Stereoselective Synthesis of β-Oxygenated α-Hydroxyphosphonates by Lewis Acid-Mediated Stereoselective Hydrophosphonylation of α-Benzyloxy Aldehydes. An Application to the Synthesis of Phosphonic Acid Analogs of Oxyamino Acids

Tsutomu Yokomatsu, Yoshinori Yoshida, and Shiroshi Shibuya*

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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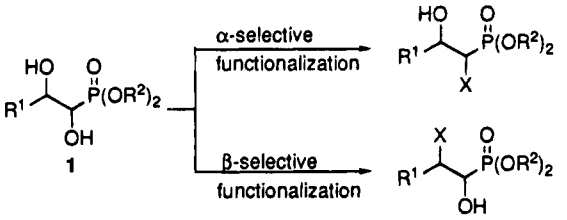
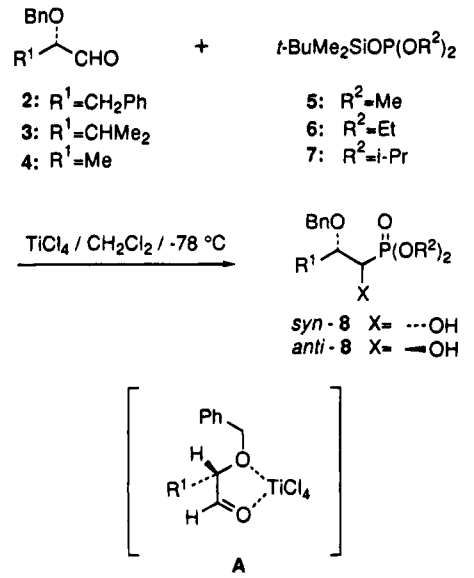
The synthesis of chiral α-substituted phosphonic acids has been an important area of research, particularly in connection with the search for the biologically active surrogates for the corresponding carboxylic acids and phosphoric acid esters.[1] α-Hydroxyphosphonic acid derivatives are gaining in interest in medicinal chemistry, since they are potentially useful inhibitor of enzymes such as protease,[2] EPSP synthase,[3] and thyrosin-specific protein kinase.[4] In contrast to extensive studies for the stereoselective synthesis of α-aminophosphonic acid,[5] stereocontrolled syntheses of α-hydroxyphosphonic acid derivatives have only recently begun to receive attention.[6] Our interest in this area centers on the development of versatile phosphonic chirons for the synthesis of various α-substituted phosphonic acid derivatives which would be of biological interest. The chiral glycol phosphonate such as **1** would constitute one of the most useful phosphonic chirons for this purpose if both hydroxy groups could subsequently be transformed selectively (Scheme 1). In this paper we disclose Lewis acid-mediated stereoselective hydrophosphonylations of α-benzyloxy aldehydes for the synthesis of α,β-dioxygenated phosphonates and their selective conversion to β-oxygenated α-aminophosphonic acids,[7] phosphonic acid analogs of oxyamino carboxylic acids.

We first investigated the stereoselective synthesis of β-(benzyloxy)-α-hydroxyphosphonates **8**, a mono-protected form of glycol **1** (Scheme 2, Table 1). The Lewis acid-mediated hydrophosphonylation of α-benzyloxy aldehydes **2**–**4**[8] with silyl phosphites **5**–**7**[9] was examined as an extension of our recent investigation on the hydrophosphonylation of α-dibenzylamino aldehydes.[10] Table 1 summarizes the stereoisomer distributions thus obtained by the use of $TiCl_4$ as the Lewis acid. All reactions proceeded with stereoregular diastereo-preference for giving *syn*-**8** *via* chelate complex **A**.[11–13] Of special interest is that the syn-selectivity observed with **2**–**4** depends on the steric bulkiness of the alkyl group (R^2) in the silyl phosphite **5**–**7**;[14] the syn-selectivity increases from 75 to 84% on going from R^2 = *i*-Pr to R^2

Scheme 1



Scheme 2



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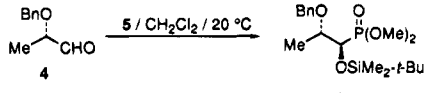
(12) The reaction of an aldehyde **4** with silyl phosphite **5** in the absence of $TiCl_4$ in CH_2Cl_2 at room temperature proceeded very slowly to give the silyoxy adduct **i** with *anti*-stereochemistry (36% *de*). The similar results were reported by Hammerschmidt: Hammerschmidt, F. *Liebig Ann. Chem.* **1991**, 469.



