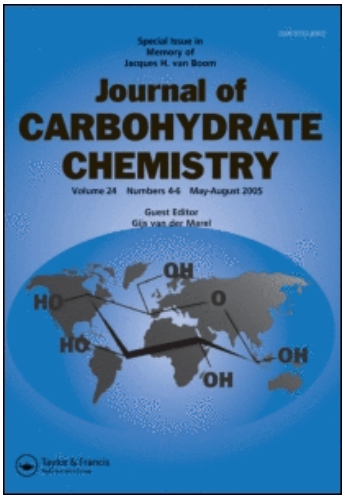

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Regioselective Synthesis of Phosphonylated Sugars from Reactions of Glycals with Diphenylphosphenium Cation

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ABSTRACT

Reaction of methyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside **1** with two equivalents of diphenylphosphenium cation at 0°C gave the 1-phosphonylated 2-enopyranosides **3α** and **3β** as major products. Similarly, reaction of diphenylphosphenium cation with tri-*O*-acetylglycal afforded the same products in a similar ratio. In contrast, a reaction with tri-*O*-benzylglucal at reflux temperature of dichloromethane afforded the 3-phosphonylated sugar **13** as a major product. These reactions may proceed via stable allyl cations.

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INTRODUCTION

During the last three decades, the synthesis of glycosyl phosphates and phosphonates has become an area of intense study among organic chemists and biochemists.[1] These compounds are important not only because they have important biological properties, but they are chiral building blocks in the synthesis of a variety of natural products. In regard to the biological activities of sugar phosphonates, many reports of their synthesis have been reported. Paulsen and his research group reported the synthesis of enopyranosyl phosphonates and their structural analysis in the 1970's.[2–5] Vasella reported a synthesis of a phosphonic acid analogue of *N*-acetyl-2,3-didehydro-2-deoxyneuramimic acid, a strong inhibitor of the Vibrio cholerae sialidase.[6] Wightman and his co-workers reported a synthesis of D-*arabino*-hexopyranosylphosphonates as an important intermediate for the shikimate pathway.[7] In addition, synthesis of pyranosylphosphonate nucleosides was reported by El-Hamid and Ismail.[8]

Phosphonylations of sugars are significant strategies for synthesis of chiral ligands. Shibasaki and his co-workers reported a synthesis of 6-phosphonylated sugar derivatives and their application for catalytic asymmetric reactions.[9,10] In this paper, we wish to report a regio and stereoselective synthesis of C-phosphonylated sugars from the reactions of unsaturated sugars with a phosphenium cation.

RESULTS AND DISCUSSION

Reaction of methyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside **1** with two equivalents of diphenylphosphenium cation generated from a reaction of chlorodiphenylphosphine with aluminum chloride in dichloromethane at 0°C gave the 1-phosphonylated 2-enopyranosides **3α** and **3β** in 46 and 11% yields, respectively, along with a minor product **4** in 4% yield (Scheme 1). The structures of these products were determined from spectral data, and the stereochemistries were determined from NOESY spectra. In particular, a correlation between the signals of H-1 and H-6 in the product **3α** was observed together with the absence of any such interaction between H-1 and H-5, suggesting the configuration of the diphenylphosphinoyl group to be α. Similarly, the correlations between H-1 and H-5 in the product **3β** and between H-3 and H-5 in the product **4** were observed. The formation of these products (Scheme 2) could be explained by a similar pathway that we reported previously.[11,12] This pathway is supported by the results of Saito and his co-workers,[13] who reported that allyl and propargyl ethers form a stable allyl and allenyl cation in the presence of Lewis acid.

Using an equimolar amount of tri-*O*-acetyl-D-glucal **2** as a starting material instead of 2-enopyranoside **1** under the same conditions, the same products, Ferrier rearrangement[a] products **3α** and **3β** and **4**, were obtained in a similar ratio as shown in Scheme 2. These results suggest that the reactions proceeded via the same intermediate allyl cation **A** as above. The phosphenium cation, which has strong Lewis acidity, would

[a]Recent reports: Refs. [14,15].

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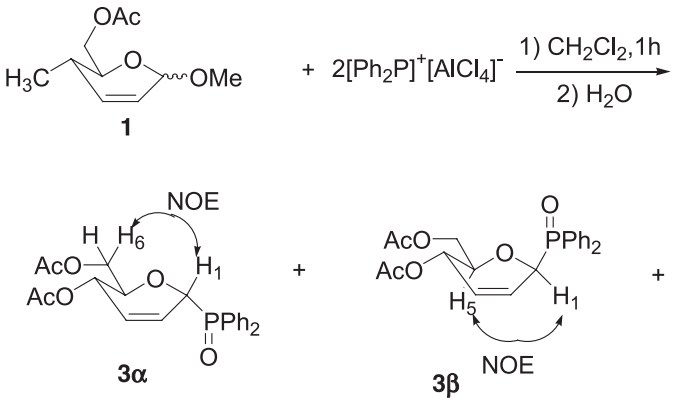


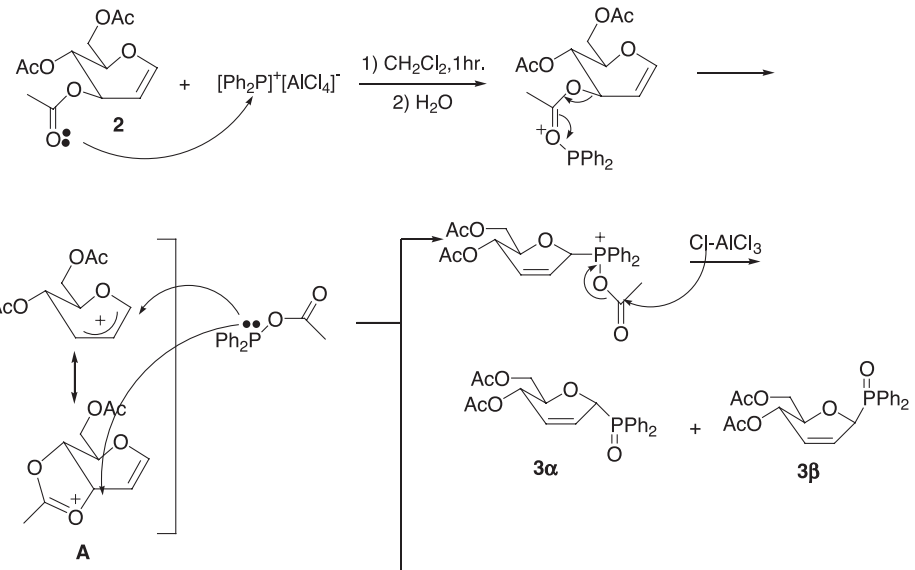
entry	temp.	yield[a] (%)		
		3α	**3β**	**4**
1	-78	16	4	-
2	0	46[b]	11[b]	4[b]
3	0 → rt	36	12	5
4	rt	49	16	3

