), 1.29 (s), 1.33 (s), 3.41−3.47 (m), 3.67−3.78 (m), 3.82−3.97 (m), 4.67 (d, ^3J = 4.6 Hz), 4.75 (d, ^3J = 5.2 Hz). ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 18.0, 19.8, 24.8, 26.1, 64.3, 65.9, 66.1, 66.9, 79.1, 79.3, 107.7, 107.7. Anal. Calcd for ($C_7H_{14}O_3$): C, 57.5; H, 9.90. Found: C, 57.2; H, 9.90.

(3*R*)-3,4-*O*-Isopropylidene-3,4-dihydroxy-2-butanone (9). (2*R*,3*RS*)-1,2-*O*-Isopropylidene-1,2,3-butanetriol (**8**) (9.9 g, 68 mmol) was dissolved in 100 mL of chloroform. Water (100 mL), 30 g of potassium carbonate (0.22 mol), and 50 mg of ruthenium dioxide hydrate was added. The suspension was stirred vigorously at room temperature, and 29 g (0.14 mol) of sodium periodate was added in small portions. The pH was repeatedly adjusted to 8−8.5 by the addition of solid potassium carbonate. After the addition of periodate was complete, the suspension was stirred for 2 days at room temperature. Prior to workup, an aliquot of the reaction mixture was checked by ^{1}H NMR spectroscopy. If starting material was still present, an additional amount of periodate was added. When the oxidation was complete, the suspension was filtered by suction, and the filtrate was extracted with chloroform (4 × 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was removed under reduced pressure affording 7.2 g (50 mmol, 74%) of (3*R*)-3,4-*O*-isopropylidene-3,4-dihydroxy-2-butanone as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.4 (s, 3H), 1.5 (s, 3H), 2.27 (s, 3H), 4.0 (dd, ^2J = 8.5 Hz, ^3J = 5.5 Hz, 1H), 4.2 (dd, ^2J = 8.5 Hz, ^3J = 8.0, 1H), 4.41 (dd, ^3J = 7.9 Hz, ^3J = 5.5 Hz, 1H). ^{13}C NMR (62 MHz, $CDCl_3$): δ (ppm) 25.3, 25.6, 26.3, 66.4, 80.4, 110.9. Anal. Calcd for ($C_7H_{12}O_3$): C, 58.4; H, 8.33. Found: C, 57.9; H, 8.30. TLC R_f 0.71 (hexane/EtOAc 1:4, v/v). $[\alpha]^{22}_D$ +49.0° (*c* 0.72, CH_2Cl_2) (lit. $[\alpha]^{20}_D$ +53.3° (*c* 1.56, $CHCl_3$),[28] $[\alpha]^{20}_D$ +47.1° (*c* 1.87, $CHCl_3$)[29]).

(2*R*,3*RS*)-1,2-*O*-Isopropylidene-3-*O*-trimethylsilyl-1,2,3-trihydroxy-3-cyano-butane (10). (3*R*)-3,4-*O*-Isopropylidene-3,4-dihydroxy-2-butanone (**9**) (7.2 g, 50 mmol) was dissolved in 50 mL of dry dichloromethane. Catalytic amounts of potassium cyanide (20 mg) and 18-crown-6 (20 mg) were added. Under cooling with ice, 9.4 mL (70 mmol) of trimethylsilyl cyanide was added within 20 min. The solvent and excess trimethylsilyl cyanide were removed under reduced pressure. The orange colored oily residue (12.0 g, 49.3 mmol, 99%) was a mixture of the *erythro* and *threo* compound in a ratio of 3:1. The unstable compound was used immediately without further purification. ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 0.17 and 0.18 (2s, 9H), 1.12, 1.29, 1.40, 1.43, 1.46 and 1.57 (6s, 9H), 3.85−3.90 (m, 1H), 3.97−4.10 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$): *erythro* δ (ppm) 1.2, 24.0, 25.0, 26.0, 65.0, 80.4, 110.9; *threo* δ (ppm) −3.1, 25.2, 26.2, 26.4, 66.4, 80.8, 120.7. Anal. Calcd for ($C_{11}H_{21}NO_3Si$): C, 54.3; H, 8.63; N, 5.76; Si, 11.6. Found: C, 53.9; H, 8.79; N, 5.51; Si, 12.4.