(13) During the formation of the phosphorus to carbon bond in these reactions, no racemization of **2** and **3** takes place; optical purities (>98% ee) of **8a,b** were confirmed by NMR analysis of the corresponding Mosher esters derived from (+)- and (−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acids.

(14) The effects of bulkiness of the ester alkyl group on the stereochemical outcome are not clearly explained at present.

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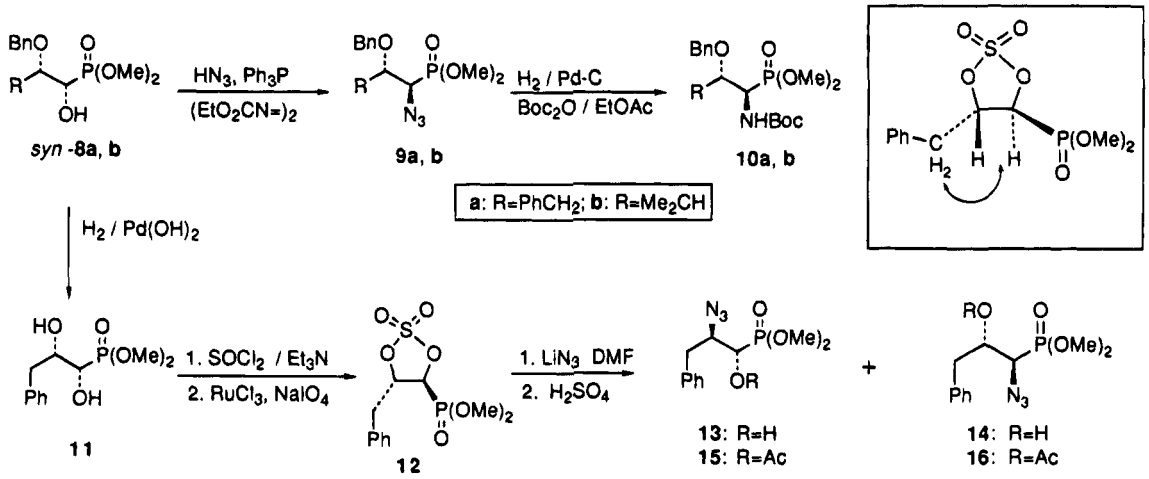
Table 1. Lewis Acid-Mediated Stereoselective Hydrophosphonylation of α-Benzyloxy Aldehydes with Silyl Phosphites 5–7

entry	aldehyde	phosphite[a]	product	yield (%)	ratio (*syn/anti*)[b]
1	**2**	**5**	**8a** (R^1 = CH_2Ph; R^2 = Me)	72[c]	>98:<2
2	**3**	**5**	**8b** (R^1 = CHMe; R^2 = Me)	73[c]	>98:<2
3	**2**	**6**	**8c** (R^1 = CH_2Ph; R^2 = Et)	75	88:12
4	**3**	**6**	**8d** (R^1 = CHMe; R^2 = Et)	72[c]	91:9
5[d]	±**4**	**5**	**8e** (R^1 = Me; R^2 = Me)	88	84:16
6[d]	±**4**	**6**	**8f** (R^1 = Me; R^2 = Et)	66	80:20
7[d]	±**4**	**7**	**8g** (R^1 = Me; R^2 = *i*-Pr)	43	75:25

[a] The amount of phosphite utilized was 1.2 equiv. [b] Determined by ^1H NMR (300 MHz) analysis of crude adducts. [c] Isolated yield for major diastereomer. [d] This experiment was conducted with the racemic aldehyde.