[a] Estimated by HPLC [b] Isolated yields

Scheme 1.

attack the acetyl group at C-3 followed by elimination of acetylphosphine to form an allyl cation **A**. A nucleophilic phosphorus atom then reacts with cation **A** at C-1 predominantly, because C-3 is somewhat protected by a neighbor acetyl group (Scheme 2). Hiyama and his co-worker reported easy formation of allyl cations from allyl acetates in the presence of Lewis acid.[16]

By a similar pathway, reaction of tri-*O*-acetyl-D-galactal **5** with diphenylphosphenium cation at room temperature gave **6α**, **6β**, and **7** in 42%, 22%, and 7% yields, respectively. An NOE correlation between H-1 and H-4 in compound **6β** was observed, but not between H-1 and H-4 in compound **6α**, nor between H-3 and H-4 in compound **7** in the NOESY spectrum of these compounds (Scheme 3). An acid hydrolysis of the compound **3** in methanol gave the deprotected **8**, quantitatively, whose structure was determined after conversion to di-*O*-*tert*-butyl-2-enopyranosides **9α** and **9β**. In contrast, base catalyzed hydrolysis of **3** gave a rearranged product **10** in 71% yield (Scheme 4). El-Hamid and Ismail reported a similar base catalyzed rearrangement of 2-enopyranosylphosponate to 1-enopyranosylphosphonate.[9,10]



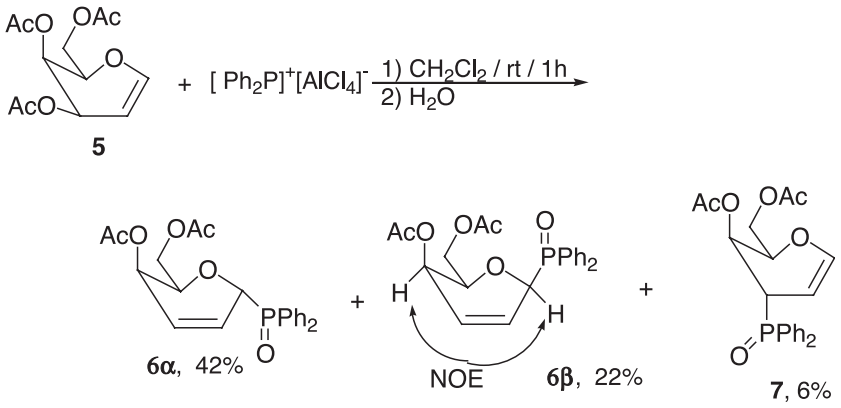
entry	temp.	yield[a] (%) 3α	3β	4
1	reflux	41	8	16
2	0 → rt	51[b]	21[b]	6[b]
3	rt	48	21	4

[a] Estimated by HPLC [b] Isolated yield

Scheme 2.

Similarly, reactions of 3,4,6-tri-*O*-benzylglucal **11** with two equivalents of diphenylphosphenium cation at − 78°C and 0°C gave phosphonylated sugars **12α**, **12β**, and **13** in similar ratios compound to the products from acetylated glucal. However, under reflux conditions in dichloromethane, the reaction gave the 3-phosphonylated **13** as a major product (Scheme 5). The structures of **12α**, **12β**, and **13** were determined from spectral data, and the stereochemistries were determined from NOESY spectra. In addition, the structure of **13** was confirmed by X-ray crystal analysis (Figure 1),[b] after hydrogenation of **13** followed by *tert*-butyldimethylsilylation of the primary hydroxyl group at C-6 of compound **16** (Scheme 6). Hydrogenation over 10% Pd/C (Aldrich) at atmospheric pressure did not occur, but hydrogenation over 10% Pd/C (Degussa type N101NE/W)[c] at 4.5–4.2 atm for 36 h gave deprotected saturated

[b]Further details of the crystal structure determination are available on request from Cambridge Crystallographic Centre; CCDC-190156 for compound **17**.
[c]Pd/C(Degussa type N101NE/W) was purchased from Aldrich.

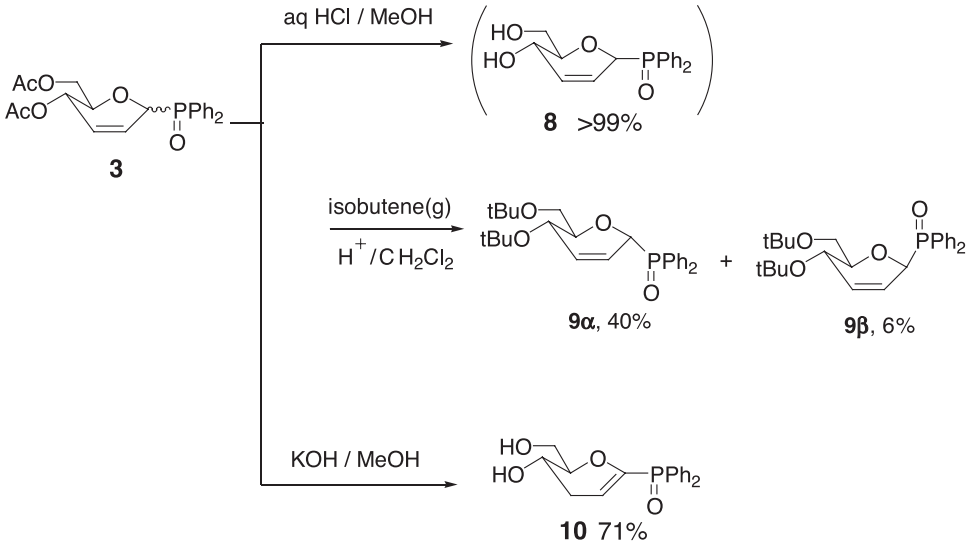


Scheme 3.

sugar **16** in 64% yield along with 8% of 4-*O*-benzylated sugar **15** (Table 1). The X-ray analysis of **17** (Figure 1) shows that the bulky diphenylphosphinoyl group occupies an equatorial position.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting apparatus. IR spectra were recorded as films on NaCl plates or as KBr pellets on a JASCO A-100 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL FX-90, BRUKER DRX-400 and BRUKER DRX-500 spectrometers. ^{1}H and ^{13}C chemical



Scheme 4.

