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Synthesis of Glycosyl Phosphonates and Related Compounds

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ABSTRACT

The synthesis of glycosylphosphonates, isopolar, nonisosteric analogues of glycosylphosphates, from halonitro ethers, glycosyl acetates, or glycosyl trichloroacetimidates is reviewed. A new approach to phosphonate analogues of myo-inositol trisphosphate (**50**) *is described. Based on a hypothetical reaction mechanism for the formation of thioethers from a glyoxalase I inhibitor, an advanced intermediate* **59** *for the synthesis of diphosphonate–phosphate analogues of* **50** *is obtained by an addition–elimination–addition sequence from* **54**. *Finally, glucosylphosphines, characterized as the corresponding phosphine oxides* **61** *and* **62** *have been prepared from the glycosylidene diazirine* **60**, *a precursor of the tetra-O-benzylglucopyranosylidene carbene. The phosphine oxides* **61** *and* **62** *were also obtained by reaction of the glycosyl acetate* **18** *with methyl diphenylphosphinite.*

By 1970–1975, phosphonoyl substituents had been introduced at almost every position of aldoses, with the exception of the anomeric position of pyranoses and furanoses [1, 2]. There was no method for the synthesis of glycosyl phosphonates of the type illustrated by glucose-1-phosphonate **1** and ribose-1-phosphonate **2**, which were of particular interest as (presumably) isopolar, nonisosteric analogues of the biologically important glycosyl-1-phosphates and as enantiomerically pure α-heteroatom substituted phosphonates [3] of potential use for the "Umpolung" of the reactivity at the anomeric center [4, 5].

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Paulsen's group had thoroughly investigated the Michaelis-Becker and the Arbuzov reaction of variously protected glycosyl halides and had shown that mainly elimination products are formed, presumably according to an E_2C mechanism. Dialkoxyphosphonates of type **3** were obtained when silver dialkyl phosphites and $AgClO_4$ or the corresponding halomercury compounds were used. The desired C(1), P bond was formed by treating allylic glycosyl halides with trialkyl phosphites under acidic conditions, to give allylic phosphonates of type **4** (Figure 1). These compounds were hydrogenated and used for the determination of the anomeric effect of the $-PO_3Me_2$ group (0.56 kcal/Mol) (see [2] and earlier papers of the series). Unfortunately, the olefinic double bond could not be epoxidized or dihydroxylated. The desired glycosyl phosphonates remained inaccessible.

Our interest in the chemistry of phosphonic acids [6] and in new carbohydrate derivatives involving the anomeric center led to the questions formulated in Scheme 1. We expected that the reaction of dialkyl phosphite anions with halonitroalkanes and 1-nitrosulfones reported by Russell and Hershberger [7] to give 1-nitrophosphonates [8] would proceed similarly with halonitroethers, which we knew to undergo $S_{RN}1$ reactions with weakly basic carbanions [9]. As tert nitroethers are smoothly reduced [10] and as halonitroethers of type **7** are easily available from the corresponding aldose oximes [4, 11], the proposed sequence seemed promising. In fact, dialkyl phosphite attacked the nitro group of the bromonitroribose **7a** (Scheme 2) [12]. At −40° under irradiation a transient blue color was observed. The main product was the phosphate **9** of the corresponding hydroximolactone **10** [4b], which was isolated as a byproduct. The blue color indicated the intermediate formation of the bromoni-

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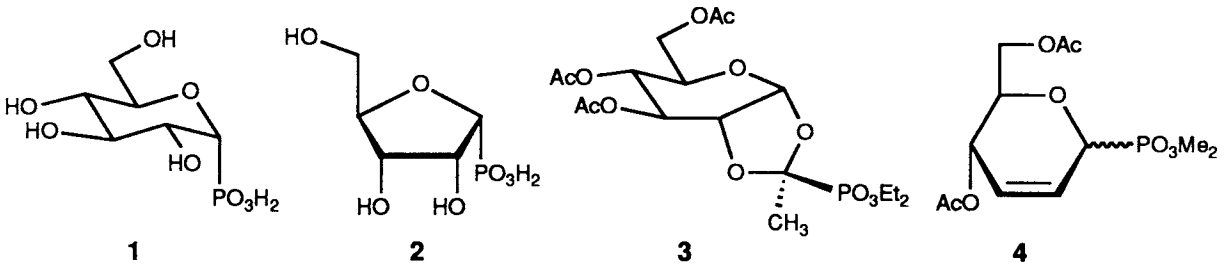
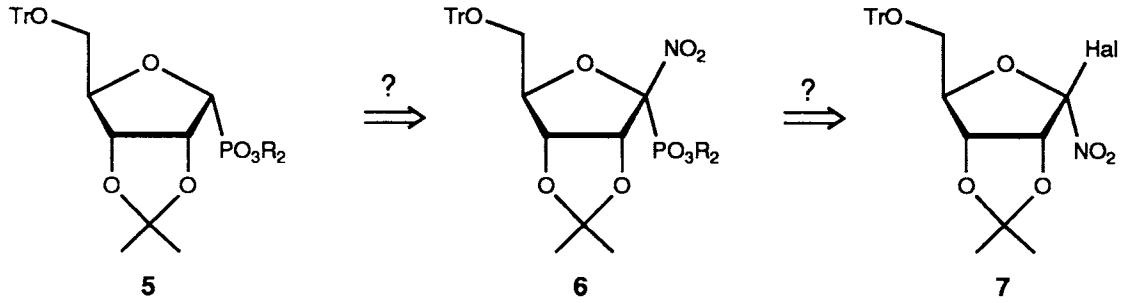
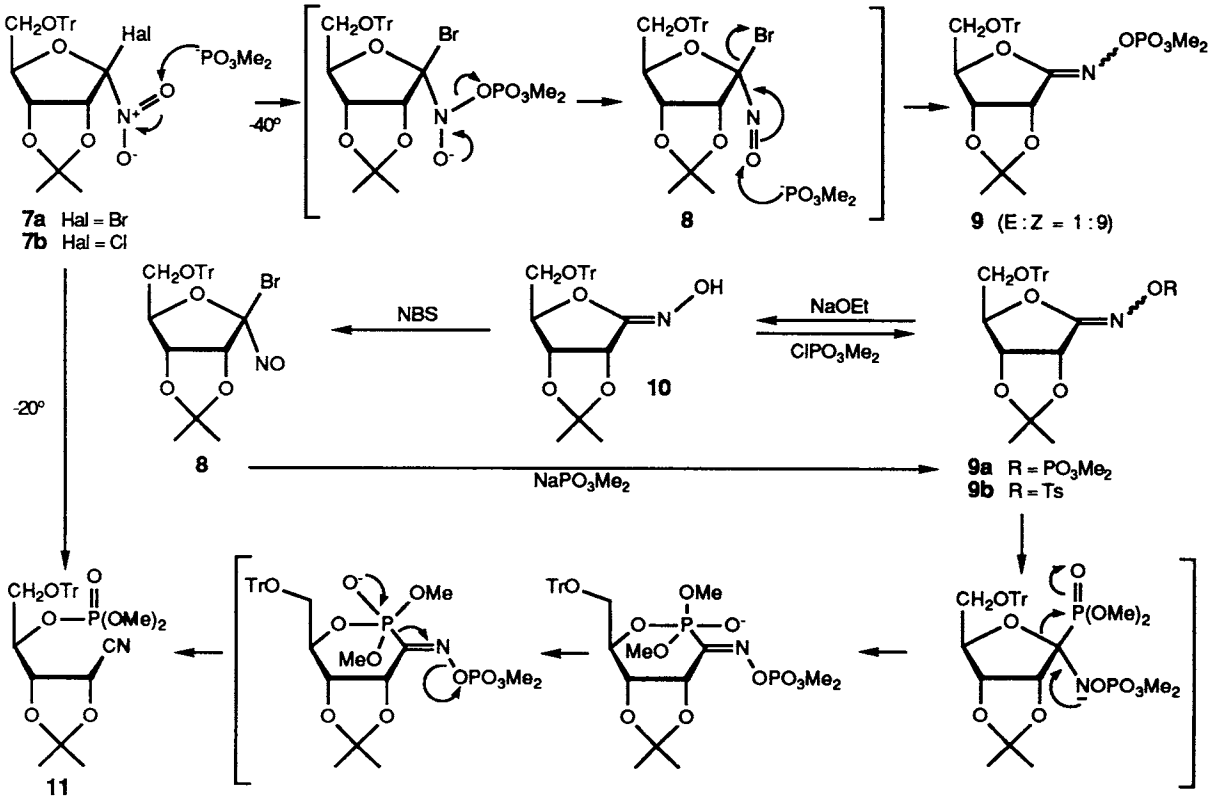