Scheme 3



= Me when an aldehyde **4** (R^1=Me) was utilized (entries 5–7). This trend was also observed in the reaction with aldehydes **2** and **3** having benzyl and *i*-Pr side chains (entry 1, 2 *vs* 3, 4) and the remarkably high syn-selection (>98%) was achieved upon treatment with silyl phosphite **5** (R^2 = Me) (entries 1 and 2).

Having established the method for the stereoselective synthesis of β-(benzyloxy)-α-hydroxyphosphonates **8**, our attention was focussed on their chemical transformations to biologically interesting α,β-disubstituted phosphonic acid derivatives (Scheme 3). Initially, the stereoselective introduction of amino functional group to C-1 position was examined. Reactions of **8a** and **8b** with triphenylphosphine (1 equiv), diethyl azodicarboxylate (1.2 equiv), and hydrazoic acid (2 equiv) in THF–benzene at −35 → 25 °C for 12 h in an S_N2 manner[15] furnished the azides **9a** and **9b** in 68 and 65% yields, respectively. Catalytic hydrogenation of **9a** and **9b** over 10% Pd–C in EtOAc in the presence of di-*tert*-butyl dicarbonate (Boc_2O) under atmospheric pressure afforded the corresponding *N*-Boc-α-aminophosphonic acid dimethyl esters **10a** and **10b** in 85 and 83% yields.[16,17]

Secondly, the ring opening reaction of cyclic sulfates **12** was attempted, which would be potentially useful for the regioselective introduction of functional groups to either the C-1 or C-2 position under appropriate conditions. Hydrogenolysis of *syn*-**8a** in MeOH in the presence of $Pd(OH)_2$[18] gave the diol **11** (mp 104–105 °C). Treatment of **11** with $SOCl_2$ in CH_2Cl_2, followed by oxidation with $RuCl_3{\cdot}H_2O$ and $NaIO_4$ according to the method of Sharpless[19] gave the cyclic sulfates **12** in 65% yield. The stereochemistry of **12** was unambiguously determined to be trans by 2D-NOESY experiment using phase sensitive puls program. The relatively strong correlations between benzylic and C-1 protons were observed (inset in Scheme 3).

Treatment of the sulfates **12** with LiN_3 (2 equiv) in dimethylformamide (DMF) at room temperature for 2 h, followed by hydrolysis (50% aqueous H_2SO_4/THF) gave the azido alcohols **13** (13% yield) and **14** (25% yield) after column chromatography on silica gel. Regiochemistry of the adducts **13** and **14** was deduced by their comparison on NMR spectra of the corresponding acetates [**15**: δ 5.42 (1H, dd, J = 4.75, 11.0 Hz, C*H*OAc); **16**: δ 5.39–5.32 (1H, m, C*H*OAc)]. Although regioselectivity and yield for the reaction are modest, the results show that the dialkyl phosphonate is a potentially useful group inducing the 1,2-cyclic sulfate opening reaction at the C-1 position, preferentially. Further improvement of the method on regioselective ring opening reaction of phosphono 1,2-cyclic sulfates and applications of chiral glycol phosphonates to the synthesis of biologically interesting phosphonic acid derivatives are in progress in our laboratory.

Experimental Section

General. Melting points are uncorrected. All reactions were conducted under an atmosphere of nitrogen unless otherwise noted. THF was distilled from Na/benzophenone ketyl and CH_2Cl_2 was distilled from P_2O_5. ^1H-NMR spectra were recorded at 300 or 400 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ as

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internal references. ^{31}P-NMR (160 MHz) was taken in $CDCl_3$ using 85% H_3PO_4 as an external standard with broad-band ^{1}H decoupling.

General Procedure for the Synthesis of *tert*-Butyldimethylsilyl Dialkyl Phosphites (5–7). To a stirred suspension of NaH [3.3 g (82 mmol); 60% in mineral oil dispersion] in THF (100 mL) was added dialkyl phosphite (68 mmol) under ice-cooling. The mixture was stirred under reflux for 3 h. Upon cooling to room temperature, 12 g (75 mmol) of *tert*-butyldimethylchlorosilane was added in one portion. The mixture was heated at 80 °C for 3 h. Distillation at atmospheric pressure removed the solvent. Subsequent vacuum distillation afforded *tert*-butyldimethylsilyl phosphites **5–7**.