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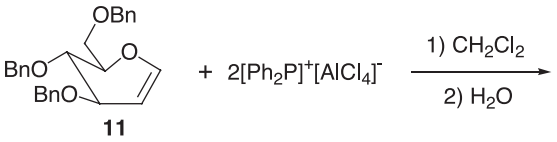

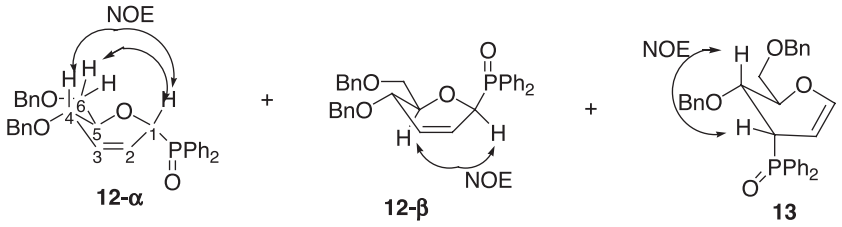

		yield[a] (%)		
entry	temp.	**12β**	**12α**	**13**
1	-78	29[b]	41[b]	20[b]
2	0	27	42	17
3	rt	14	12	50
4	reflux	6	6	75

[a] Estimated by HPLC [b] Isolated yield

Scheme 5.

shifts are reported in (δ) ppm from tetramethylsilane and coupling constants are in Hz. DEPT-^{13}C, HMQC, 2D-COSY, 2D-NOESY spectra were also measured on BRUKER DRX-400 and BRUKER DRX-500 spectrometers. Mass spectra were taken with a JEOL JMS-DX303 spectrometer.

Reaction of methyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside 1 with diphenylphosphenium cation. General procedure. To a solution of aluminum chloride (anhydrous) (0.27 g, 2 mmol) in dichloromethane (10 mL) was added dropwise a solution of chlorodiphenylphosphine (0.44 g, 2 mmol) in dichloromethane (10 mL) at 0°C under a nitrogen atmosphere. After stirring at room temperature for 1 h, to the resulting mixture was added a solution of methyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside **1** (0.24 g, 1 mmol) in dichloromethane (10 mL) and the reaction mixture stirred for 1 h. Water was then added and the mixture was extracted with dichloromethane. The solvent was evaporated and the residue was chromatographed on silica gel to afforded **diphenyl(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)phosphine oxide 3α** (0.19 g, 46%), **diphenyl(4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)phosphine oxide 3β** (0.046 g, 11%), and **1,5-anhydro-4,6-di-*O*-acetyl-2,3-dideoxy-3-diphenylphosphinoyl-D-*arabino*-hex-1-enitol 4** (0.018 g, 4%).

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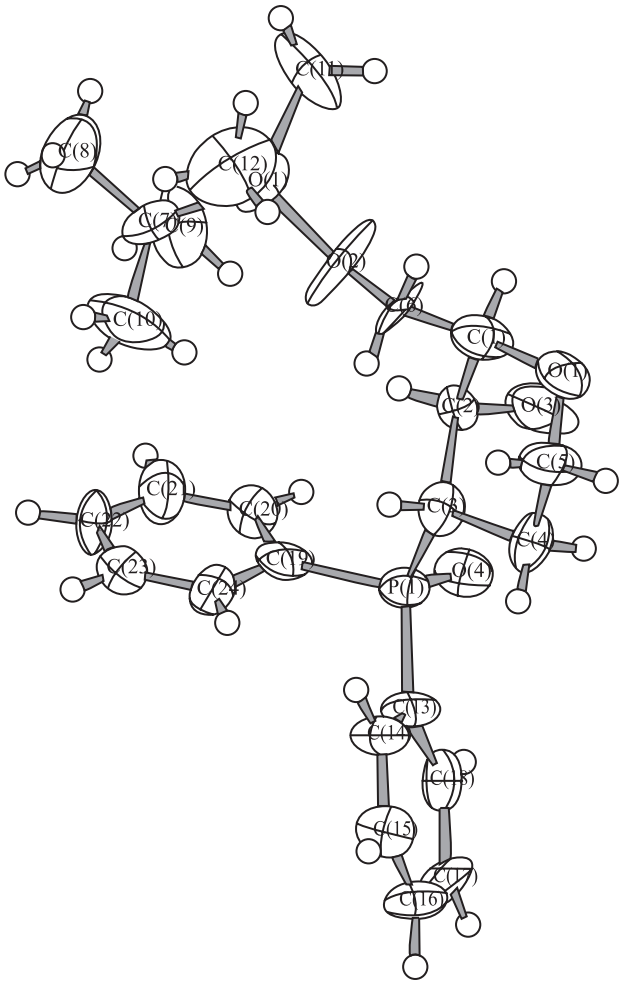

Figure 1. Ortep drawing of the compound **17**.

3α; white crystals; mp 124–125°C; IR (KBr); ν 3050, 2900, 1730, 1440, 1370, 1220, 1180, 1100, 1090, 1030, 970, 880, 820, 780, 720, and 690 cm^{-1}, 1H NMR (500.13 MHz, $CDCl_3$): δ 7.90–7.47 (m, 10H, Ph), 6.14 (br.d, 1H, $J_{1,2}$ = 2.2 Hz, $J_{2,3}$ = 10.4 Hz, H2), 6.01 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.0 Hz, H3), 5.17 (dd, 1H, $J_{1,2}$ = 2.2 Hz, J_{PH} = 9.3 Hz, H1), 5.08 (br.s, 1H, H4), 4.27–4.22 (m, 2H, H5 and H6), 4.08–4.04 (m, 1H, H6′), 2.00 (s, 6H, $C(O)CH_3$); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 170.6 (s, C═O), 170.3 (s, C═O), 132.4–128.3 (m, Ph), 126.4 (d, $^3J_{PC}$ = 9.2 Hz, C3), 125.4 (d, $^2J_{PC}$ = 2.4 Hz, C2), 72.4 (d, $^1J_{PC}$ = 81.5 Hz, C1), 72.2 (d, $^3J_{PC}$ = 3.5 Hz, C5), 63.8 (s, C4), 62.2 (s, C6), 20.9 (s, C(O)CH3), 20.7 (s, $C(O)CH_3$); ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 28.8. HRMS (Fab): Calcd for $C_{22}H_{24}O_6P$: M + 1, 415.1311. Found: M^++ 1, *m/z*, 415.1314.

