Synthesis of Cyclic Phosphonate Analogs of Ribose and Arabinose

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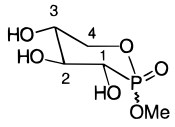
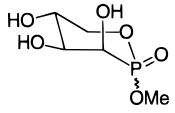
The cyclic phosphonates of ribose and arabinose (phostones) **10**−**13** were synthesized by a Lewis acid-catalyzed addition of trimethyl phosphite to the partially protected D-threose **7** to give the acyclic phosphonates **8** and **9**. This Abramov reaction was moderately stereoselective (3:1). A base-catalyzed cyclization of the mixture of **8** and **9** gave the four isomeric phosphonates **10**−**13**. Two of the isomers, **10** and **11**, could be crystallized from the reaction mixture. The stereochemistries of **11** and **16**, the tribenzyl ether from **10**, were proven by X-ray crystallography, and the stereochemistries of the other isomers and derivatives were determined by ^{31}P NMR chemical shift data. The X-ray data and solution NMR data indicate that these phostones and their derivatives exist exclusively in a chair conformation.

Recently, there has been renewed interest in the synthesis of phosphonate derivatives of carbohydrates.[1,2] In these cases the cyclic phosphonate analogs (phostones) of hexopyranoses were synthesized and characterized. Such compounds are potential inhibitors of glycosidases since they can be viewed as potential analogs of the transition state of these reactions.[3] They are also, therefore, starting points for the generation of catalytic antibodies to effect glycoside hydrolysis. At this time we report the synthesis of the cyclic phosphonate analogs of pentoses, namely, the *xylo* analogs **1** and **2** and *lyxo* analogs **3** and **4**.



1, α-OMe
2, β-OMe



3, α-OMe
4, β-OMe

Our synthesis is outlined in Scheme 1 and starts with D-xylal (**5**).[4] The two hydroxyl groups in **5** were protected as benzyl ethers. The double bond in the protected xylal **6** was oxidatively cleaved, and the resulting aldehyde **7** was not purified but was immediately treated with trimethyl phosphite in an acid-catalyzed Abramov reaction.[1a,5] This reaction gave two chromatographically inseparable isomers, **8** and **9**, in a ratio of 3:1 as determined by NMR. The major isomer is assigned as **8** on the basis of subsequent transformations. Darrow and Drueckhammer found that the analogous reaction with the arabinose derivative was not stereoselective.[1a] However, the Lewis acid-catalyzed addition of phosphite to α-benzyloxy aldehydes is stereoselective and has the same stereochemical preference that we find in the reaction of **7**.[6] Cleavage of the formate ester followed by *in situ* cyclization gave a mixture of the four isomers, **10**−**13**. While flash chromatography provided isomerically enriched product, none of the four isomers could be obtained chromatographically pure. We can estimate the relative amounts of the four isomers as 10:5:2:3 from the NMR spectra of the crude material.

One of the isomers crystallized from the syrup and was isolated in 19% yield. The single phosphorus peak at δ 21.96 and the clean doublet at δ 3.82 due to the methyl group in the ^{1}H NMR spectra were strong evidence that the crystals were of a single compound. The stereochemistry of this material was determined by converting it into the corresponding tri-*O*-acetate by hydrogenolysis of the benzyl protecting groups followed by acetylation (Scheme 2). The stereochemistry of this product was determined to be that shown in **14**. The signal for the proton on C-1 was a triplet at δ 5.25 (J = 9 Hz) due to coupling with phosphorus and H-2. The large $J_{1,2}$ is consistent with a xylose, or trans stereochemistry for C-1 and C-2. The stereochemistry of the phosphorus was suggested from NOE experiments. Irradiation of the signal due to the phosphorus methyl group resulted in an enhancement of H-1 only, which suggests that the methyl group is equatorial (*vide infra*). Thus, the compound leading to **14** should have the stereochemistry shown in **10** (Scheme 1). This was confirmed by forming the tri-*O*-benzyl ether **16** from **10** which gave crystals suitable for X-ray crystallography.