FIGURE 1 Formulae **1–4**



SCHEME 1



SCHEME 2

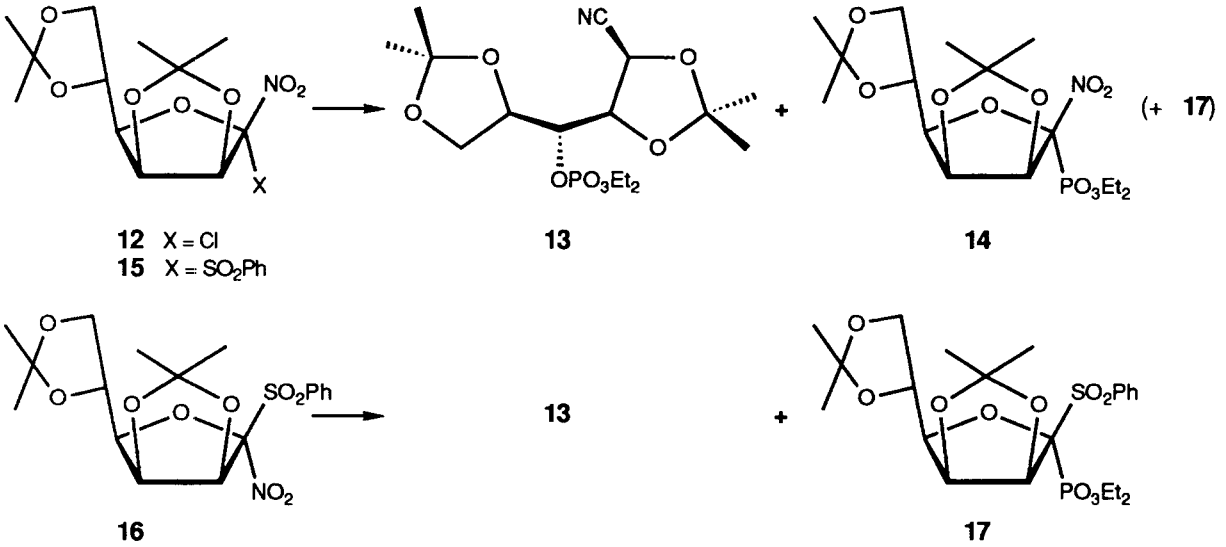
trosoether **8**, which was prepared by bromination of **10** and indeed reacted with $NaPO_3Me_2$ to form **9a**. Transesterification of **9a** gave **10** and treatment of **10** with dimethyl phosphorochloridate gave **9a**. A similar formation of an oxime phosphate had been observed by Russell et al. [7] when 2,2-dinitropropane was treated with $KOP(OR)_2$ and rationalized by assuming an attack of phosphite at the *N*-atom of one of the nitro groups.

The reaction with phosphite does not stop at the formation of **9a**. At a somewhat higher temperature, **9a** reacted with dimethyl phosphite anion and gave the nitrile **11** in good yields. The same nitrile was obtained from the tosylate **9b** and directly from **7b**. Obviously, no $S_{RN}1$-reaction had occurred, but instead a nucleophilic attack had taken place, first at the *O*-atom of the nitro group, leading to deoxygenation, followed by a second nucleophilic attack at the *O*-atom of the nitroso group and again followed by a third nucleophilic attack at C(1), leading after a 1,2-migration of the C,O bond, pseudorotation, and elimination to the nitrile.

The chloronitromannose **12** reacted similarly with $KPO(OMe)_2$. In the presence of $KPO(OEt)_2$, at −60°, however, it gave 51% of the nitrile **13** and 21% of the desired nitrophosphonate **14** (Scheme 3). That competition of nucleophilic attack and single electron transfer [6, 13] had occurred with the sterically slightly more hindered diethyl phosphite was evident from the suppression of the formation of **14** in the presence of O_2 or dinitrobenzene and by the reaction of the nitrosulfonates **15** and **16**. While the isomer **15**, possessing an endo-oriented, sterically shielded nitro group reacted with KPO_3Et_2 at −40° to give 11% of the nitrile **13** and 61% of the phosphonate, the isomer **16** with the exo-oriented nitro group gave 58% of the nitrile and 15% of **14**. In the presence of 18-crown-6, a 1:1 mixture of the nitrosulfones **15** and **16** gave 67% of the desired **14**. The nitrophosphonate **14** was reductively denitrated and deprotected to yield the corresponding phosphonate, but the route was not pursued.