5 (R^2 = Me): bp 54–55 °C (4 mmHg) [lit.,[9] bp 85–90 °C (16 mmHg)]; ^{1}H-NMR δ 3.46 (6H, d, J = 10 Hz), 0.93 (9H, s), 0.18 (6H, s); ^{31}P-NMR δ 127.2.

6 (R^2 = Et): bp 64–65 °C (4 mmHg); ^{1}H-NMR δ 4.20–4.03 (4H, m), 1.32 (3H, t, J = 7.1 Hz), 0.95 (9H, s), 0.26 (6H, s), ^{31}P-NMR δ 126.6.

7 (R^2 = $CHMe_2$):[20] bp 74–75 °C (4 mmHg); ^{1}H-NMR δ 4.32–4.50 (1.35H, m), 4.65–4.5 (0.65H, m), 1.31 (4H, broad d, J = 6.2 Hz), 1.22 (8H, broad d, J = 6.2 Hz), 0.94 (3H, s), 0.92 (6H, s), 0.15 (6H, s),^{31}P-NMR δ 128.2, −1.85.

General Procedure for the Hydrophosphonylation of α-Benzyloxy Aldehydes (2–4). To a stirred solution of **2, 3**, or **4** (3 mmol) in CH_2Cl_2 (6 mL) was added $TiCl_4$ (3.6 mL of 1 M solution in CH_2Cl_2) at −78 °C (dry ice–acetone). A solution of **5, 6**, or **7** (3.6 mmol) in CH_2Cl_2 (3 mL) was added dropwise and the reaction mixture was stirred at the same temparature for 1.5 h. Water was added to quench the reaction and the mixture was warmed to room temperature. The biphasic mixture was extracted with $CHCl_3$, and the organic extracts was washed with brine, dried over Na_2SO_4, and concentrated to give the crude adducts. Purification by column chromatography on silica gel (Et_2O:EtOAc = 1:1) gave **8**.

***syn*-8a**: mp 106–107 °C; $[\alpha]^{20}_D$ −40.0 (*c* 1.1, $CHCl_3$), ^{1}H-NMR δ 7.4–7.2 (10H, m), 4.62 (1H, d, J = 10.7 Hz), 4.52 (1H, d, J = 10.7 Hz), 4.1–4.0 (1H, m), 3.82 (1H, dd, J = 2.3, 10.3 Hz), 3.74 (3H, d, J = 10.4 Hz), 3.73 (3H, d, J = 10.5 Hz), 3.1–2.9 (2H, m); ^{31}P-NMR δ 25.0; IR (KBr) 3290, 1206, 1055 cm^{-1}; EIMS *m/z* 351 (M^+ + 1). Anal. Calcd for $C_{18}H_{23}O_5P$: C, 61.71; H, 6.62. Found: C, 61.65; H, 6.72.

***syn*-8b**: an oil; $[\alpha]^{20}_D$ −1.71 (*c* 0.9, $CHCl_3$); ^{1}H-NMR δ 7.4–7.2 (5H, m), 4.82 (1H, d, J = 10.7 Hz), 4.66 (1H, d, J = 10.7 Hz), 4.01 (1H, d with a small split, J = 9.0 Hz), 3.82 (3H, d, J = 10.4 Hz), 3.81 (3H, d, J = 10.4 Hz), 3.62 (1H, dd, J = 2.0, 7.0 Hz), 2.11–2.01 (1H, m), 1.02 (3H, d, J = 7.1 Hz), 0.99 (3H, d, J = 7.5 Hz); ^{31}P-NMR δ 25.4; IR (neat) 3310, 1218, 1029 cm^{-1}; EIMS *m/z* 303 (M^+ + 1); HRMS calcd for $C_{14}H_{23}O_5P$(MH^+): 303.1674. Found: 303.1347.