Further crystallization of the mother liquors from the reaction of **8** and **9** gave a second crystalline product. The ^{31}P NMR had a single peak at δ 19.98 indicating that the product was isomeric with **10**. The stereochemistry of this compound was determined by X-ray crystallography to be **11**. Compound **11** was also subjected to the hydrogenolysis−acetylation sequence (Scheme 2) to yield **15**. Again the H-1 signal was a triplet at δ 5.46 (J = 9.5 Hz) consistent with the xylo configuration for C-1 and C-2. When the phosphorus methyl in **15** was irradiated, there was an enhancement of H-2 consistent with these two substituents having a 1,3-diaxial relationship. Both **11** and **16** have a well-defined chair conformation in the solid state,[7] despite the fact that it has been

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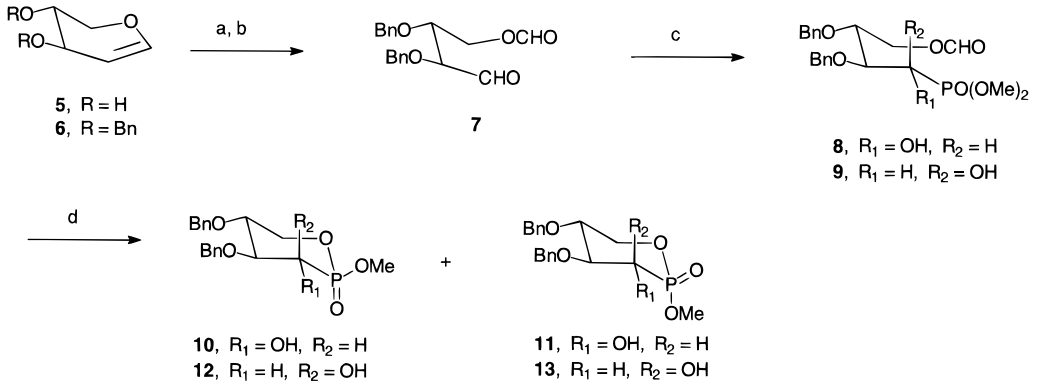
S0022-3263(97)00638-5 CCC: $14.00

Scheme 1



5, R = H
6, R = Bn

7

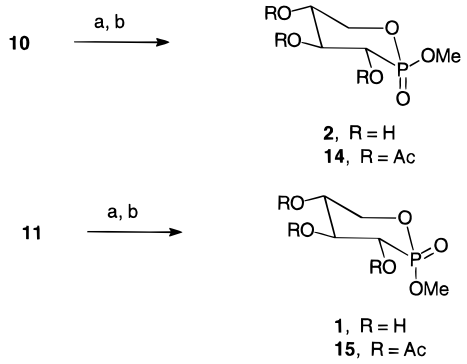
8, R_1 = OH, R_2 = H
9, R_1 = H, R_2 = OH

10, R_1 = OH, R_2 = H
12, R_1 = H, R_2 = OH

11, R_1 = OH, R_2 = H
13, R_1 = H, R_2 = OH

[a] (a) BnCl, NaH, DMF (90%); (b) $NaIO_4$, cat. OsO_4, H_2O-Et_2O; (c) $(MeO)_3P$, AcOH (69% for two steps); (d) NaOMe, MeOH (95%).

Scheme 2

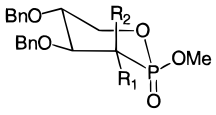


2, R = H
14, R = Ac

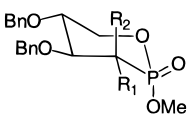
[a] (a) H_2, Pd−C, EtOH (93% for **2**, 77% for **1**); (b) Ac_2O, pyridine (15% for **14**, 22% for **15**).

suggested that such six-membered-ring phosphonates with an axial P-OMe group may also exist in a twist-boat conformation.[8]

The mixture of phosphonates **10**−**13** was benzoylated, and we were able to isolate two pure compounds from this mixture. The first was shown to be identical to the ester obtained by benzoylation of **11** and thus has structure **19**. The second benzoate was shown to have structure **20**. A dd at δ 5.92 ($J_{1,2}$ = 3.3 Hz, $J_{1,P}$ = 11.7 Hz) was assigned to H-1, and a ddd at δ 4.15 ($J_{1,2}$ = 3.3 Hz, $J_{2,P}$ = 7 Hz, $J_{2,3}$ = 13.7 Hz) was assigned to H-2. These coupling constants indicated a lyxose-like configuration for C-1 to C-3. The two remaining compounds were isolated as an inseparable mixture, and their structures were determined to be **17** and **18** by ^{1}H NMR. Compound **17** was identical to the benzoate from **10**.