3β; white crystals; mp 135–137°C; IR (KBr); ν 3050, 2825, 1740, 1440, 1370, 1240, 1180, 1140, 1100, 1080, 1040, 950, 880, 740, and 690 cm^{-1}; ^1H NMR (500.13

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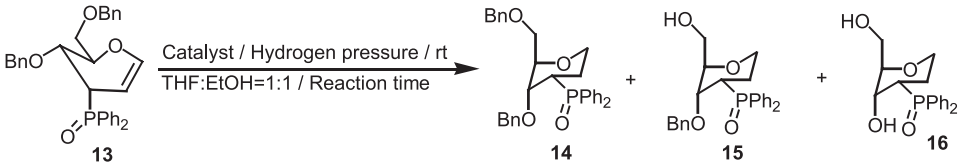
Scheme 6.

MHz, $CDCl_3$): δ 7.97–7.26 (m, 10H, Ph), 6.33 (br.d, $J_{2,3}$ = 10.0 Hz., 1H, H2), 5.80 (br.d, $J_{2,3}$ = 10.0 Hz, 1H, H3), 5.13 (br.d, J_{PH} = 13.4 Hz, 1H, H1), 5.00 (br.s, 1H, H5), 4.20–4.19 (m, 2H, H6 and H6′), 3.71 (dd, $J_{3,4}$ = 4.5 Hz, $J_{4,5}$ = 8.7 Hz, 1H, H4), 2.17 (s, 6H, $C(O)CH_3$); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 170.5 (s, C═O), 170.3 (s, C═O), 132.4–128.1 (m, Ph), 127.6 (d, $^3J_{PC}$ = 8.7 Hz, C3), 125.1 (s, C2), 75.2 (d, $^1J_{PC}$ = 90.2 Hz, C1), 74.1 (d, $^3J_{PC}$ = 8.3 Hz, C5), 64.5 (s, C4), 63.0 (s, C6), 20.9 (s, $C(O)CH_3$), 20.7 (s, $C(O)CH_3$); ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 28.8. HRMS (Fab): Calcd for $C_{22}H_{24}O_6P$: M + 1, 415.1311. Found: M^++ 1, *m/z*, 415.1326.

4: white crystals mp 138–141°C; IR (KBr); ν 3060, 2950, 2910, 1725, 1645, 1440, 1360, 1205, 1165, 1070, 1040, 950, 860, 820, 760 and 690 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$): δ 7.90–7.27 (m, 10H, Ph), 6.53–6.51 (m, 1H, H1), 5.32 (m, 1H, H4), 5.17, 5.15 (m, 1H, H5), 4.41 (dd, 1H, J_{gem} = 12.3 Hz, $J_{5,6}$ = 3.8 Hz, H6), 4.23 (dd, 1H, J_{gem} = 13.1 Hz, $J_{56'}$ = 1.3 Hz, H6′), 4.20 (dd, $J_{1,2}$ = 8.95 Hz, $J_{2,3}$ = 5.70 Hz, 1H, H2), 3.71 (dd, $J_{2,3}$ = 5.70 Hz, J_{PH} = 11.5 Hz, 1H, H3), 2.03 (s, 3H, $C(O)CH_3$), 1.15 (s, 3H, $C(O)CH_3$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 170.7 (s, C═O), 170.2 (s, C═O), 146.3 (d, $^3J_{PC}$ = 9.6 Hz, C1), 134.0–128.6 (m, Ph), 92.5 (d, $^2J_{PC}$ = 7.8 Hz, C2), 71.8 (s, C5), 66.6 (d, $^2J_{PC}$ = 7.7 Hz, C4), 62.0 (s, C6), 35.3 (d, $^1J_{PC}$ = 76.9 Hz, C3), 20.7 (s,

Table 1. Hydrogenation of **13**.



Entry	Catalyst	Hydrogen pressure (atm)	Reaction time (h)	Products (yield*)
1	10% Pd/C (Aldrich)	1.0	24	No reaction
2	5% Pd/C (Wako)	5.0–4.8	24	**14** (44%)
3	10% Pd/C (Aldrich)	5.0–4.8	24	**15** (48%)
4	10% Pd/C (Degussa type N101NE/W)	4.5–4.2	9	**15** (25%)/**16** (25%)
5	10% Pd/C (Degussa type N101NE/W)	4.5–4.2	36	**15** (6%)/**16** (64%)

*Isolated yield.

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$C(O)CH_3$), 19.5 (s, $C(O)CH_3$); ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 26.0. HRMS (Fab): Calcd for $C_{22}H_{24}O_6P$: M + 1, 415.1311. Found: M^++ 1, *m/z*, 415.1298.

Reactions of glucal with phosphenium cation. General procedure. To a solution of aluminum chloride (anhydrous) (1.47 g, 11.1 mmol) in dichloromethane (10 ml) was added dropwise a solution of chlorodiphenylphosphine (2.43 g, 11.0 mmol) in dichloromethane (10 ml) at 0°C under a nitrogen atmosphere. After stirring at room temperature for 1 h, to the resulting mixture was added a solution of methyl 3,4,6-tri-*O*-acetyl-D-glucal **2** (2.0 g, 7.35 mmol) in dichloromethane (10 ml) and the reaction mixture was stirred for 1 h at room temperature. Water was then added and the mixture was extracted with dichloromethane. The solvent was evaporated and the residue was chromatographed on silica gel to afford phosphonylated sugars, **3α** (1.56 g, 51%), **3β** (0.64 g, 21%), and **4** (0.17 g, 6%).

Similarly, from the reaction of tri-*O*-acetyl galactal **5** (2.0 g, 7.33 mmol) with chlorodiphenylphosphine (1.2 g, 8.8 mmol) in the presence of anhydrous aluminum chloride (1.2 g, 8.8 mmol), **diphenyl(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranosyl)phosphine oxide 6α** (1.27 g, 42%), **diphenyl(4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*threo*-hex-2-enopyranosyl)phosphine oxide 6β** (0.68 g, 22%), and **1,5-anhydro-4,6-di-*O*-acetyl-2,3-dideoxy-3-dipheylphosphinoyl-D-*xylo*-hex-1-enitol 7** (0.21 g, 7%) were obtained.