***syn*-8c** (for a sample of 76% *de*): mp 108–109 °C; $[\alpha]^{20}_D$ −25.7 (*c* 0.8, $CHCl_3$); ^{1}H-NMR δ 7.4–7.2 (5H, m), 4.62 (1H, d, J = 10.7 Hz), 4.50 (1H, d, J = 10.7 Hz), 4.2–4.0 (5H, m), 3.78 (1H, dd, J = 2.5, 10.3 Hz), 3.02 (2H, broad d, J = 7.2 Hz) 1.29 (3H, t, J = 7.1 Hz), 1.24 (3H, t, J = 7.1 Hz); ^{31}P-NMR δ 22.7; IR (KBr) 3253, 1200, 1060 cm^{-1}; EIMS *m/z* 379 (M^+ + 1). Anal. Calcd for $C_{20}H_{27}O_5P$: C, 63.48; H, 7.19. Found: C, 63.13; H,7.15.

***syn*-8d**: an oil; $[\alpha]^{20}_D$ −2.6 (*c* 1.1, $CHCl_3$); ^{1}H-NMR δ 7.4–7.2 (5H, m), 4.84 (1H, d, J=10.7 Hz), 4.65 (0.94H, d, J = 10.7 Hz), 4.18 (4H, dq J = 7.1, 7.1 Hz), 3.94 (1H, dd, J = 2.1, 9.2 Hz), 3.62 (1H, ddd, J = 2.1, 6.8, 6.8 Hz), 2.12–2.01 (1H, m), 1.35 (3H, t, J = 7.1 Hz), 1.30 (3H, t, J = 7.1 Hz), 1.01 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz); ^{31}P-NMR δ 23.2; IR (neat) 3310, 1218, 1029 cm^{-1}; EIMS *m/z* 331 (M^+ + 1); HRMS calcd for $C_{16}H_{28}O_5P$(MH^+): 331.1674. Found: 331.1657.

8e (for a sample of 68% *de*): an oil; ^{1}H-NMR δ 7.4–7.2 (5H, m), 4.67 (0.84H, d, J = 11.3 Hz), 4.63 (0.16H, d, J = 11.5Hz), 4.53 (0.84H, d, J = 11.3 Hz), 4.52 (0.16H, d, J = 11.5 Hz), 4.15–3.60 (2H, m), 3.78 (3H, d, J = 10.6 Hz), 3.77 (3H, d, J = 10.5 Hz), 1.38 (0.16H, d, J = 6.5 Hz), 1.35 (0.84H, d, J = 6.3 Hz); IR (neat) 3305, 1217, 1068 cm^{-1}; EIMS *m/z* 275 (M^+ + 1); HRMS calcd for $C_{12}H_{20}O_5P$(MH^+): 275.1050. Found: 275.1048.

8f (for a sample of 60% *de*): an oil; ^{1}H-NMR δ 7.35–7.25 (5H, m), 4.67 (0.8H, d, J = 11.3 Hz), 4.62 (0.2H, d, J = 11.3 Hz), 4.53 (0.8 H, d, J = 11.3 Hz), 4.51 (0.2H, d, J = 11.7 Hz), 4.25–3.85 (5H, m), 3.76 (1H, dd, J = 4.6, 9.1 Hz), 1.38–1.24 (13H, m); ^{31}P-NMR 22.0; IR (neat) 3305, 1212, 1029 cm^{-1}; EIMS *m/z* 303 (M^+ + 1); HRMS calcd for $C_{14}H_{24}O_5P$ (MH^+): 303.1361. Found: 303.1380.