16, R_1 = OBn, R_2 = H
17, R_1 = OBz, R_2 = H
18, R_1 = H, R_2 = OBz



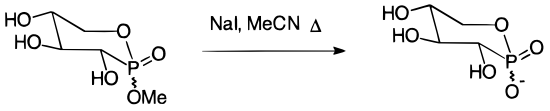
19, R_1 = OBz, R_2 = H
20, R_1 = H, R_2 = OBz
22, R_1 = OBn, R_2 = H

Table 1 contains a summary of the ^{31}P NMR shifts for the compounds which have firmly established structures. In general, the signal for the axial P-OMe isomer is 2 ppm upfield from the corresponding equatorial isomer. This trend has been observed in the cyclic phosphonates of hexopyranoses[1,2] and in other six-membered ring phosphonates.[8,9] The one exception is the **18** and **20** pair in which the difference in chemical shift for the two isomers is 0.89 ppm. In related cases, it has been suggested that some of the isomers which would have an equatorial P-OR group may in fact have a significant amount of the twist-boat conformation present, thus leading to a reduction in the difference in ^{31}P NMR shifts between the two isomers.[9] We believe that is the reason for the small difference in ^{31}P NMR shifts between **18** and **20**.

Table 1. ^{31}P NMR Shifts for Cyclic Phosphonates

compd	P-OMe stereochemistry	^{31}P shift	Δ(eq − ax)
10	eq	21.90	
11	ax	20.04	1.9
2	eq	26.44	
1	ax	24.07	2.3
14	eq	16.37	
15	ax	14.06	2.3
17	eq	18.34	
19	ax	15.90	2.4
18	eq	17.13	
20	ax	16.23	0.9

A mixture of **1** and **2** was demethylated with NaI (eq 1).[10] The reaction was readily monitored by ^{31}P NMR.

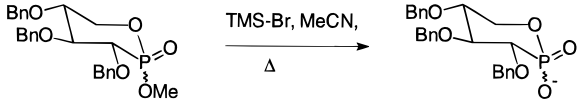


1, α-OMe
2, β-OMe

21

(1)

Thus, the disappearance of the peaks at δ 26.44 and 24.07, and the appearance of a single new peak at δ 19.98 showed that **1** and **2** differed only in the stereochemistry at the phosphorus center. In addition, the tribenzyl ethers **16** and **22** were each hydrolyzed with trimethylsilyl bromide[11] to give the same phosphonic acid **23** (eq 2).



16, α-OMe
22, β-OMe

23

(2)

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We shall report the glycosidase inhibition studies with these phostones[12] and their use as haptens in the generation of catalytic antibodies elsewhere.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 200 or 400 MHz relative to TMS using the solvent as standard. ^{13}C NMR spectra were recorded at 50 MHz relative to TMS using the solvent as standard. ^{31}P NMR spectra were recorded at 81 MHz using 85% H_3PO_4 as an external standard. Reactions were monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 (F_{254}) analytical plates. Spots were detected under UV light or by charring with 10% H_2SO_4 in MeOH. Flash chromatography[13] was performed using Merck silica gel 60 (230−400 mesh).

3,4-Di-*O*-benzyl-D-xylal (6). To a solution of D-xylal (**5**) (2.14 g, 18.4 mmol) in DMF at 0 °C was added NaH (2.56 g, 60% in mineral oil, 64.0 mmol). After the mixture was stirred for 15 min, the reaction was treated with 8.0 mL (69 mmol) of benzyl chloride, and the mixture was then stirred at room temperature for an additional 6 h. The reaction mixture was then cooled to 0 °C and treated with MeOH to destroy the excess NaH. The solution was concentrated, diluted with $CHCl_3$, and washed with water. Evaporation of the organic solvents gave an oil which was purified by flash chromatography (eluant gradient: hexanes−EtOAc, 97:3; hexanes−EtOAc, 93:7) to give 5.0 g (91%) of **6** as a colorless syrup. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.25 (m, 10H), 6.55 (d, J = 6.0 Hz, 1H), 5.00 (ddd, J = 1.4, 4.6, 6.0 Hz, 1H), 4.66 (s, 2H), 4.62 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.14 (ddd, J = 1.4, 4.0, 12.0 Hz, 1H), 3.97 (dd, J = 2.0, 12.0 Hz, 1H), 3.86 (ddd, J = 1.4, 2.7, 4.6 Hz, 1H), 3.69 (dddd, J = 1.4, 2.0, 2.7, 4.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 146.7, 138.4, 138.0, 128.5, 128.5, 127.9, 127.8, 127.7, 99.0, 72.8, 71.3, 70.0, 69.2, 64.0. CIMS (NH_3) m/z: 314 $(M + NH_4)^+$.