The results of Paulsen's group may be interpreted as meaning that trialkyl phosphites do react with carbocations, particularly with stabilized ones, but that the way of generating such cations used by Paulsen's group—the reaction of glycosyl halides with $AgPO_3Et_2$—gave the phosphite, not a phosphonate, because of the P–Ag interaction. Generation of glycosyl cations by other means may lead to the desired phosphonates. Indeed, treatment of the *O*-benzylated glucosyl acetates **18** with a small excess of $P(OMe)_3$ in the presence of trimethylsilyl triflate at room temperature gave almost exclusively the 1,2-*cis* configurated glycosylphosphonate **19** in high yields (Scheme 4). Surprisingly, the *manno*-acetate **21** also gave the 1,2-*cis* phosphonate **22** and a similar behavior was observed in the furanose series, where the *O*-benzylated D-*ribo* and D-*arabino* glycosyl acetates yielded mainly the 1,2-*cis* configurated phosphonates **24** and **26**, respectively, in yields between 86% and 92%. Small amounts of the 1,2-*trans* products **20**, **23**, **25**, and **27** were also isolated.

The preferred formation of 1,2-*cis* phosphonates is independent of the configuration of the glycosyl acetates. It may be rationalized on the basis of the postulates that the intermediate phosphonium ions [14] equilibrate and that the C(2) alkoxy group stabilizes a cis oriented trialkoxy phosphonium center [15] (Scheme 5). Equilibration may be possible because of the weakness of the nucleophiles generated in the reaction. With $BF_3{\cdot}OEt_2$ as promoter (→BF_3—OAc), the 1,2-*trans* **27** was in-



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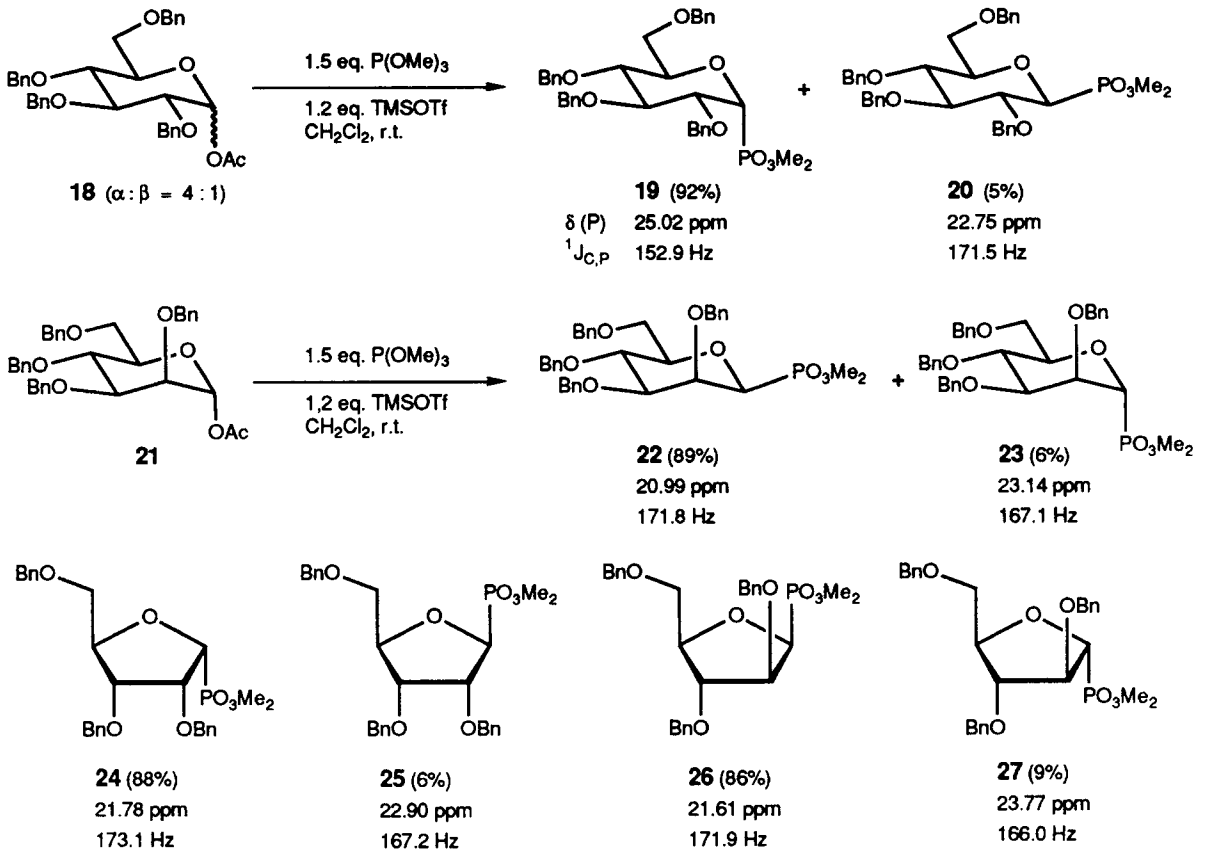