8g (for a sample of 50% *de*): mp 62–63 °C; ^{1}H-NMR δ 7.35–7.25 (5H, m), 4.8–4.70 (2H, m), 4.67 (0.75H, d, J = 11.3 Hz), 4.61 (0.25H, d, J = 11.6 Hz), 4.55 (0.75H, d, J = 11.3 Hz), 4.52 (0.25H, d, J = 11.6 Hz), 4.02 (0.25H, dd, J = 9.5, 4.5 Hz), 3.98–3.92 (0.75H, m), 3.91–3.84 (0.25H, m), 3.67 (0.75H, dd, J = 9.0 Hz, 6.6 Hz), 1.39–1.21 (12.75H, m), 1.24 (2.25H, d, J = 6 Hz); ^{31}P-NMR δ 20.22; IR (KBr) 3246, 1200, 1072 cm^{-1}; EIMS *m/z* 331 (M^+ + 1). Anal. Calcd for $C_{16}H_{27}O_5P$+0.5H_2O: C, 56.63; H, 8.32. Found: C, 56.57; H, 8.33.

General Procedure for the Synthesis of α-Azido Phosphonates (9). To a stirred solution of alcohol **8** (2 mmol) and triphenylphosphine (629 mg, 2.4 mmol) in THF (14 mL) were added successively HN_3 (338 mg, 6.1 mmol) in benzene (6 mL) and diethyl azodicarboxylate (420 mg, 2.4 mmol) at −35 °C. Then the mixture was stirred for 30 min at the same temparature. After 12 h at room temparature, 0.5 mL of H_2O was added. The precipitate (Ph_3P=O) was removed by filtration. The filtrate was concentrated *in vacuo* and then chromatographed on silica gel (Hex:EtOAc = 3:1) to give azido phosphonates **9**.[21]

9a: yield 68%; an oil; $[\alpha]^{20}_D$ −47.6 (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ 7.35–7.20 (5H, m), 4.52 (1H, d, J = 11.0 Hz), 4.41 (1H, d, J = 11.0 Hz), 4.02–3.97 (1H, m), 3.95 (3H, d, J = 13.7 Hz), 3.70 (3H, d, J = 13.7 Hz), 3.68 (1H, dd, J = 4.3, 12 Hz), 3.20 (1H, dd, J = 4.7, 14.0 Hz), 3.01 (1H, dd, J = 7.7, 14.0 Hz); ^{31}P-NMR δ 22.12; IR (neat) 2108, 1262, 1034 cm^{-1}.

9b: yield 65%; an oil; $[\alpha]^{20}_D$ −52.9 (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ 7.4–7.2 (5H, m), 4.83 (1H, d, J = 10.9 Hz), 4.59 (1H, d, J = 10.9 Hz), 3.79 (3H, d, J = 10.7 Hz), 3.70 (3H, d, J = 10.7 Hz), 3.77 (1H, d, J = 7.7 Hz), 3.55 (1H, ddd, J = 4.6, 6.7, 13.2 Hz), 2.22–2.06 (1H, m), 1.04 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.8 Hz); ^{31}P-NMR δ 23.4; IR (neat) 2108, 1256, 1030 cm^{-1}.

General Procedure for the Synthesis of *N*-Boc-α-Aminophosphonates (10). A solution of azides **9** (2 mmol) in EtOAc (20 mL) was hydrogenated at room temperature for 12 h over 10% Pd–C (50 mg) under atmospheric pressure in the presence of Boc_2O (480 mg, 2.2 mmol). The catalyst was removed by filtration through Celite, and the filtrate was concentrated. The residue was purified by chromatography on silica gel [hexane:EtOAc = 5:1] to give *N*-Boc-α-aminophosphonate **10**.

10a: yield 85%; an oil; $[\alpha]^{20}_D$ +35.6 (*c* 0.6, $CHCl_3$); ^{1}H-NMR δ 7.4–7.1 (10H, m), 4.95 (1H, broad d, J = 9 Hz), 4.46 (1H, d, J = 11.0 Hz), 4.30 (1H, d, J = 11.0 Hz), 4.5–4.3 (1H, m), 4.0–3.8 (1H, m), 3.78 (3H, d, J = 10.7 Hz), 3.74 (3H, d, J = 10.7 Hz), 3.15 (1H, dd, J = 3.36, 14.0 Hz), 2.93 (1H, dd, J = 9.0, 14.0 Hz), 1.43 (9H, s); ^{31}P-NMR δ 25.0; IR (neat) 3264, 1713, 1247, 1032 cm^{-1}; EIMS *m/z* 450 (M^+ + 1). Anal. Calcd for $C_{23}H_{33}NO_6P$-(MH^+): 450.2045. Found: 450.2005.