2,3-Di-*O*-benzyl-4-*O*-formyl-D-threose (7). 3,4-Di-*O*-benzyl-D-xylal (**6**) (2.81 g, 9.48 mmol) was dissolved in Et_2O (8 mL). To this solution was added water (60 mL), followed by $NaIO_4$ (22.0 g, 103 mmol) and a catalytic quantity of OsO_4 solution (400 μL, 4% in H_2O). The reaction flask was covered with foil and stirred vigorously at room temperature for 24 h. The solution was filtered, and the filtrate was extracted with EtOAc (2 × 30 mL). The organic layers were dried ($MgSO_4$), filtered, and evaporated at low temperature (less than 40 °C) to yield the aldehyde **7** as a colorless syrup which was used immediately in the next step.

(1*S*,*R*)-3,4-Di-*O*-benzyl-4-*O*-formyl-D-threose 1-(Dimethyl phosphonate) (8) and (9). Trimethyl phosphite (1.17 mL, 9.95 mmol) was added to a solution of the crude **7** from above in glacial acetic acid (30 mL). The reaction was stirred at room temperature for 2 h until TLC showed one predominant compound (EtOAc:R_f = 0.6). The solution was diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (5 × 40 mL). The aqueous washes were combined and extracted with EtOAc (2 × 30 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (3 × 30 mL). The organic extracts were dried ($MgSO_4$) and concentrated to give a colorless oil. Flash chromatography (eluant gradient: hexanes−EtOAc, 1:1; EtOAc) gave a mixture of **8** and **9**, 3:1 by NMR, as a colorless syrup (2.88 g, 69% from **6**). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (s, 0.75H), 7.97 (s, 0.25H), 7.28 (m, 10H), 4.70 (m, 2H), 4.52 (m, 2H), 4.20−4.39 (m, 3H), 4.02 (m, 0.25H), 3.85 (m, 0.75H), 3.81 (d, J = 10.4 Hz, 0.75H), 3.77 (d, J = 10.4 Hz, 2.25H), 3.76 (d, J = 10.6 Hz, 2.25H), 3.72 (d, J = 10.6 Hz, 0.75H); ^{31}P NMR (81 MHz, $CDCl_3$) δ: 22.21 and 22.17 ppm; FABMS (+) m/z: 439 $(M^+ + H)$.

(1*S*,*R*)-2,3-Di-*O*-benzyl-D-threose 1-(Methyl phostone) (10, 11, 12 and 13). The mixture of **8** and **9** (4.0 g, 9.1 mmol) was dissolved in MeOH (80 mL) and a catalytic amount of NaOMe (40 mg) was added. The solution was stirred at room temperature, and the reaction was monitored by ^{1}H and ^{31}P NMR because the products had the same R_f values as the starting materials. After being stirred for 4 h, the solution was concentrated and purified by flash chromatography (EtOAc) to give a colorless syrup (3.3 g, 95%) containing the four isomers **10**, **11**, **12**, and **13**. Analysis of the ^{31}P NMR spectrum of the crude material revealed that the ratio of isomers **10**−**13** was 10:5:2:3. Crystallization of the mixture of four isomers from EtOAc:hexanes gave **10** as white crystals (0.467 g, 19%), mp 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 10 H), 4.77 (s, 2H), 4.65 (s, 2H), 4.05−4.25 (m, 2H), 4.02−3.87 (m, 2H), 3.82 (d, J = 10.9 Hz, 3H), 3.60 (ddd, J = 4.0, 6.0, 7.2 Hz, 1H). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.90 ppm. FABMS(+) m/z: 379 $(M^+ + H)$. Anal. Calcd for $C_{19}H_{23}O_6P$: C, 60.32; H, 6.13. Found: C, 60.34; H, 6.01.