6α; white crystals; mp 126–128°C; IR (KBr); ν 2900, 1720, 1590, 1440, 1370, 1160, 1080, 1020, 900, 840, 810, 780, 740, and 680 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.89–7.48 (m, 10H, Ph), 6.21 (m, 1H, H3), 6.14 (dd, $J_{1,2}$ = 2.2 Hz, $J_{2,3}$ = 10.2 Hz, 1H, H2), 5.26 (br.d, J_{PH} = 8.0 Hz, 1H, H1), 5.07 (br.s, 1H, H4), 4.48 (br.s, 1H, H5), 4.23–4.18 (m, 1H, H6′), 4.06–4.02 (m, 1H, H6), 2.05 (s, 3H, $C(O)CH_3$), 1.92 (s, 3H, $C(O)CH_3$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.5 (s, C═O), 170.3 (s, C═O), 132.5–128.5 (m, Ph), 127.0 (s, C2), 125.6 (d, $^3J_{PC}$ = 10.1 Hz, C3), 73.6 (d, $^1J_{PC}$ = 84.5 Hz, C1), 72.1 (s, C5), 63.4 (s, C4), 62.7 (s, C6), 21.0 (s, $C(O)CH_3$), 20.6 (s, $C(O)CH_3$); ^{31}P NMR (161.97 MHz, $CDCl_3$): δ 28.5. HRMS (Fab); Calcd for $C_{22}H_{24}O_6P$: M + 1, 415.1310. Found: M^++ 1, *m/z*, 415.1257.

6β: white syrup; IR (neat); ν 3450, 3060, 2975, 1740, 1590, 1485, 1440, 1370, 1240, 1120, 1090, 1040, 980, 950, 910, 860, 830, 750, 720, and 690 cm^{-1}; ^1H NMR (400.13 MHz,$CDCl_3$): δ 7.94–7.43 (m, 10H, Ph), 6.49 (ddd, $J_{1,2}$ = 1.96 Hz, $J_{2,3}$ = 10.32 Hz, J_{PH} = 4.68 Hz, 1H, H2), 6.09 (ddd, $J_{2,3}$ = 10.32 Hz, $J_{3,4}$ = 3.52 Hz, J_{PH} = 6.28 Hz, 1H, H3), 5.12 (dd, $J_{1,2}$ = 1.96 Hz, J_{PH} = 15.0 Hz, 1H, H1), 5.02 (dd, $J_{3,4}$ = 3.52 Hz, $J_{4,5}$ = 2.12 Hz, 1H, H4), 4.32 (dd, $J_{56'}$ = 5.16 Hz, J_{gem} = 11.48 Hz, 1H, H6′), 4.07 (dd, $J_{5,6}$ = 7.64 Hz, J_{gem} = 11.48 Hz, 1H, H6), 3.95 (br.m, 1H, H5), 2.01 (s, 3H, $C(O)CH_3$), 1.90 (s, 3H, $C(O)CH_3$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.5 (s, C═O), 170.1 (s, C═O), 132.6–127.8 (m, Ph), 128.6 (d, $^2J_{PC}$ = 4.5 Hz, C2), 124.2 (d, $^3J_{PC}$ = 8.5 Hz, C3), 75.3 (d, $^1J_{PC}$ = 90.6 Hz, C1), 74.1 (d, $^3J_{PC}$ = 10.3 Hz, C5), 63.2 (d, $4J_{PC}$ = 1.97 Hz, C4), 62.6 (s, C6), 20.7 (s, $C(O)CH_3$), 20.6 (s, $C(O)CH_3$); ^{31}P NMR (161.96 MHz, $CDCl_3$): δ 29.2; MS (Fab) *m/z* 415 (M^++ 1).

7: white amorphous solid; IR (KBr); ν 3200, 3020, 2900, 1730, 1640, 1590, 1435, 1370, 1220, 1090, 1020, 960, 890, 720, and 690 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.80–7.49 (m, 10H, Ph), 6.65 (d, $J_{1,2}$ = 9.24 Hz, 1H, H1), 5.11 (br.d, $J_{4,5}$ = 7.92 Hz, 1H, H5), 4.83 (m, 1H, H4), 4.35 (dd, $J_{1,2}$ = 9.24 Hz, $J_{2,3}$ = 3.2 Hz, 1H, H2), 4.21–4.16 (m, 1H, H6′), 4.09–4.04 (m, 1H, H6), 3.37 (ddd, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 1.35 Hz, J_{PH} = 11.7 Hz, 1H,

H3), 2.06 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.5 (s, C═O), 170.2 (s, C═O), 146.3 (d, $^3J_{PC}$ = 9.2 Hz, C1), 132.4–128.7 (m, Ph), 91.4 (d, $^2J_{PC}$ = 7.4 Hz, C2), 72.1 (s, C4), 65.1 (d, $^2J_{PC}$ = 15.3 Hz, C5), 62.9 (s, C6), 37.2 (d, $^1J_{PC}$ = 65.9 Hz, C3), 20.8 (s, C(O)CH_3), 20.6 (s, C(O)CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$): δ 27.1; MS(Fab) *m/z* 415 (M^++ 1).

Diphenyl(4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-phosphine oxide 12α; white syrup; IR (neat); ν 3050, 2930, 2860, 1750, 1590, 1460, 1440, 1260, 1180, 1120, 1090, 1020, 800, 720 and 690 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 7.96–7.19 (m, 20H, Ph), 6.18 (br.d, $J_{2,3}$ = 10.60 Hz, 1H, H2), 6.12 (dd, $J_{2,3}$ = 10.60 Hz, $J_{3,4}$ = 3.00 Hz, 1H, H3), 5.12 (dd, J_{12} = 2.5 Hz, J_{PH} = 10.9 Hz, 1H,H1), 4.54 (d, J_{gem} = 12.0 Hz, $PhCH_2$), 4.45 (d, J_{gem} = 12.0 Hz, $PhCH_2$), 4.41 (d, J_{gem} = 11.7 Hz, $PhCH_2$), 4.31 (d, J_{gem} = 11.7 Hz, $PhCH_2$), 3.97–3.93 (m, 2H, H4 and H5), 3.61–3.54 (m, 2H, H6 and H6′); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 138.2–127.6 (m, Ph, C3), 124.0 (d, $^2J_{PC}$ = 2.1 Hz, C2), 73.8 (d, $^3J_{PC}$ = 3.4 Hz, C5), 73.2 (s, $PhCH_2$), 72.8 (d, $^1J_{PC}$ = 82.1 Hz, C1), 69.9 (s, $PhCH_2$), 68.8 (s, C4), 68.7 (s, C6); ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 27.3. HRMS (Fab): Calcd for $C_{32}H_{32}O_4P$: M + 1 511.2038. Found: M^++ 1, *m/z*, 511.2037.