2-*C*-Methyl-*D*-erythrono-1,4-lactone (12) and 2-*C*-Methyl-*D*-threono-1,4-lactone (13). (2*R*,3*RS*)-1,2-*O*-Isopropylidene-3-*O*-trimethylsilyl-1,2,3-trihydroxy-3-cyano-butane (**10**) (12.0 g, 49.3 mmol) was suspended in 30 mL of 25% hydrochloric acid. Ethanol (10 mL) was added to improve the solubility of the lipophilic cyanohydrin. The reaction mixture was stirred at 45 °C for 30 min and subsequently under reflux for 3 h. The mixture became brown, and a precipitate of ammonium chloride was formed. The acid was neutralized with concentrated ammonia. The mixture was evaporated to dryness. The product mass was triturated with 50 mL of methanol. Insoluble ammonium chloride was filtered off. Methanol was removed under reduced pressure. The residual oil contained the lactones **12** and **13** and the open chain carboxylic acids **11**. All three compounds can be purified on an analytical scale by column chromatography (silica, 1 cm × 30 cm) developed with EtOAc/2-propanol/water (65:24:

(28) Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814-823.
(29) Hagen, S.; Anthonsen, T.; Kilaas, L. *Tetrahedron* **1979**, *35*, 2583.

12, v/v/v). Lactonization was brought to completion by boiling the residue with 60% formic acid (30 mL) for 2 h. When no more open chain carboxylic acids were present (detected by TLC with lead tetraacetate), the reaction mixture was concentrated under reduced pressure. The residual oil was dissolved in a EtOAc/2-propanol/water (5 mL, 65:24:12, v/v/v). The solution was placed on a column of silica gel (acidic form) and was eluted with the EtOAc/2-propanol/water mixture. Fractions were combined and concentrated under reduced pressure. The residue was lyophilized. The residual colorless oil (5.9 g, 45 mmol, 91%) contained 2-*C*-methyl-D-erythrono-1,4-lactone and 2-*C*-methyl-D-threono-1,4-lactone in a ratio of about 3:1 as determined by NMR spectroscopy.

2-*C*-Methyl-D-threono-1,4-lactone. ^{1}H NMR (250 MHz, CD_3OD): δ (ppm) 1.30 (s, 3H), 3.92 (dd, ^2J = 4.3 Hz, ^3J = 9.2 Hz, 1H), 4.13 (dd, ^2J = 4.3 Hz, ^3J = 5.5 Hz, 1H), 4.44 (dd, ^2J = 5.5 Hz, ^3J = 9.2 Hz, 1H). ^{13}C NMR (63 MHz, CD_3OD): δ (ppm) 17.9, 73.1, 78.8, 85.8, 161.8. IR (film): 1770 cm^{-1}. Anal. Calcd for ($C_5H_8O_4$): C, 45.5; H, 6.06. Found: C, 44.9; H, 6.07. TLC R_f 0.79 (EtOAC/2-propanol/water 65:24:12, v/v/v). $[\alpha]_D^{22}$ −35.9° (*c* 1.8, water) (lit. $[\alpha]_D^{28}$ −18° (*c* 0.4, water)[19]).

2-*C*-Methyl-D-erythrono-1,4-lactone. ^{1}H NMR (250 MHz, CD_3OD): δ (ppm) 1.33 (s, 3H), 4.00 (dd, ^2J = 1.8 Hz, ^3J = 4.3 Hz, 1H), 4.09 (dd, ^2J = 1.8 Hz, ^3J = 9.8 Hz, 1H), 4.38 (dd, ^2J = 4.3 Hz, ^3J = 10.4 Hz, 1H). ^{13}C NMR (63 MHz, CD_3OD): δ (ppm) 21.9, 73.6, 75.0, 75.8, 164.9. IR (film): 1770 cm^{-1}. Anal. Calcd for ($C_5H_8O_4 \cdot 0.3H_2O$): C, 43.7; H, 6.26. Found: C, 43.0; H, 6.17. TLC R_f 0.62 (EtOAc/2-propanol/water 65:24:12, v/v/v). $[\alpha]_D^{22}$ −60.9° (*c* 0.6, water) (lit. $[\alpha]_D^{25}$ −61.2 (*c* 0.2, water)[20]; −58.6° (*c* 0.61, water)[17]).