10b: yield 83%; mp 104–105 °C; $[\alpha]^{20}_D$ -7.48 (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ 7.4–7.2 (5H, m), 4.91 (1H, broad d, J = 10.6 Hz), 4.71 (1H, d, J = 11.0 Hz), 4.63 (1H, d, J = 11.0 Hz), 4.4–4.2 (1H, m), 3.71 (3H, d, J = 17.0 Hz), 3.67 (3H, d, J = 17.0 Hz), 3.42 (1H, ddd, J = 5.76, 5.76, 15.6 Hz), 1.43 (9H, s), 1.04 (3H, d, J = 6.6 Hz), 1.03 (3H, d, J = 6.6 Hz); ^{31}P-NMR δ 26.0; IR (KBr) 3286, 1712, 1232, 1043 cm^{-1}. Anal. Calcd for $C_{19}H_{32}NO_6P$: C, 56.84; H, 8.03; N, 3.59. Found: C, 56.80; H, 7.99; N, 3.50.

Hydrogenation of 8a: Dimethyl (1(*S*),2(*S*))-Dihydroxy-3-phenylpropyl)phosphonate (11). A solution of **8a** (700 mg, 2 mmol) in MeOH (20 mL) was hydrogenated at room temperature for 12 h over $Pd(OH)_2$[18] (70 mg) under atmospheric pressure. The catalyst was removed through Celite, and the filtrate was concentrated to give gylcol phosphonate **11** (365 mg, 70%): mp 102–103 °C; $[\alpha]^{20}_D$ −4.25 (*c* 1.0, MeOH); ^{31}P-NMR 26.3; IR (KBr) 3281, 1220, 1047 cm^{-1}; EIMS *m/z* 261 (M^+ + 1). Anal. Calcd for $C_{11}H_{17}O_5P$: C, 50.76, H, 6.61. Found: C, 50.76; H, 6.64.

Preparation of Cyclic Sulfate 12. Diol **11** (520 mg, 2 mmol) and Et_3N (810 mg, 8 mmol) were treated with $SOCl_2$ (357 mg, 3 mmol) in CH_2Cl_2 (6 mL) at 0 °C for 5 min. The mixture was diluted with ether (10 mL) and quenched with cold water. The biphasic mixture was extracted with ether. The extract was

(20) This sample contains a small amount of impurity, which would be presumably the corresponding phosphate tautomer.

(21) Since it was difficult to separeate azides **9** from impurities derived from diethyl azodicarboxylate, **9** was used for the next reaction without further purifications.

washed with brine, dried over $MgSO_4$, and evaporated. The residue was diluted with a cold solution of CCl_4 (6 mL), CH_3CN (6 mL) and water (9 mL) and treated with $RuCl_3 \cdot H_2O$ (2 mg) and $NaIO_4$ (856 mg, 4 mmol) at 0 °C. The mixture was stirred vigorously at same temperature for 1 h and then ether was added. The aqueous layer was extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel [Et_2O:EtOAc = 1:1] to give **12** (418 mg) as an oil in 65% yield. **12**: $[\alpha]^{20}_D$ −51.0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ 7.4−7.2 (5H, m), 5.32−5.20 (1H, m), 4.73 (1H, dd, J = 0.9, 9.4 Hz), 3.92 (3H, d, J = 10.9 Hz), 3.91 (3H, d, J = 10.9 Hz), 3.34 (1H, dd, J = 3.3, 15.0 Hz), 3.20 (1H, dd, J = 7.7, 15.0 Hz); ^{31}P-NMR 12.0; IR (neat) 1396, 1215, 1034 cm^{-1}; EIMS *m/z* 323 (M^+ + 1), 322 (M^+); HRMS calcd for $C_{11}H_{15}O_7PS$ (M^+): 322.0276. Found: 322.0275.