Diphenylphosphinoyl 4,6-di-*O*-benzyl-1,2,3-trideoxy-β-D-*erythro*-hex-2-enopyranoside 12β; white syrup; IR (neat); ν 3050, 2850, 1720, 1630, 1580, 1490, 1440, 1360, 1300, 1260, 1180, 1110, 1090, 740, 720 and 690 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$):δ 7.94–7.22 (m, 20H,Ph), 6.16 (ddd, $J_{1,2}$ = 2.60 Hz, $J_{2,3}$ = 10.5 Hz, JPH = 4.25 Hz, 1H, H2), 6.01–5.99 (m, 1H, H3), 5.14 (dd, $J_{1,2}$ = 2.60 Hz, J_{PH} = 9.05 Hz, 1H, H1), 4.57–4.34 (m, 4H, $PhCH_2$), 3.77–3.71 (m, 2H, H4, H6), 3.66–3.57 (m, 2H, H6′, H5); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 138.4–127.5 (m, Ph), 129.3 (d, $^3J_{PC}$ = 9.3 Hz, C3), 123.3 (d, $^2J_{PC}$ = 5.3 Hz, C2), 76.5 (d, $^3J_{PC}$ = 7.3 Hz, C5), 75.0 (d, $^1J_{PC}$ = 91.9 Hz, C1), 73.3 (s, $PhCH_2$), 71.2 (s, $PhCH_2$), 69.6 (d, $^4J_{PC}$ = 2.3 Hz, C4), 69.4 (s, C6); ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 27.8. HRMS: Calcd for $C_{32}H_{31}O_4P$: M, 510.1960. Found: M^+, *m/z*, 510.1957.

1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-diphenylphosphinoyl-D-*ribo*-hex-1-enitol 13; white crystals: mp 126–128.5°C; IR (KBr); ν 3050, 2900, 1640, 1440, 1370, 1330, 1260, 1210, 1170, 1100, 920, 890, 840,and 690 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$):δ 7.82–7.79, 7.42–7.11, 6.79–6.78 (m, 20H, Ph), 6.48–6.46 (m, 1H, H1), 4.85–4.82 (m, 1H, H5), 4.50 (d, J_{gem} = 12.1 Hz, 1H, $PhCH_2$), 4.44 (d, 1H, J_{gem} = 12.1 Hz, $PhCH_2$), 4.30–4.27 (m, 1H, H2), 4.27 (d, J_{gem} = 12.1 Hz, 1H, $PhCH_2$), 4.24–4.19 (m, 1H, H4), 4.14 (d, J_{gem} = 11.3 Hz, 1H, PhCH2), 3.78 (dd, J_{gem} = 10.7 Hz, $J_{5,6}$ = 3.8 Hz, 1H, H6), 3.67 (dd, J_{gem} = 10.7 Hz, $J_{5,6'}$ = 2.8 Hz, 1H, H6′), 3.59–3.55 (m, 1H, H3); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 145.9 (d, $^3J_{PC}$ = 9.8 Hz, C1), 138.1, 137.4, 134.6, 134.1, 133.8, 133.3, 131.3–130.9, 128.5–125.9 (m, Ph), 92.8 (d, $^2J_{PC}$ = 6.8 Hz, C2), 74.5 (d, $^3J_{PC}$ = 1.9 Hz, C5), 73.5 (s, $PhCH_2$), 72.73 (d, $^2J_{PC}$ = 6.7 Hz, C4), 72.72 (s, $PhCH_2$), 68.7 (s,C6), 37.2 (d, $^1J_{PC}$ = 72.4 Hz, C3); ^{31}P NMR (202.46 MHz,$CDCl_3$): δ 27.7. HRMS: Calcd for $C_{32}H_{31}O_4P$: M, 510.1960. Found: M^+, *m/z*, 510.1958.

Acid catalyzed hydrolysis of 3. To a solution of **3** (2.07 g, 5 mmol) in methanol (20 ml) was added one-drop of 10% hydrochloric acid and the resulting mixture was refluxed for 18 h. After cooling, the solvent was removed in vacuo, and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was

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chromatographed on silica gel to give quantitatively **diphenyl(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)phosphine oxide 8** (1.66 g).

To a mixture of **8** (1.66 g, 5 mmol) and catalytic amounts of concentrated sulfuric acid in dichloromethane (10 ml) was passed isobutene gas for 42 h with stirring at room temperature. Then the resulting mixture was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography to give **diphenyl(4,6-di-*O*-*tert*-butyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)phosphine oxide 9α** (0.88 g, 40%) and **diphenyl(4,6-di-*O*-*tert*-butyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)phosphine oxide 9β** (0.13 g, 6%).

9α: white syrup; IR (neat); ν 2980, 2330, 1720, 1630, 1590, 1440, 1360, 1190, 1120, 1090, 1060, 1020, 880, 750, 720 and 690 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$):δ 8.02–7.39 (m, 10H, Ph), 6.08 (dd, $J_{1,2}$ = 2.46 Hz, $J_{2,3}$ = 10.58 Hz, 1H, H2), 5.97–5.93 (ddd, $J_{2,3}$ = 10.58 Hz, $J_{3,4}$ = 3.13 Hz, J_{PH} = 3.13 Hz, 1H, H3), 5.05 (dd, $J_{1,2}$ = 2.46 Hz, J_{PH} = 12.3 Hz, 1H, H1), 3.84 (br.s, 1H, H4), 3.62 (ddd, $J_{4,5}$ = 5.08 Hz, $J_{5,6}$ = 4.20 Hz, $J_{5,6'}$ = 5.37 Hz, 1H, H5), 3.45 (dd, 1H, $J_{5,6}$ = 4.20 Hz, J_{gem} = 10.18 Hz, H6), 3.39 (dd, $J_{5,6'}$ = 5.37 Hz, J_{gem} = 10.18 Hz, 1H, H6′), 1.18 (s, 9H, CH_3), 1.16 (s, 9H, CH_3); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 132.6–128.1 (m, Ph and C3), 122.0 (d, $^2J_{PC}$ = 2.3 Hz, C2), 75.8 (d, $^3J_{PC}$ = 3.9 Hz, C5), 74.3 (s, $C(CH_3)_3$), 73.0 (d, $^1J_{PC}$ = 83.9 Hz, C1), 72.9 (s, $C(CH_3)_3$), 62.5 (s, C4), 60.6 (s, C6), 28.4 (s, CH_3), 27.4 (s, CH_3); ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 26.4. HRMS (Fab): Calcd for $C_{26}H_{36}O_4P$: M + 1, 443.2351. Found: M^++ 1, *m/z*, 443.2352.