Open Chain Carboxylic Acids (Isomeric Mixture 1:1). ^{1}H NMR (250 MHz, D_2O): δ (ppm) 1.14 (s, 3H), 1,17 (s, 3H), 3,45−3,85 (m, 6H). ^{13}C NMR (63 MHz, D_2O): δ (ppm) 19.8, 20.7, 64.9, 65.2, 70.1, 70.3, 77.8, 77.9, 182.5, 182.8. TLC R_f 0.45 (EtOAc/2-propanol/water 65:24:12, v/v/v).

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone (14). Anhydrous zinc chloride (14.1 g, 103 mmol) was dissolved in 100 mL of acetone. The solution was cooled with ice, and 5.9 g of a mixture of 2-*C*-methyl-D-erythrono-1,4-lactone (**12**) (34 mmol) and 2-*C*-methyl-D-threono-1,4-lactone (**13**) (11 mmol) dissolved in 13 mL of acetone was added. After 18 h the solution was diluted with 150 mL of chloroform. Zinc chloride and unreacted 2-*C*-methyl-D-threono-1,4-lactone were removed by washing with water (3 × 100 mL). The organic layer was dried with magnesium sulfate, and the solvent was removed under reduced pressure, affording pure 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythronolactone (4.4 g, 26 mmol, 76% from 2C-methyl-D-erythrono-1,4-lactone) as a colorless oil that crystallized at −20 °C. To recycle unreacted **13**, the combined water phases were lyophilized, and the solid residue was extracted three times with 50 mL of boiling methanol. The precipitate was filtered off, and methanol was removed under reduced pressure. The residue was dissolved in EtOAc/2-propanol/water (65:24:12, v/v/v, 2 mL) and was placed onto a column of silica (1 cm × 20 cm), which was developed with the same solvent. Fractions containing **13** were pooled and evaporated to dryness, affording 1.1 g of **13** as colorless oil (analytical data for **13** see above). ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 1.33 (s, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 4.24 (dd, ^3J = 3.54 Hz, ^2J = 11.1 Hz, 1H), 4.34 (dd, ^2J = 11.1 Hz, ^3J = 0 Hz, 1H), 4.41 (dd, ^2J = 3.5 Hz, ^3J = 0 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 18.4, 26.5, 26.9, 68.9, 80.3, 81.4, 113.0, 176.7. Anal. Calcd for ($C_8H_{12}O_4$): C, 55.8; H, 6.97. Found: C, 55.1; H, 7.04. TLC R_f 0.77 ($CHCl_3$/EtOAc 1:4, v/v). $[\alpha]_D^{22}$ −82.5° (*c* 2.1, acetone) (lit. $[\alpha]_D^{22}$ −40°).[22]