Ring Opening Reaction of 12. The mixture of sulfate **12** (644 mg, 2 mmol) and LiN_3 (98 mg, 4 mmol) in DMF (10 mL) was stirred for 2 h at 25 °C. The solvent was then removed under reduced pressure (2 mmHg). The residue was suspended in THF (10 mL), and 50% H_2SO_4 (4 drops) was added to the stirred suspension. After being stirred for 18 h, excess sodium bicarbonate was added. Filtration through a Celite and concentration of the filtrate gave an oil. Column chromatography (silica gel/hexane−EtOAc = 1:1) of the oil gave **13** (74 mg, 13%) and **14** (143 mg, 25%).

13: an oil; $[\alpha]^{20}_D$ +6.7 (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ 7.4−7.2 (5H, m), 4.41 (1H, t, J = 6.04 Hz), 4.0 (1H, dd, J = 6.7, 13.2 Hz), 3.87 (3H, d, J = 10.6 Hz), 3.86 (3H, d, J = 10.6 Hz), 3.28 (1H, dd, J = 3.7, 14.2 Hz), 2.91 (1H, dd, J = 10.0, 14.2 Hz); IR (neat) 3266, 2109, 1219, 1030 cm^{-1}; EIMS *m/z* 242(M^+ − HN_3).

14: mp 70−71 °C; $[\alpha]^{20}_D$ −50.1 (*c* 0.9, $CHCl_3$); ^{1}H-NMR δ 7.4−7.2 (5H, m), 4.05−4.15 (1H, m), 3.91 (3H, d, J = 10.7 Hz), 3.85 (3H, d, J = 10.8 Hz), 3.54 (1H, dd, J = 7.1, 11.5 Hz), 3.16 (1H, dd, J = 3.7, 14.0 Hz), 2.87 (1H, dd, J = 8.2, 14.0 Hz); ^{31}P-NMR δ 23.5; IR (neat) 3365, 2110, 1259, 1068 cm^{-1}; EIMS *m/z* 242 (M^+ − HN_3). Anal. Calcd for $C_{11}H_{16}N_3O_4P$: C, 46.32; H, 5.65; N, 14.73. Found C, 46.59; H, 5.59; N, 14.43.

Acetylation of **13** and **14** under standard conditions (Ac_2O/Et_3N/CH_2Cl_2) gave the corresponding acetates **15** [an oil, ^{1}H-NMR δ 7.4−7.2 (5H, m), 5.42 (1H, dd, J = 4.8, 11.0 Hz), 4.1−3.9 (1H, m), 3.87 (3H, d, J = 11.0 Hz), 3.83 (3H, d, J = 10.7 Hz), 3.19 (1H, dd, J = 3.8, 14.1 Hz), 2.88 (1H, dd, J = 10.4, 14.1 Hz), 2.17 (3H, s), ^{31}P-NMR δ 19.4; IR (neat) 2114, 1757, 1216, 1029 cm^{-1}, EIMS *m/z* 284 (M^+ − HN_3)] and **16** [an oil; ^{1}H-NMR δ 7.4−7.2 (5H, m), 5.39−5.32 (1H, m), 3.90 (1H, d, J = 4.2 Hz), 3.90(3H, d, J = 10.8 Hz), 3.89 (3H, d, J = 10.8 Hz), 3.21 (1H, dd, J = 4.2, 14.3 Hz), 3.02 (1H, dd, J = 8.9, 14.3 Hz), 2.0 (3H, s), ^{31}P-NMR δ 20.3; IR (neat) 2110, 1747, 1230, 1030 cm^{-1}, EIMS *m/z* 284 (M^+ − HN_3)] in quantitative yields, respectively.

Supplementary Material Available: Photocopies of NMR spectra (^{1}H, ^{13}C, and/or ^{31}P) for compounds **5−7**, ***syn*-8a−d**, **8e−g**, **9a,b**, **10a,b**, **and 11−16** (32 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.