Crystallization of the mother liquor using the same solvent system gave **11** as white crystals (0.374 g, 15%), mp 97−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 10H), 4.85 (d, J = 11.2 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.15 (ddd, $J_{4e,3}$ = 4.5 Hz, $J_{4e,4a}$ = 11.5 Hz, $J_{4e,P}$ = 22.5 Hz, 1H), 4.02 (ddd, $J_{1,2} = J_{1,P}$ = 8.6 Hz, $J_{1,OH}$ = 5.7 Hz, 1H), 3.77−3.90 (m, 2H), 3.87 (d, $J_{CH3,P}$ = 10.4 Hz, 3H), 3.63 (ddd, $J_{3,2} = J_{3,4a}$ = 8.5 Hz, $J_{3,4e}$ = 4.5 Hz, 1H), 3.3 (dd, $J_{OH,1}$ = 5.7 Hz, 1H). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 20.04 ppm. FABMS (+) m/z 379: $(M^+ + H)$. Anal. Calcd for $C_{19}H_{23}O_6P$: C, 60.32; H, 6.13. Found: C, 60.10; H, 6.00.

Data for the mixture of **12** and **13**. ^{31}P NMR for **12** (81 MHz, $CDCl_3$) δ: 21.58 ppm. ^{31}P NMR for **13** (81 MHz, $CDCl_3$) δ: 19.97 ppm.

(1*S*)-D-Threose 1-(Methyl phostone) (2). Compound **10** (270 mg, 0.71 mmol) was dissolved in EtOH (60 mL), and 200 mg of 10% Pd on C was added. The reaction was stirred at room temperature under a H_2 atmosphere for 8 h. The solution was filtered through Celite, and the filtrate was evaporated to give **2** (131 mg, 93%) as a colorless syrup. ^{1}H NMR (400 MHz, CD_3CN) δ: 4.10 (ddd, $J_{4e,3}$ = 4.7 Hz, $J_{4e,4a}$ = 11.3 Hz, $J_{4e,P}$ = 23.1 Hz, 1H), 3.84 (ddd, J = 6.0, 9.6, 11.3 Hz, 1H), 3.75 (d, $J_{CH3,P}$ = 10.8 Hz, 3H), 3.70 (m, 1H), 3.67 (ddd, J = 4.8, 8.3, 9.2 Hz, 1H), 3.58 (ddd, J = 4.7, 8.3, 9.6 Hz, 1H). ^{31}P NMR (81 MHz, D_2O) δ: 26.44 ppm; FABMS m/z: 199 $(M^+ + H)$. Anal. Calcd for $C_5H_{11}O_6P$: C, 30.31; H, 5.60. Found: C, 30.29; H, 5.77.

(1*S*)-1,2,3-Tri-*O*-acetyl-D-threose 1-(Methyl phostone) (14). Compound **1** (43 mg, 0.21 mmol) was acetylated as described for the preparation of **15**. After the solution was washed with water, evaporation of the organic solvents gave a syrup which crystallized from EtOAc−hexanes to give pure **14** (11 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.55 (ddd, $J_{2,1} = J_{2,3}$ = 9 Hz, $J_{2,P}$ = 6 Hz, 1H), 5.25 (dd, $J_{1,P} = J_{1,2}$ = 9 Hz, 1H), 5.05 (ddd, $J_{3,4e}$ = 4.8 Hz, $J_{3,2} = J_{3,4a}$ = 9 Hz, 1H), 4.28 (ddd, $J_{4e,3}$ = 4.8 Hz, $J_{4e,4a}$ = 12 Hz, $J_{4e,P}$ = 21 Hz, 1H), 4.17 (ddd, $J_{4a,3}$ = 9 Hz, $J_{4a,4e}$ = 12 Hz, $J_{4a,P}$ = 9 Hz, 1H), 3.85 (d, $J_{CH3,P}$ = 10.8 Hz, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H); ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.37 ppm. FABMS (+) m/z: 325 $(M^+ + H)$.