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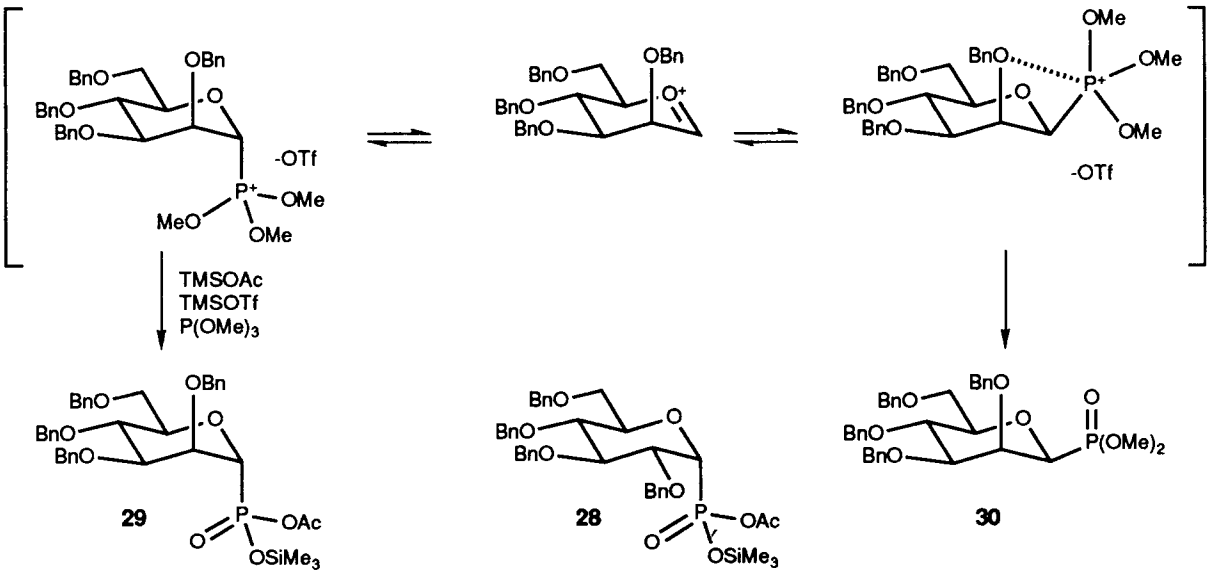


SCHEME 5

deed obtained in 19% instead of 9% ($SnCl_4$ led only to a low conversion). A modification of this procedure by Vaghefi et al. [16], who used a larger excess of $P(OMe)_3$ and TMSOTf at higher temperatures, gave the phosphonic acetic anhydride **28** from the α-D-acetate **18** [17] and the α-D-configurated *manno*-phosphonic acetic anhydride **29** from **21**. As indicated in Scheme 4, the values for $^1J_{C,P}$ and the chemical shifts (^{31}P) correspond well to those reported earlier for 2,3-dideoxy-glycosyl phosphonates [2].

If it is correct that a shift from an attempted S_N2 to a S_N1-type substitution by $P(OR)_3$ is responsible for the successful synthesis of aldose-1-phosphonates, then the factors invoked in explaining the reactivity of glycosyl donors in the synthesis of glycosides [18] should be valid also for the preparation of glycosyl phosphonates. Thus, *O*-benzylated ulose phosphates and 2-deoxyglycosyl phosphonates should be easily available, while electron withdrawing substituents, particularly at C(2) should render the synthesis more difficult. The first contention was tested in the preparation of the phosphonoyl analogue **35** (Scheme 6) [19] of fructose 2,6-bisphosphate **36**, the regulating agent of glycolysis and gluconeogenesis [20]. The reaction of the acetate **30** with trimethyl and triphenyl phosphite, respectively, proceeded smoothly and yielded mostly the expected β-D-phosphonate **31**, presumably because of the interaction in the phosphonium ion with the conformationally biased OBn group at C(3). Regioselective debenzylation, phosphonylation, and deprotection gave the desired phosphonate–phosphate **35**.

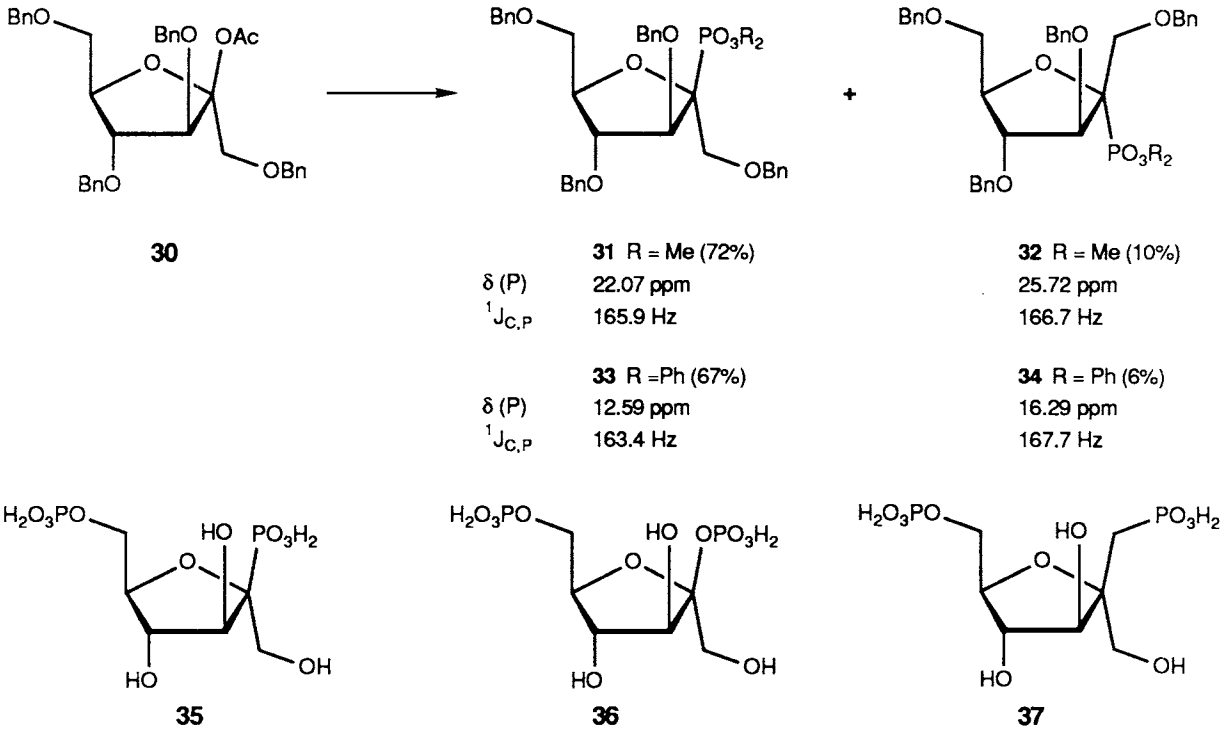
The isosteric phosphonate **37** was also prepared [21], and the two analogues allowed a reinterpretation of the role of fructose-1,6-bisphosphatase and fructose-1-phosphate phosphotransferase in higher plants [22].