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrofuranose (15). 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone (**14**) (2.2 g, 13 mmol) was dissolved in 60 mL of dry tetrahydrofuran. The mixture was cooled to −78 °C under an atmosphere of nitrogen. A solution of diisobutylaluminum hydride (DIBAH) (1 M in hexane, 17 mL, 17 mmol) was added slowly. The solution was allowed to stand in the cooling bath overnight. Wet ether (180 mL) and wet silica gel (30 g) were added. The mixture was stirred for 1 h and was allowed to warm to room temperature. The mixture was then filtered. The solution was dried with magnesium sulfate, and the solvent was removed under reduced pressure. The residual oil was purified by chromatography on silica gel with a mixture of hexane/EtOAc (1:2, v/v), affording 2.0 g (12 mmol, 89%) of 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrofuranose as an anomeric mixture. ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 1.29 (s), 1.30 (s), 1.34 (s), 1.35 (s), 1.37 (s) (18 H), 3.46 (dd, ^3J = 3.5 Hz, ^2J = 11.1 Hz, 1H), 3.55 (m, 1H), 3.78 (d, ^2J = 11.5 Hz, 2H), 3.84 (d, ^2J = 11.1 Hz, 1H), 3.97 (dd, ^3J = 3.8 Hz, ^2J = 10.4 Hz, 1H), 4.29 (dd, ^3J = 3.1 Hz, ^3J = 8.9 Hz, 2H), 4.52 (d, ^2J = 11.1 Hz, 1H), 5.13 (d, ^3J = 2.7 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 19.4, 21.4, 26.3, 26.9, 27.2, 28.0, 67.1, 71.5, 84.9, 86.0, 86.1, 91.4, 101.4, 103.3, 112.4, 112.9. Anal. Calcd for ($C_8H_{14}O_4$): C, 55.2; H, 8.04. Found: C, 54.7; H, 8.11. TLC R_f 0.61 (hexane/EtOAc 1:2 v/v).

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrose-(*O*-benzyl)-oxime (16). 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrofuranose (**15**) (0.5 g, 3 mmol) was dissolved in 12 mL of dry dichloromethane. Dry pyridine (1 mL) and 0.88 g (5.5 mmol) of *O*-benzylhydroxylamine hydrochloride were added in one portion. The hydroxylamine dissolved within 20 min, and the reaction mixture became turbid after 40 min. The mixture was stirred for 15 h at room temperature and was evaporated to dryness under reduced pressure. The residue was suspended in a mixture of chloroform/EtOAc (1:4, v/v, 1 mL). The solution was placed on a silica gel column (1 cm × 30 cm), and the product was eluted with the solvent mixture. Fractions containing the product were combined, and the solvent was removed under reduced pressure, affording 0.53 g (1.9 mmol, 66%) of **16** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.26 (s, 3H), 1.31 (s, 3H), 1.33 (s, 3H), 3.42−3.56 (m, 2H), 3.86 (dd, ^3J = 4.9 Hz, ^3J = 6.7 Hz, 1H), 4.92 (s, 2H), 7.15−7.25 (m, 5H), 7.32 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) 22.8, 26.6, 27.9, 60.7, 76.0, 80.5, 84.3, 109.4, 127.9, 128.2, 128.3, 137.2, 152.0. Anal. Calcd for ($C_{15}H_{21}NO_4$): C, 64.5; H, 7.52; N, 5.02. Found: C, 65.4; H, 7.53; N, 5.07. TLC R_f 0.80 ($CHCl_3$/EtOAc 1:4, v/v). $[\alpha]^{22}_D$ −24.0 (*c* 0.75, acetone).