(1*S*)-D-Threose 1-(Methyl phostone) (1). Compound **11** (243 mg, 0.64 mmol) was debenzylated as described for the preparation of **2** to give **1** (98 mg, 77%) as a colorless syrup. ^{1}H NMR (400 MHz, D_2O) δ: 4.17 (ddd, $J_{4e,3}$ = 2.5 Hz, $J_{4e,4a}$ = 10.4 Hz, $J_{4e,P}$ = 26.5 Hz, 1H), 3.55−3.95 (m, 4H), 3.84 (d, $J_{CH3,P}$ = 10.4 Hz, 3H). ^{31}P NMR (81 MHz, D_2O) δ: 24.07 ppm. CIMS (isobutane) m/z: $(M^+ + H)$ calcd for $C_5H_{12}O_6P$ 199.0371, found 199.0378. Anal. Calcd for $C_5H_{11}O_6P \cdot {}^1/_3H_2O$: C, 29.42; H, 5.76. Found: C, 29.65; H, 5.93.

(1*S*)-1,2,3-Tri-*O*-acetyl-D-threose 1-(Methyl phostone) (15). Compound **2** (15 mg, 0.07 mmol) was acetylated in 2:1 pyridine−Ac_2O (2 mL). The reaction was stirred at room temperature for 12 h, then diluted with CH_2Cl_2, and washed with water. Evaporation gave a syrup which crystallized from EtOAc−hexanes to give pure **15** (5 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.46 (dd, $J_{1,2} = J_{1,P}$ = 9.5 Hz, 1H), 5.38 (ddd, $J_{2,1} = J_{2,3}$ = 9.5 Hz, $J_{2,P}$ = 3.7 Hz, 1H), 5.10 (ddd, $J_{3,4e}$ = 5.1 Hz, $J_{3,2} = J_{3,4a}$ = 9.5 Hz, 1H), 4.28 (ddd, $J_{4e,3}$ = 5.1 Hz, $J_{4e,4a}$ = 11 Hz, $J_{4e,P}$ = 21 Hz, 1H), 3.92 (d, $J_{CH3,P}$ = 10.7 Hz, 3H), 3.92 (m, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 14.06 ppm. FABMS (+) m/z: 325 $(M^+ + H)$.

(1*S*)-1,2,3-Tri-*O*-benzyl-D-threose 1-(Methyl phostone) (16). The tribenzyl ether **16** was prepared by two methods.

(12) For a discussion of this nomenclature, see: Thiem, J.; Günther, M.; Paulsen, H.; Kopf, J. *Chem. Ber.* **1977**, *110*, 3190.

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.***1978**, *43*, 2923.

Method A. NaH (5.0 mg, 60% in mineral oil, 0.13 mmol) was added to a solution of **10** (50 mg, 0.13 mmol) in 5 mL of THF at 25 °C. After being stirred for 5 min, the solution was treated with benzyl bromide (23 mg, 0.13 mmol) and a catalytic amount of *n*-Bu_4NI (1 mg). After 2 h of stirring, the reaction was treated with an additional 5 mg of NaH (0.13 mmol) to ensure that the reaction was complete. After stirring for an additional 0.5 h, the reaction was carefully treated with H_2O (0.5 mL) to quench any remaining NaH and then diluted with EtOAc and brine (1:1, 20 mL). The layers were separated, and the organic layer was washed with brine (1 × 10 mL). The aqueous washes were combined and extracted with EtOAc (1 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a nearly colorless oil. Flash chromatography (eluant gradient: 50:50 hexanes−EtOAc; EtOAc) provided 44 mg (71%) of **16** as a colorless, crystalline solid. Recrystallization from EtOAc−hexanes gave crystals suitable for X-ray crystallography.

Method B. Benzyl 2,2,2-trichloroacetimidate (316 mg, 1.25 mmol) and a catalytic amount of triflic acid (12 mg) were added to a solution of **16** (394 mg, 1.04 mmol) in CH_2Cl_2 (25 mL) at 25 °C. After 1 h of stirring, the reaction had proceeded about half-way according to TLC and was not progressing any further. Thus, another 150 mg of benzyl 2,2,2-trichloroacetimidate (0.59 mmol) and a catalytic amount of triflic acid (10 mg) were added. The reaction was stirred an additional 2 h and then washed with $NaHCO_3$ (2 × 20 mL). The aqueous washes were combined and extracted with CH_2Cl_2 (1 × 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to provide a colorless oil/solid. Flash chromatography (eluant gradient: 70:30 hexanes−EtOAc; 50:50 hexanes−EtOAc) provided 387 mg (79%) of **16** as a colorless, crystalline solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.23−7.40 (m, 15H), 4.70−4.90 (m, 4H), 4.75 (d, J = 11.8 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 3.85−4.10 (m, 3H), 3.53−3.80 (m, 2H), 3.70 (d, J = 11.0 Hz, 3H). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 22.98. CIMS (NH_3) m/z: 469 $(M + H)^+$.