The influence of the acceptor properties of protective groups became apparent in a synthesis of the phosphonate analogue of Lipid X, a biosynthetic precursor of Lipid A, that is the lipophilic moiety of bacterial lipopolysaccharides. In the course of this work (Scheme 7) [23] the azidoacetate **38** was treated with $P(OMe)_3$/TMSOTf to give only the phosphoramidate **39**, showing that a better leaving group was required. The trichloroacetimido group [24] proved suitable and the peracetylated imidate **40** reacted smoothly to the α-D-phosphonate **41** that was transformed into Lipid X and hence enzymatically into the biologically active phosphonate analogue of Lipid A [25]. The diastereoselectivity of this reaction appears to be the result of the properties of **40** as a glycosyl donor rather than being the result of a neighboring group effect of the azido function.

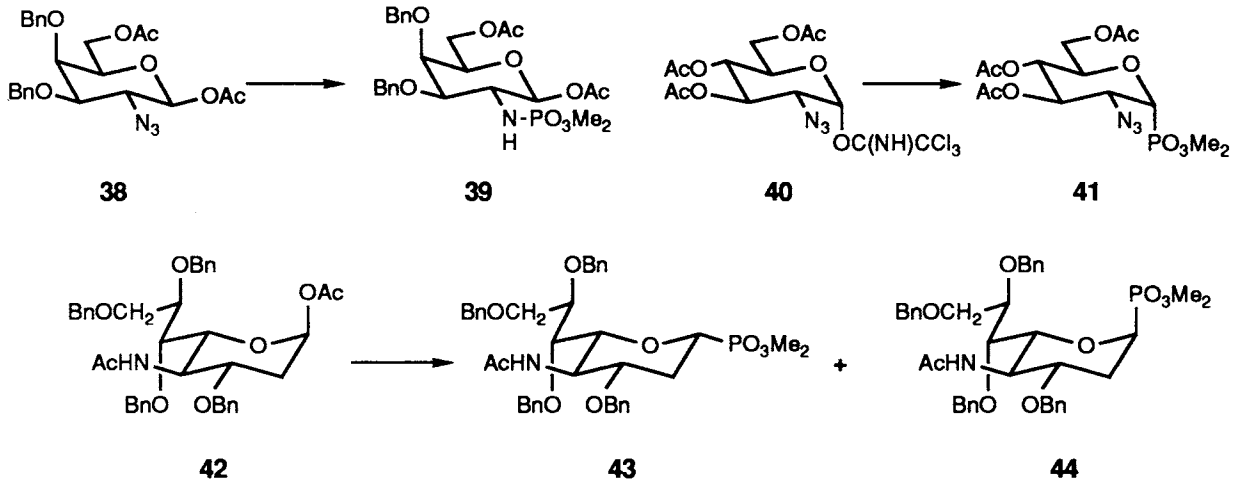
Finally, we prepared the protected phosphonate analogues **43** and **44** of *N*-acetyl-2-deoxyneuraminic acid to evaluate the inhibition of sialidases by the corresponding deprotected acids **45** and **46** (Scheme 7 and Figure 2). As expected, the axial 2-deoxyacetate **42** gave a mixture of the anomeric phosphonates, with the product of a single inversion in slight excess (68%, 1:1,3). The phosphonic acids **45** and **46** turned out to be remarkably better inhibitors than the corresponding carboxylic acids [26].

The pK'_{2HA} values of these and other glycosyl phosphonates (Figure 2) correspond fairly well to those of the α- and β-D-glucopyranosyl phosphates **47** and **48** [27].