9β: white syrup; IR (neat); ν 2980, 2330, 1720, 1630, 1590, 1480, 1440, 1390, 1360, 1190, 1120, 1100, 1060, 1030, 890, 750, 720,and 690 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$): δ 8.08–7.41 (m, 10H, Ph), 6.06–6.03 (m, 1H, H2), 5.81–5.79 (m, 1H, H3), 5.09–5.06 (dd, J_{PH} = 12.7 Hz, $J_{1,2}$ = 2.2 Hz, 1H, H1), 3.89 (bs, 1H, H4), 3.55–3.51 (m, 2H, H6 and H6′), 3.33–3.31 (m, 1H, H5), 1.21 (s, 9H, CH_3), 1.15 (s, 9H, CH_3); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 133.7 (d, $^3J_{PC}$ = 9.6 Hz, C3), 132.7–127.7 (m, Ph), 121.9 (d, $^2J_{PC}$ = 5.7 Hz, C2), 76.3 (d, $^3J_{PC}$ = 6.7 Hz, C5), 75.1 (d, $^1J_{PC}$ = 92.7 Hz, C1), 74.7 (s, $C(CH_3)_3$), 72.6 (s, $C(CH_3)_3$), 62.2 (s, C4), 60.1 (s, C6), 28.5 (s, CH_3), 27.2 (s, CH_3); ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 26.7. HRMS (Fab): Calcd for $C_{26}H_{36}O_4P$: M + 1, 443.2351. Found M^++ 1, *m/z*, 443.2339.

Base catalyzed hydrolysis of 3. A mixture of **3** (0.48 g, 1.16 mmol) and KOH (1.6 g, 24 eq) in methanol was stirred for 1 h at room temperature. The mixture was then neutralized with diluted hydrochloric acid and the solvent was evaporated in vacuo. The residue was extracted with dichloromethane, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the residue was chromatographed over silica gel to give quantitatively **diphenyl(2,3-dideoxy-D-*erythro*-hex-1-enopyranosyl)phosphine oxide 10** (0.27 g, 71%).

10: white amorphous solid; IR (Nujol); ν 3400, 3050, 3000, 1640, 1440, 1270, 1180 1120, 1080, 1030, 1000, 900, 740, and 700 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$): δ 7.75–7.26 (m, 10H, Ph), 5.59–5.57 (m, 1H, H2), 4.63 (s, 1H, OH), 4.03–4.02 (m, 2H, H4 and OH), 3.89–3.86 (m, 1H, H6), 3.77–3.74 (m, 1H, H6′), 2.46–2.41 (1H, H3), 2.21–2.16 (m, 1H, H3′); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 147.8 (d, $^1J_{PC}$ = 132.7 Hz, C1), 132.4–128.5 (m, Ph), 114.4 (d, $^2J_{PC}$ = 20.0 Hz, C2), 80.8 (d, $^3J_{PC}$ = 5.9 Hz, C5), 63.0 (s, C4), 61.5 (s, C6), 30.0 (d, $^3J_{PC}$ = 10.3 Hz, C3); ^{31}P NMR

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(202.46 MHz, $CDCl_3$): δ 22.0. HRMS (Fab): Calcd for $C_{18}H_{20}O_4P$: M + 1 331.1099. Found: M^++ 1, *m/z*, 331.1119.

Hydrogenation of 13. Compound **12** (4.54 g, 8.90 mmol) was dissolved in THF/EtOH (1/1) in a Parr flask. To this was added 2.25 g of 10% Degussa Type N101NE/W palladium on charcoal (contains 50% H_2O). The flask was placed in a medium pressure hydrogenator at 4.5–4.2 atm of hydrogen for 38 h, after which time, the solution was filtered through celite, and concentrated. The residue was chromatographed on silica gel using ethyl acetate–methanol (6:1–2:1, gradient) to give 1.90 g (64%) of **1,5-anhydro-2,3-dideoxy-3-diphenylphosphinoyl-D-*ribo*-hexitol 16** and 0.23 g (6%) of **1,5-anhydro-2,3-dideoxy-4-*O*-benzyl-3-diphenylphosphinoyl-D-*ribo*-hexitol 15**. Hydrogenation using 5% Pd/C (Wako) gave **1,5-anhydro-2,3-dideoxy-4,6-di-*O*-benzyl-3-diphenylphosphinoyl-D-*ribo*-hexitol 14** as a major product (44%), and hydrogenation using 10% Pd/C (Aldrich) gave **15** in 48% yield.

16; white amorphous solid; IR (KBr) ν 3360, 2925, 2330, 1640, 1428, 1160, 1105, 1038, 980, 885, 850, 740, and 690 cm^{-1}; ^1H NMR (400.13 MHz, CD_3OD): δ 7.95–7.46 (m, 10H, Ph), 4.05–3.93 (m, 1H, H5), 3.86–3.62 (m, 5H, H1, H4, and H6), 3.14–3.10 (m, 1H, H3), 2.05–1.97 (m, 1H, H2), 1.65–1.58 (m, 1H, H2); ^{13}C NMR (100.31 MHz, CD_3OD): δ 133.96–129.69 (m, Ph), 80.38 (d, $^3J_{PC}$ = 6.1 Hz, C5), 66.93 (d, $^2J_{PC}$ = 6.1 Hz, C4), 63.21 (d, $^3J_{PC}$ = 8.4 Hz, C1), 61.74 (s, C6), 37.21 (d, $^1J_{PC}$ = 73.2 Hz, C3), 23.07 (s, C2); ^{31}P NMR (161.97 MHz, CD_3OD): δ 39.27. HRMS (FAB): Calcd for $C_{18}H_{22}O_4P$, M + 1 333.1117. Found M^++ 1, *m/z*, 333.1255.