Benzoylation of the Mixture of 10, 11, 12 and 13. To an ice-cold solution of **10**, **11**, **12**, and **13** (0.95 g, 2.5 mmol) and pyridine (1 mL) in CH_2Cl_2 (25 mL) was added benzoyl chloride (650 μL, 5.6 mmol). The reaction was stirred overnight. TLC (EtOAc:hexanes 1:1) showed three new spots. Purification by flash chromatography (EtOAc:hexanes 1:2) gave three fractions A, B, and C. Fraction A (443 mg) was a mixture of compounds **17** and **18** in a ratio of 3:2 (by NMR) and a total yield of 40%. The major component was identical to the product from benzoylation of **10** and thus must have structure **17**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.10−8.10 (m, 15H), 6.00 (dd, J = 3, 12 Hz, 0.4H, H-1 of **18**), 5.50 (dd, J = 9.5, 9.5 Hz, 0.6H, H-1 of **17**), 4.50−4.85 (m, 4H), 4.05−4.45 (m, 3H), 3.70−3.94 (m, 1H), 3.87 (d, J = 10.9 Hz, 1.2H, P-OMe of **18**), 3.80 (d, J = 10.9 Hz, 1.8H, P-OMe of **17**). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 18.34 (**17**), 17.13 (**18**). FABMS (+) m/z: 483 $(M^+ + H)$.

Fraction B (400 mg, 36%) was compound **19**. The ^{1}H and ^{31}P NMR spectra of this compound were identical to the spectra of the compound obtained by benzoylation of **11**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05−8.00 (m, 15H), 5.71 (dd, $J_{1,P} = J_{1,2}$ = 9.9 Hz, 1H), 4.77 (d, J = 11.2 Hz, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.66 (d, J = 11.2 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.17 (ddd, $J_{4e,3}$ = 4.7 Hz, $J_{4e,4a}$ = 11.2 Hz, $J_{4e,P}$ = 24.2 Hz, 1H), 3.97 (ddd, $J_{2,P}$ = 4.9 Hz, $J_{2,3}$ = 8.5 Hz, $J_{2,1}$ = 9.9 Hz, 1H), 3.91 (ddd, $J_{4a,P}$ = 5.3 Hz, $J_{4a,3}$ = 9.8 Hz, $J_{4a,4e}$ = 11.2 Hz, 1H), 3.87 (d, $J_{CH_3,P}$ = 10.6 Hz, 3H), 3.79 (ddd, $J_{3,4e}$ = 4.7 Hz, $J_{3,2}$ = 8.5 Hz, $J_{3,4a}$ = 9.8 Hz, 1H). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 15.90. FABMS (+) m/z: 483 $(M^+ + H)$.

Fraction C (260 mg, 23%) was compound **20**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.2−8.1 (m, 15 H), 5.92 (dd, $J_{1,2}$ = 3.3 Hz, $J_{1,P}$ = 11.7 Hz, 1H), 4.85 (d, J = 11.7 Hz, 1H), 4.71 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.57 (d, J = 11.7 Hz, 1H), 4.48 (ddd, $J_{4e,3}$ = 3.4 Hz, $J_{4e,4a}$ = 11.9 Hz, $J_{4e,P}$ = 14.8 Hz, 1H), 4.15 (ddd, $J_{2,1}$ = 3.3 Hz, $J_{2,P}$ = 7.0 Hz, $J_{2,3}$ = 13.7 Hz, 1H), 4.02 (ddd, J = 6.4, 11.9, 13.0 Hz, 1H), 3.78−3.90 (m, 1H), 3.82 (d, $J_{CH_3,P}$ = 10.9 Hz, 3H). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.23 ppm. FABMS (+) m/z: 483 $(M^+ + H)$.