During a synthesis of the glyoxalase I inhibitor



SCHEME 6



SCHEME 7

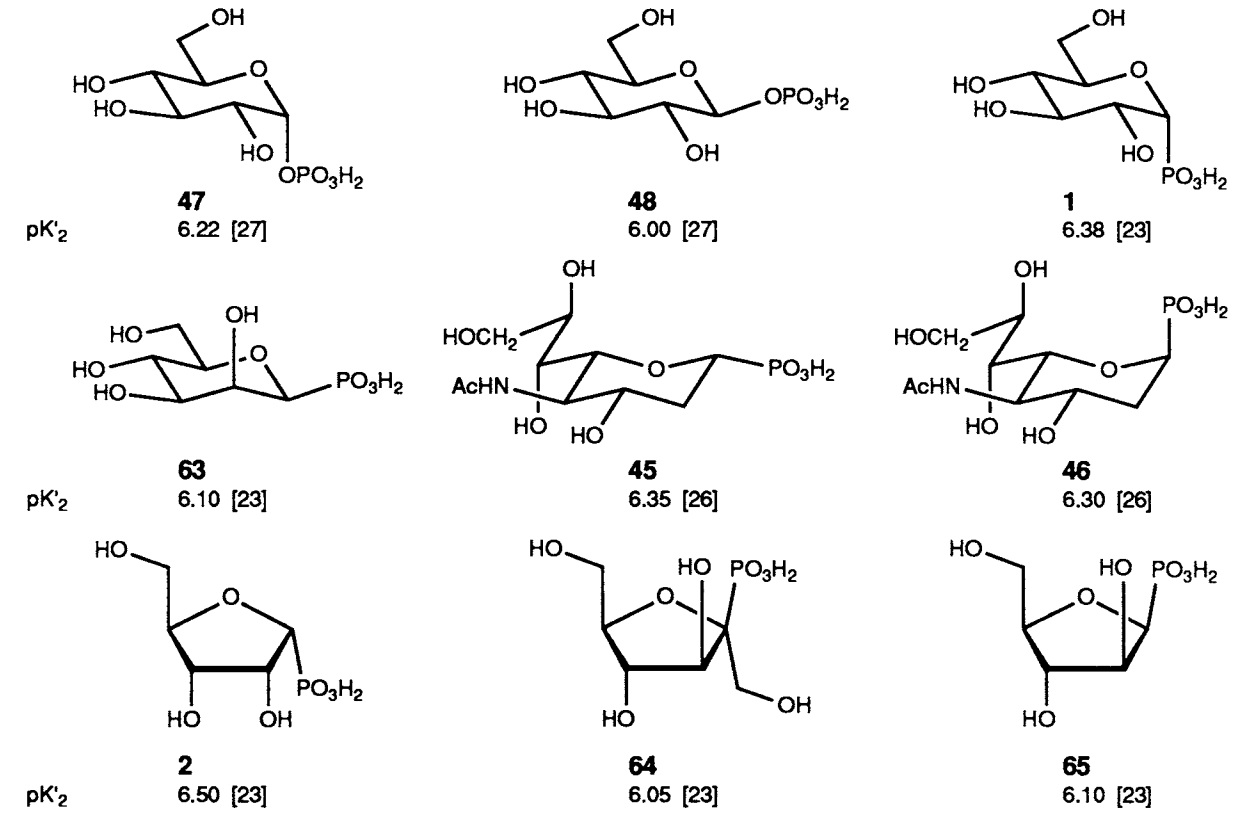
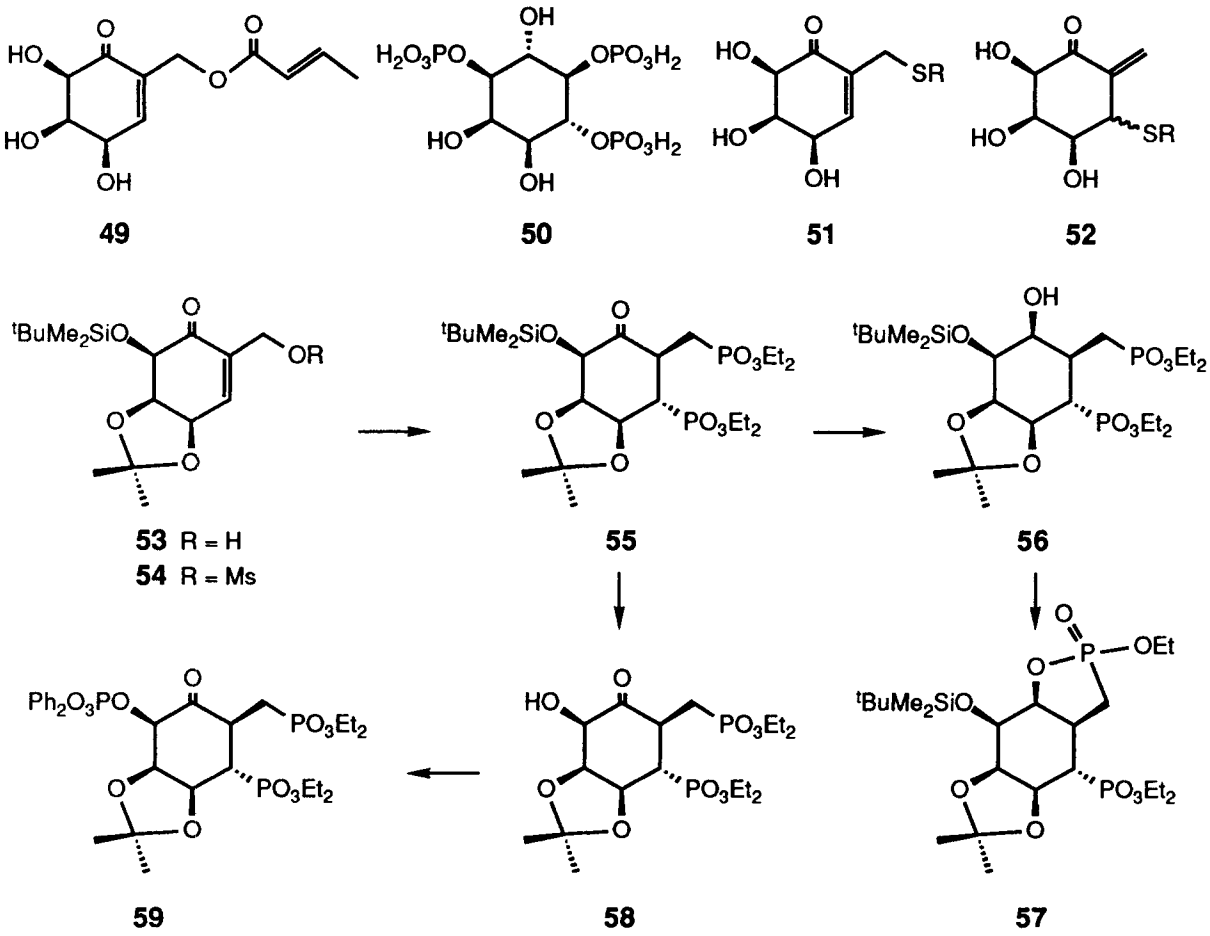


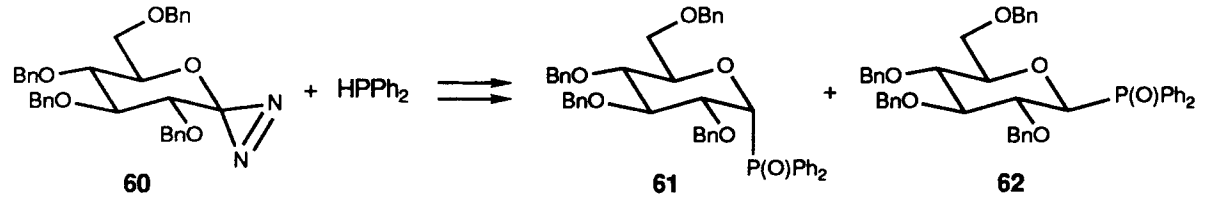
FIGURE 2 pK_2'-Values of Phosphates and Phosphonates

49 [28], we noticed a configurational overlap of **49** and myo-inositol trisphosphate **50** (Scheme 8). This inhibitor reacts with thiols to give (formal) substitution products of type **51** [29]. We speculated that **51** is formed via a sequence of two β-addition/β-elimination processes with the intermediate formation of an enone **52**. Addition of dialkyl phosphite anions to **49** and similarly substituted analogues should then lead to the bisphosphonate **55**. When the mesylate **54** was treated with $LiPO_3Et_2$, it indeed yielded 76% of the bisphosphonate **55**. Reduction of **55** gave the undesired alcohol **56**, which cyclized very easily to the phostone **57**. The ketone **55** was desilylated (→**58**) and phosphorylated to give **59**, an advanced intermediate in the synthesis of phosphonic acid analogues of dehydro-myo-inositol trisphosphate and of myo-inositol trisphosphate.