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrose-(*O*-benzyl)-oxime 4-Dibenzyl Phosphate (17). Tribenzyl phosphite (1.3 g, 3.7 mmol) was dissolved in 20 mL of dry dichloromethane. The solution was cooled to −20 °C. Iodine (0.96 g, 3.8 mmol) was added in one portion. The mixture was protected from light and was allowed to come to room temperature when the violet color had disappeared. 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrose-(*O*-benzyl)oxime (**18**) (0.53 g, 1.9 mmol) was dissolved in 20 mL of dichloromethane, and 2.5 mL of pyridine was added. The solution was cooled to −20 °C, and the solution of dibenzyl iodophosphate was added slowly. The reaction mixture was stirred for 2 h at room temperature and was washed subsequently with sodium hydrogen sulfate (30%, w/v, 2 × 10 mL), a solution of sodium hydrogen carbonate (5%, w/v, 10 mL), and water (10 mL). The organic phase was dried with magnesium sulfate. The solution was evaporated to dryness. The residue was suspended in a mixture of hexane/EtOAc (3:1, v/v, 2 mL). The mixture was placed on a silica gel column (1 cm × 20 cm), which was developed with hexane/EtOAc (3:1, v/v) until benzyl iodide was completely washed out. The product was then eluted with a mixture of chloroform/EtOAc (1:4, v/v). Fractions were combined, and the solvent was removed under reduced pressure, affording 0.73 g (1.4 mmol, 71%) of **17**. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.31 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 3.90−3.99 (m, 3H), 4.94 (s, 1H), 4.97−5.02 (m, 6H), 7.24−7.33 (m, 15H). ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) 22.0, 26.6, 28.0, 65.3 (d, $^2J_{CP}$ = 5.5 Hz), 69.1−69.5 (m), 76.2, 80.2, 82.5 (d, $^3J_{CP}$ = 7.9 Hz), 109.7, 127.9−128.5, 135.6 (d, $^3J_{CP}$ = 6.8 Hz), 137.9, 150.3. ^{31}P NMR (101 MHz, $CDCl_3$): δ (ppm) −0.8 (s). HRMS(EI) calcd for ($C_{29}H_{34}NO_7P$) 539.20728, found 539.20746 ± 3.9 ppm. Anal. Calcd for ($C_{29}H_{34}NO_7P$): C, 64.6; H, 6.30; N, 2.06; P, 5.75. Found: C, 64.5; H, 6.49; N, 2.09; P, 5.60. TLC R_f 0.32 (hexane/EtOAc 3:1, v/v). $[\alpha]^{22}_D$ −7.4 (*c* 1.0, acetone).

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrose 4-Dibenzyl Phosphate (18). 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrose-(*O*-benzyl)oxime 4-dibenzyl phosphate (**17**) (0.26 g, 0.43 mmol) was dissolved in 15 mL of dichloromethane containing 2 mL of pyridine. The solution was cooled to −78 °C and was ozonized for 7 min with an ozone flow of about 3 g/min (0.4 mmol). Nitrogen was then bubbled through the dark blue reaction mixture. When the blue color had vanished, 2 mL of dimethylsulfide was added. The mixture was allowed to stand at −78 °C for 1 h and was then brought to room temperature. Solvent and pyridine were removed under reduced pressure, and the crude

oil was purified by column chromatography (silica gel; chloroform/EtOAc 1:4, v/v) ,affording 0.17 g (0.39 mol, 91%) of **18**. Because of its instability **18** should be used immediately for the next reaction step. ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 1.24 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 3.93−4.02 (m, 2H), 4.05−4.13 (m, 1H), 4.92−5.00 (m, 4H), 7.23−7.30 (m, 10H), 9.51 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 19.7, 26.5, 27.8, 64.3 (d, $^2J_{CP}$ = 6.0 Hz), 69.5 (m), 82.7 (d, $^3J_{CP}$ = 8.7 Hz), 85.1, 110.9, 126.8 (d, $^4J_{CP}$ = 14.5 Hz), 127.9, 128.6, 135.6 (d, $^3J_{CP}$ = 7.3 Hz), 202.0; ^{31}P NMR (101 MHz, $CDCl_3$): δ (ppm) −1.0 (s). TLC R_f 0.23 ($CHCl_3$/EtOAc 1.5:1, v/v).