D-Threose (1*S*)-1-Phostone (21). A mixture of **1** and **2** (137 mg, 0.69 mmol) was dissolved in CH_3CN (20 mL) and heated to reflux in the presence of NaI (155 mg). After 12 h a white precipitate formed and was filtered off to give the sodium salt of **21** (109 mg, 77%). ^{1}H NMR (400 MHz, D_2O) δ: 3.95 (m, 1H), 3.4−3.75 (m, 4H). ^{31}P NMR (81 MHz, D_2O) δ: 16.99. FABMS (−) m/z: 183 $(M^- - H)$.

(1*R*)-1,2,3-Tri-*O*-benzyl-D-threose 1-(Methyl phostone) (22). Benzyl 2,2,2-trichloroacetimidate (363 mg, 1.44 mmol) and a catalytic amount of triflic acid (10 mg) were added to a solution of **10**−**13** that was enriched with isomer **11** (455 mg, 1.20 mmol) in CH_2Cl_2 (20 mL) at 25 °C. After 2 h of stirring, the reaction had proceeded about half-way according to TLC and was not progressing any further. Thus, another 363 mg of benzyl 2,2,2-trichloroacetimidate (1.44 mmol) was added. After an additional 2 h of stirring, the reaction was washed with $NaHCO_3$ (2 × 30 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (1 × 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to afford a colorless oil. Flash chromatography (eluant gradient: 50:50 hexanes−EtOAc; EtOAc) provided 490 mg (87%) of the four possible isomers of the tribenzyl ethers. One set of pooled fractions gave 206 mg (37%) of a colorless oil that was highly enriched with **22** and with only a minor amount of **16** present (10:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.00−7.25 (m, 15H), 5.07 (d, J = 11.0 Hz, 1H), 4.92 (s, 2H), 4.86 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 11.4 Hz, 1 H), 4.64 (d, J = 11.4 Hz, 1H), 3.60−4.20 (m, 5H), 3.94 (d, J = 10.0 Hz, 3H). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 18.52.

(1*S*)-1,2,3-Tri-*O*-benzyl-D-threose 1-Phostone (23). Trimethylsilyl bromide (0.33 mL, 2.48 mmol) was added to a solution of **16** (387 mg, 0.826 mmol) in 10 mL of CH_2Cl_2. The solution was warmed to reflux. After 1 h of stirring, the reaction was treated with 3 N HCl (2 mL) and stirred for another 15 min at 25 °C. The aqueous layer of the reaction was separated and extracted with CH_2Cl_2 (1 × 3 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford a brown oil. Flash chromatography (eluant gradient: 50:50 hexanes−EtOAc; EtOAc) gave 257 mg (69%) of **23** as a colorless oil. Structure proof of **23** was realized after coupling of a side chain in the equatorial position at the phosphorus stereocenter that was suitable for our work in catalytic antibody production (details to be presented elsewhere).

Beginning with (1*S*)-1,2,3-tri-*O*-benzyl-D-threose 1-(methyl phostone) (**22**), which is the stereoisomer of **16** at the phosphorus center, the same product **23** was prepared. Hence, trimethylsilyl bromide (202 mg, 1.32 mmol) was added to a solution of **22** (206 mg, 0.440 mmol) in 7 mL of CH_2Cl_2. The solution was warmed to reflux. After 1 h of stirring, the reaction was treated with 3 N HCl (2 mL) and stirred for another 15 min at 25 °C. The aqueous layer of the reaction was separated and extracted with CH_2Cl_2 (1 × 2 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford a whitish oil. Flash chromatography (eluant gradient: 50:50 hexanes−EtOAc; 80:20 EtOAc−MeOH; MeOH) gave 189 mg (95%) of **23** as a colorless oil. As with the product from **16**, structure proof of **23** was realized after coupling of a side chain in the equatorial position at the phosphorus stereocenter that was suitable for our work in catalytic antibody production (details to be presented elsewhere). Thus, both **16** and **22** led to the same product, indicating that they differ only at the phosphorus stereocenter.

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Supporting Information Available: Spectral data for compounds **1**, **2**, **6**, **10**−**11**, **14**−**16**, and **19**−**21** and the mixtures of **8** and **9** and **17** and **18**. X-ray structural diagrams for compounds **11** and **16** (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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