SCHEME 8

Finally, we have begun to study a new aspect of the synthesis of aldoses possessing a C(1),P bond, viz. the (formal) insertion of glycosylidene carbenes into P,H bonds. Glycosylidene carbenes are formed from glycosylidene diazirines [30] either photochemically [31] or thermally and insert well into O,H bonds. Both kinetic [32] and structural [33] evidence shows that for nucleophilic (alkoxy)alkyl carbenes a deprotonation precedes recombination of an ion pair. To the best of our knowledge, insertion of carbenes into the P,H bond is not known for nucleophilic or ambiphilic carbenes. That the tetra-*O*-benzylglucosylidene diazirine **60** [29] inserts smoothly into the P,H bond of diphenylphosphine under thermal or photochemical conditions to give a ca. 1:1 mixture of anomeric phosphines (76%), which were isolated and characterized as the corresponding phosphine oxides **61** and **62** (Scheme 9), may indicate the initial formation of an ylide or a surprisingly high base strength of the carbenes. From a preparative point of view it proved more convenient to synthesize the glycosylphosphine oxides by reaction of glycosyl acetates such as **18** with diphenylphosphinite in the presence of trimethylsilyl



SCHEME 9

triflate [34]. The yields were about the same, but the second method proceeded with a higher stereoselectivity ($\alpha:\beta = 86:14$). The relative magnitude of $^1J_{C,P}$ in **61** and **62** appears to remain a valid criterion for the equatorial or (pseudo)axial orientation of the $Ph_2P(O)$ group. Similarly, the relative chemical shift in the ^{31}P-NMR spectrum may correlate with the configuration of the anomeric center. Not unexpectedly, the α-D-anomer **61** possesses a flattened $^4C_1$ conformation (distorted towards S_5), due to the high A-value of the $Ph_2P(O)$ group and its anomeric effect [2, 35].

EXPERIMENTAL

*(4R,5R,6R)-6-*O*-[(tert-Butyl)-dimethylsilyl]-4,5-*O*-isopropylidene-2-(mesyloxymethyl)-4,5,6-trihydroxy-cyclohex-2-enone* (**54**)

A solution of **53** [28a] (3 g, 9.13 mmol) in dry CH_2Cl_2 (60 mL) was cooled to 0° under Ar. Triethylamine (1.91 mL, 13.7 mmol, 1.39 g) and then mesyl chloride (0.92 mL, 11.87 mmol, 1.36 g) were added dropwise. The mixture was stirred for 45 min. at 0°. Workup with CH_2Cl_2 and ice water, cold 10% HCl solution, and saturated $NaHCO_3$ solution followed by FC (AcOEt/Hex 1:2) afforded 3.68 g (99.1%) of **54** as a white solid, rapidly turning yellow at room temperature. R_f(AcOEt/hexane 1:1) = 0.52. $[\alpha]_D^{25}$ = +36.9° (c = 1, $CHCl_3$). Mp 64–65.5°. UV (EtOH): 232 (8091). IR ($CHCl_3$): 3031w, 2987w, 2947w, 2925m, 2896w, 2884w, 2853m, 1708s, 1467w, 1462w, 1453w, 1408w, 1380m, 1369s, 1360s, 1331m, 1296w, 1249m, 1230m, 1198m, 1170s, 1119m, 1079w, 1049s, 1004m, 998m, 970m, 950m, 934s, 921s, 904m, 888w, 834s. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.68 (m, H—C(3)); 4.88 (m, H—C(4) and H_2—C(7)); 4.71 (m, H—C(5)); 4.50 (d, J = 3.00, H—C(6)); 3.07 (s, OSO_2CH_3); 1.39 (s, CH_3 acetal); 1.33 (s, CH_3 acetal); 0.95 (s, $SiC(CH_3)_3$); 0.23 (s, $SiCH_3$); 0.10 (s, $SiCH_3$). ^{13}C-NMR ($CDCl_3$): 194.06 (s, C(1)); 142.78 (d, C(3)); 130.80 (s, C(2)); 111.58 (s, $O_2C(CH_3)_2$); 79.20 (d); 74.20 (d); 72.33 (d); 65.80 (t, C(7)); 37.47 (q, OSO_2CH_3); 27.77 (q, CH_3 acetal); 26.57 (q, CH_3 acetal); 25.77 (q, $SiC(CH_3)_3$); 18.56 (s, $SiC(CH_3)_3$); −4.30 (q, $SiCH_3$); −5.48 (q, $SiCH_3$). CI-MS: 408 (13); 407 (52, $[M + 1]^+$); 392 (11); 391 (35); 350 (20); 349 (100); 333 (14); 311 (12); 254 (24); 253 (89); 237 (23); 225 (14); 195 (17). Anal. Calcd. for $C_{17}H_{30}O_7SSi$ (406.57): C, 50.22; H, 7.44. Found: C, 50.28; H, 7.43.

*1D-(1/2,4,5,6)-4-*O*-[(tert-Butyl)-dimethylsilyl]-1-(diethylphosphonyl)-2-(diethylphosphinylmethyl)-5,6-*O*-isopropylidene-4,5,6-trihydroxycyclohexan-3-one* (**55**)