15; mp 139–142°C; IR (KBr) ν 3440, 3090, 2950, 2900, 2350, 1660, 1655, 1450, 1150, 1040, 1005, 906, 875, 745, 727, and 700 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.88–6.92 (m, 20H, Ph), 4.51 (dd, J = 28.7 Hz, J = 11.9 Hz, 2H, $PhCH_2$), 4.34–4.29 (m, 2H, H6), 4.17 (d, J = 11.4 Hz, 1H, H1), 4.04–3.95 (m, 2H, H1, H4), 3.81–3.77 (m, 1H, H5), 3.12–3.09 (m, 1H, H3), 2.09–2.06 (m, 1H, H2), 1.9–1.76 (m, 1H, 2H); ^{13}C NMR (100.31 MHz, $CDCl_3$): δ 138.4–127.7 (m, Ph), 76.05 (d, $^2J_{PC}$ = 3.0 Hz, C4), 74.79 (d, $^3J_{PC}$ = 5.3 Hz, C5), 71.92, 62.02 (s, C6 and C7), 63.24 (d, $^3J_{PC}$ = 4.6 Hz, C1), 36.38 (d, $^1J_{PC}$ = 72.4 Hz, C3), 25.55 (s, C2); ^{31}P NMR (161.97 MHz, $CDCl_3$): δ 32.89. HRMS (FAB): Calcd for $C_{25}H_{27}O_4P$, M + 1 423.1647. Found M^++ 1, *m/z*, 423.1721.

14; mp 164–166°C; IR (KBr) ν 3400, 3050, 2860, 2350, 1450, 1430, 1170, 1110, 900, 730, and 690 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.82–6.95 (m, 20H, Ph), 4.48 (dd, J = 28.0 Hz, J = 12.0 Hz, 2H, H8), 4.31–4.29 (m, 2H, H7), 4.14 (d, J = 11.4 Hz), 4.01–3.92 (m, 2H, H1, H4), 3.79–3.74 (m, 1H, H5), 3.09–3.06 (m, 1H, 3H), 2.01–1.79 (m, 2H, H2); ^{13}C NMR (100.31 MHz, $CDCl_3$) δ 138.1–127.3 (m, Ph), 75.0 (d, $^2J_{PC}$ = 5.3 Hz, C4), 74.3 (d, $^3J_{PC}$ = 5.3 Hz, C5), 73.5, 71.8, 69.8 (s, C6, CH2Ph), 63.2 (d, $^3J_{PC}$ = 6.9 Hz, C1), 36.8 (d, $^1J_{PC}$ = 72.0 Hz, C3), 23.9 (s, C2); ^{31}P NMR (161.97 MHz, $CDCl_3$): δ 32.69. HRMS (FAB): Calcd for $C_{32}H_{33}O_4P$, M + 1 512.2116. Found M^++ 1, *m/z*, 521.2158.

1,5-anhydro-2,3-dideoxy-6-*O*-*tert*-butyldimethylsilyl-3-diphenylphosphinoyl-D-*ribo*-hexitol 17. To a solution of diol **15** (0.754 g, 2.27 mmol) in DME (10 ml) was added imidazole (0.62 g, 9.08 mmol) and *tert*-butyldimethylsilyl chloride (0.40 g, 2.72 mmol) at room temperature under argon atmosphere, and the mixture was stirred for 48 h. After the usual workup, the organic layer was concentrated, and the residue was chromatographed on silica gel using ethyl acetate as eluent to give **17** as white crystals

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in 75% (0.754 g) yield. For the X-ray crystal analysis, a sample recrystallized from dichloromethane was used.

mp 146–150°C; IR (KBr) ν 3350, 3150, 2960, 2880, 2350, 1610, 1470, 1450, 1380, 1375, 1350, 1255, 1175, 1105, 1090, 985, 900, 845, 795, 765, 725, 715, and 705 cm^{-1}; ^1H NMR (400.13 MHz): δ 7.49–7.46 (m, 10H, Ph), 4.79 (s, 1H, OH), 4.24 (d, 1H, J = 8.4 Hz, H5), 3.843.79 (m, 3H, H1 and H4), 3.75–3.72 (m, 2H, H6), 2.89–2.83 (m, 1H, 3H), 2.31–2.24 (m, 1H, 2H), 1.44–1.38 (m, 1H, 2H), 0.83 (s, 9H, t-Bu); ^{13}C NMR (100.31 MHz, $CDCl_3$): δ 131.97, 131.84, 131.00, 130.87, 130.78, 130.74, 130.65, 128.81, 128.70, 128.60, 133.04, 132.54, 77.79 (d, $^3J_{PC}$ = 7.6 Hz, C5), 66.03 (d, $^2J_{PC}$ = 4.6 Hz, C4), 63.64 (s, C6), 62.37 (d, $^3J_{PC}$ = 10.7 Hz, C1), 33.86 (d, $^1J_{PC}$ = 71.6 Hz, C3), 25.77 (s, C10, C11 and C12), 19.09 (s, C2), 18.09 (s, C9), 5.59–5.62 (s, C7 and C8); ^{31}P NMR (161.97 MHz, $CDCl_3$): δ 37.97. HRMS: Calcd for $C_{24}H_{35}O_4SiP$, M, 446.2042. Found M^+, *m/z*, 446.2041.

X-Ray Crystal Analysis of 17. Data Collection

A colorless prismatic crystal of $C_{24}H_{35}O_4PSi$ having approximate dimensions of 0.52 × 0.84 × 0.68 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Mo–Ka radiation. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range 20.13 < 2q < 23.97° corresponded to a primitive orthorhombic cell with dimensions:

$$a = 11.490(5)\ \text{Å}, b = 19.548(6)\ \text{Å}, c = 10.909(5)\ \text{Å}, V = 2450(2)\ \text{Å}3$$

For Z = 4 and F.W. = 446.60, the calculated density is 1.21 g/cm^3. The systematic absences of: h00: h ± 2n, 0k0: k ± 2n, 00l: l ± 2n, uniquely determine the space group to be: P212121 (#19).

The data were collected at a temperature of 23 + 1°C using the w-2q scan technique to a maximum 2q value of 55.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.22° with a take-off angle of 6.0°. Scans of (1.47 + 0.30 tan θ)° were made at a speed of 16.0°/min (in ω). The weak reflections (I < 10.0σ(I)) were rescanned (maximum of 3 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 258 mm, and the detector aperture was 6.0 × 6.0 mm (horizontal × vertical).

Data Reduction

A total of 3189 reflections was collected. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Mo–Ka radiation is 1.9 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.71 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement on F was based on 1349 observed reflections ($I > 2.00\sigma(I)$) and 271 variable parameters and converged (largest parameter shift was 0.24 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.099$$
$$Rw = [\Sigma w(|Fo| - |Fc|)2/\Sigma w\ Fo2]1/2 = 0.081$$

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