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol 4-Dibenzyl Phosphate (19). 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrose 4-dibenzyl phosphate (**18**) (85 mg, 0.20 mmol) was dissolved in 3 mL of dry methanol, and the solution was cooled to 0 °C. Sodium borohydride (20 mg, 0.53 mmol) was added in one portion. The mixture was stirred for 2 h. Water (5 mL) was then added to destroy the excess of borohydride, and the mixture was adjusted to pH 5 with concentrated acetic acid. The suspension was extracted 4 times with 10 mL of chloroform, and the organic solution was washed with 20 mL of a sodium hydrogen carbonate solution (5%, w/v). The organic phase was dried with magnesium sulfate, and the solvent was removed under reduced pressure, affording 86 mg (0.20 mmol, 100%) **19**. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.20 (s, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 1.89 (s, broad, 2H), 3.34 (m, 2H), 3.95 (dd, J = 4.70 Hz, J = 7.1 Hz, 1H), 4.08−4.20 (m, 2H), 5.00 (dd, J = 1.8 Hz, J = 8.6 Hz, 4H), 7.29 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) 22.1, 26.4, 28.1, 65.0, 65.2 (d, $^2J_{CP}$ = 5.5 Hz), 69.4 (dd, $^2J_{CP}$ = 2.7 Hz, $^2J_{CP}$ = 5.5 Hz), 81.1 (d, $^3J_{CP}$ = 8.2 Hz), 81.7, 108.5, 126.9, 128.6, 135.6 (d, $^3J_{CP}$ = 6.8 Hz). ^{31}P NMR (101 MHz, $CDCl_3$): δ (ppm) 0.5 (s). Anal. Calcd for ($C_{22}H_{29}O_7P$): C, 60.6; H, 6.65; P, 7.11. Found: C, 59.8; H, 6.53; P, 6.83. TLC R_f 0.65 ($CHCl_3$/EtOAc 1.5:1, v/v).

2-*C*-Methyl-D-erythritol 4-Phosphoric Acid (5). 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol 4-dibenzyl phosphate (**19**) (86 mg, 0.20 mmol) was suspended in 8 mL of a mixture containing 4 mL of methanol and 4 mL of water. A catalytic amount of palladium on charcoal was added, and the suspension was hydrogenated for 20 h at atmospheric pressure. The catalyst was removed by filtration through a 0.2 μm membrane filter. The acidic solution (pH 2) was heated to 70 °C for 60 min. Methanol was removed under reduced pressure at 40 °C, and the residue was lyophilized, affording 35.3 mg (163 μmol, 83%) of the phosphoric acid that was essentially pure (>95%). For enzymatic procedures **5** was further purified by HPLC. The phosphoric acid was dissolved in 1 mL of water. The solution was placed on a Nucleosil SB_{10} HPLC column and was eluted with 0.5 M formic acid at a flow rate of 1 mL/min. The effluent was monitored refractometrically. Fractions containing the product (retention volume 15 mL) were pooled and freeze-dried, affording 18.0 mg of pure **5**. ^{1}H NMR (500 MHz, D_2O, pH 1): δ (ppm) 1.04 (s, 3H), 3.37 (d, ^2J = 11.8 Hz, 1H), 3.50 (d, ^2J = 11.8 Hz, 1H), 3.64 (dd, ^3J = 2.6 Hz, ^3J = 8.1 Hz, 1H), 3.77 (ddd, $^3J_{HP}$ = 6.2 Hz, ^3J = 8.1 Hz, ^3J = 10.8 Hz, 1H), 4.01 (ddd, ^3J = 2.5 Hz, $^3J_{HP}$ = 6.0 Hz, ^3J = 10.8 Hz, 1H). ^{13}C NMR (125 MHz, D_2O, pH 1): δ (ppm) 18.2 (C'_2), 65.9 (d, $^2J_{CP}$ = 5.1 Hz, C_4), 66.2 (C_1), 73.1 (d, $^3J_{CP}$ = 7.6 Hz, C_3), 73.8 (C_2). ^{31}P NMR (101 MHz, D_2O, pH 1): δ (ppm) 3.7 (s). Anal. Calcd for ($C_5H_{13}O_7P$·HCOOH·0.2H_3PO_4·0.4H_2O): C, 24.9; H, 5.74; P, 13.5. Found: C, 24.9; H, 5.76; P, 13.4.

2-*C*-Methyl-D-erythrofuranose (20). 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrofuranose (**15**) (90 mg, 0.52 mmol) was suspended in 1 mL of 30% acetic acid. The mixture was heated to 70 °C for 1 h. Water and acetic acid were removed by lyophilization, affording 50 mg (0.37 mmol, 71%) of **20** in an anomeric mixture. ^{1}H NMR (360 MHz, CD_3OD): δ (ppm) 1.18 (s, 3H), 1.19 (s, 3H), 3.56 (dd, J = 5.3 Hz, J = 6.6 Hz, 1H), 3.74−3.78 (m, 1H), 3.90−4.05 (m, 4H), 4.78 (s, 1H), 4.91 (s, 1H). ^{13}C NMR (90 MHz, CD_3OD): δ (ppm) 22.6, 23.4, 72.5, 75.1, 75.7, 75.9, 101.9, 104.2. Anal. Calcd for ($C_5H_{10}O_4$·0.4H_2O): C, 42.5; H, 7.65. Found: C, 43.2; H, 7.76. TLC R_f 0.62 (EtOAc/2-propanol/water 65:24:12, v/v/v).

2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol (21). 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythono-1,4-lactone (**14**) (2.9 g, 17 mmol) was dissolved in 100 mL of THF. The solution was cooled to −78 °C. DIBAH (1 M in hexane, 40 mL, 40 mmol) was added slowly. The solution was allowed to come to room temperature, and 10 mL of water was added to destroy excess hydride. The sticky suspension was extracted with chloroform (4 × 50 mL). The organic phase was dried with magnesium sulfate and evaporated, affording 1.3 g (7.3 mmol, 43%) **21**. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.28 (s, 3H), 1.31 (s, 3H), 1.36 (s, 3H), 3.32 (d, ^2J = 11.6 Hz, 1H), 3.53 (d, ^2J = 11.0 Hz, 1H), 3.75−3.90 (m, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) 22.6, 26.5, 28.2, 60.0, 65.1, 81.7, 82.4, 107.8. Anal. Calcd for ($C_8H_{16}O_4$): C, 54.6; H, 9.09. Found: C, 53.9; h, 9.35. TLC R_f 0.33 (hexane/EtOAc 3:1 v/v). $[\alpha]^{22}_D$ −26.0° (*c* 0.36, CH_2Cl_2) (lit. $[\alpha]_{578}$ +7.92 (*c* 0.48, $CHCl_3$)[15]).

2-*C*-Methyl-D-erythritol (22). 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol (**21**) (0.44 g, 2.5 mmol) was dissolved in a mixture containing water (10 mL), acetone (5 mL), and glacial acetic acid (2 mL). The mixture was heated to 60 °C for 3 h. The solvent was then removed by lyophilization, and the colorless residue (340 mg) was dissolved in a mixture of EtOAc/2-propanol/water (1 mL, 65:24:12, v/v/v). The solution was placed on a silica gel column (1 cm × 20 cm) and eluted with the same solvent. Fractions containing the product were pooled, and the solvent was removed under reduced pressure, affording 0.12 g (0.88 mmol, 35%) of **22**. ^{1}H NMR (200 MHz, D_2O): δ (ppm) 1.09 (s, 3H), 3.43 (d, ^2J = 11.8 Hz, 1H), 3.55 (d, ^2J = 11.8 Hz, 1H), 3.50−3.65 (m, 2H), 3.81 (dd, ^2J = 10.1 Hz, ^3J = 1.5 Hz, 1H). ^{13}C NMR (63 MHz, D_2O): δ (ppm) 21.4, 65.0, 69.3, 77.1, 77.9. Anal. Calcd for ($C_5H_{12}O_4$·0.16D_2O): C, 43.1; H, 9.08. Found: C, 43.1; H, 9.15. TLC R_f 0.44 (EtOAc/2-propanol/water 65:24:12, v/v/v). $[\alpha]^{22}_D$ +9.0° (*c* 1.0, water) (lit. $[\alpha]^{28}_D$ +21.4° (*c* 7.0, water)[23]; $[\alpha]_D$ +19.6° (*c* 0.1, water)[24]).

Acknowledgment. This work was supported by grants from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Angelika Werner for the skillful help with this manuscript and the Institut für Anorganische Chemie, Technische Universität München for help with the elemental analysis.

Supporting Information Available: NMR spectra (^{1}H, ^{13}C, DEPT, ^{31}P, or NOESY) for compounds **5** and **7**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9905118