BuLi (Merck 1.62 M, 22.12 mL, 35.42 mmol) was added dropwise under Ar to a solution of diethyl phosphite (6.85 mL, 53.13 mmol, 7.34 g) in dry THF (72 mL) at −78°. The mixture was stirred for 15 min., dry acetonitrile (3.6 mL) was added and, after another 30 min., **54** (7.21 g, 17.71 mmol) in 145 mL THF. The mixture was stirred for 2 h at −78°, quenched with 10% HCl solution (35.4 mL), and allowed to warm up to room temperature. Workup with AcOEt and brine, filtration over SiO_2 (AcOEt/MeOH 9:1), and MPLC (AcOEt) gave **55**, 8.31 g (76.5%) as a pale yellow oil. R_f (AcOEt) = 0.16. $[\alpha]_D^{25}$ = −50.8° (c = 1, $CHCl_3$). IR ($CHCl_3$): 2984s, 2952m, 2928m, 2903m, 2857w, 1738m, 1600w, 1468w, 1461w, 1454w, 1441w, 1433w, 1404w, 1389m, 1382m, 1367m, 1361w, 1244s, 1201s, 1161s, 1083m, 1047s, 1026s, 969s, 940m, 893w, 871w, 849w, 837m. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.23 (d, J = 5.0, H—C(4)); 4.74 (dddd, J = 6.5, ~3.0, J(H,P) = 3.0, H—C(6)); 4.70 (dd, J = 6.5, 5.1, H—C(5)); 4.10 (m, 8H, 2P—(O—CH_2—CH_3)$_2$); 3.33 (brd, J(H,P) = 27.6, $J \leq$ 2.5, H—C(1)); 2.95 (ddddd, J(H,P) = 20.1, ~15, J = 10.5, <2.0, <2.0, H—C(2)); 2.75 (dddd, J(H,P) = 19.1, J = 15.7, ~2.8, ~2.8, H—C(7)); 2.00 (ddd, J(H,P) = 15.7, J = 15.7, 11.2, H′—C(7)); 1.34 (m, 18H, $O_2C(CH_3)_2$ and $2P(OCH_2CH_3)_2$); 0.92 (s, $SiC(CH_3)_3$); 0.15 (s, $SiCH_3$); 0.06 (s, $SiCH_3$). ^{13}C-NMR ($CDCl_3$): 205.59 (sd, J(C,P) = 17, C(3)); 108.98 (s, $O_2C(CH_3)_2$); 79.26 (d, C(4)); 75.01 (dd, J(C,P) = 2.7); 73.07 (dd, J(C,P) = 7.5); 63.20, 62.41, 61.93, 61.59 (4 td, J(C,P) = 6.8, 7.6, 6.6, 6.3, $2P(OCH_2CH_3)_2$); 40.16 (dd, J(C,P) = 3, C(2)); 38.51 (dd, J(C,P) = 138.1, C(1)); 28.1 (tdd, J(C,P) = 143, 11.5, C(7)); 26.15 (q, CH_3 acetal); 25.90 (q, $SiC(CH_3)_3$); 24.14 (q, CH_3 acetal); 18.57 (s, $SiC(CH_3)_3$); 16.46, 16.38, (2dq, $2P(OCH_2CH_3)_2$); −4.56 (q, $SiCH_3$); −5.02 (q, $SiCH_3$). ^{31}P-NMR ($CDCl_3$): 31.15 (d, J(P,P) = 1.4); 27.98 (d, J(P,P) = 1.4). CI-MS: 587 (52, $[M + 1]^+$); 511 (35); 151 (100); 117 (19); 99 (21); 89 (18); 73 (27); 61 (12). Anal. Calcd. for $C_{24}H_{48}O_{10}P_2Si$ (586.67): C, 49.13; H, 8.25; P, 10.56. Found: C, 49.29; H, 8.50; P, 10.32.

*1L-(1/2,3,4,5,6)-4-*O*-[(tert-Butyl)-dimethylsilyl]-1-(diethylphosphonyl)-6-(diethylphosphinylmethyl)-2,3-*O*-isopropylidene-2,3,4,5-tetrahydroxy-cyclohexane* (**56**)

Dry $CeCl_3$ (29.45 mg, 0.085 mmol) and Bu_4NBH_4 (211.85 mg, 0.85 mmol) were added to a solution of **55** (50 mg, 0.085 mmol) in CH_2Cl_2 (0.5 mL) under Ar. The mixture was cooled to 0°. Ethyl bromide (0.063 mL, 0.85 mmol, 0.092 mg) was added dropwise. The solution was stirred for 20 min, quenched at 0° with saturated NH_4Cl solution and extracted with $CHCl_3$. FC gave 43 mg (85.7%) of **56** as a pale yellow oil. R_f (CH_2Cl_2/AcOEt/EtOH 10:10:3) = 0.45. $[\alpha]_D^{25}$ = −2.4° (c = 1, EtOH). IR ($CHCl_3$): 3675w, 3460w (br), 2984m, 2950m, 2926m, 2900w, 2857m, 1598w, 1461w, 1453w, 1441w, 1437w, 1381w, 1372w, 1361w, 1292w, 1280w, 1237m, 1200m, 1152m, 1128m, 1104m, 1095m, 1052s, 1024s, 964s, 898w, 836m. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.28 (m, H—C(2) and H—C(3)); 4.1 (m, $2P(OCH_2CH_3)_2$ and H—C(5));

3.8 (dd, J = 4, 4, H—C(4)); 3.12 (d, J = 8, HO); 2.7 (dd, J(H,P) = 22, J = 15, H—C(7)), 2.2 (m, H—C(1) and H'—C(7)); 2.05 (m, H—C(6)); 1.50 (s, CH_3 acetal); 1.32 (m, CH_3 acetal and 2P(OCH$_2$CH_3)$_2$); 0.92 (s, SiC(CH_3)$_3$); 0.14 (s, SiCH_3); 0.13 (s, SiCH_3). ^{13}C-NMR ($CDCl_3$): 109.37 (s, O$_2$C(CH$_3$)$_2$), 76.87 (dd, J(C,P) = 13.2); 74.27 (ddd, J(C,P) = 2.75, 5.25); 70.62 (dd, J(C,P) = 13.6); 69.63 (dd, J(C,P) = 1.6); 62.30, 61.60, 61.50, 61.38 (4 td, J(C,P) = 5.5, 6.0, 6.3, 5.8, 2P(OCH$_2$CH$_3$)$_2$); 38.50 (ddd, J(C,P) = 140, 17.2, C(1)); 34.10 (d); 28.59 (q, CH$_3$ acetal); 25.71 (q, SiC(CH$_3$)$_3$ and CH$_3$ acetal); 24.50 (td, J(C,P) = 137, C(7)); 18.17 (s, SiC(CH$_3$)$_3$); 16.30 (dq, P(OCH$_2$CH$_3$)$_2$); J(C,P = 6.0, 2) −4.62 (q, SiCH$_3$); −4.74 (q, SiCH$_3$). ^{31}P-NMR ($CDCl_3$): 31.68 (d, J(P,P) = 2.54); 31.42 (d, J(P,P) = 2.54). CI-MS: 591 (9); 589 (100, [M + 1]$^+$). Anal. Calcd. for $C_{24}H_{50}O_{10}P_2Si$ (588.69): C, 48.97; H, 8.56; P, 21.05. Found: C, 48.72; H, 8.82; P, 20.79.

1D-(1/2,4,5,6)-1-(Diethylphosphonyl)-2-(diethylphosphinylmethyl)-5,6-O-isopropylidene-4,5,6-trihydroxy-cyclohexan-3-one (**58**)

N-bromosuccinimide (1 g, 5.62 mmol) was added to a solution of **55** (3 g, 5.11 mmol) in a mixture of DMSO (28.5 mol) and H_2O (1.5 mL). The solution was stirred for 18 h at room temperature. Workup (AcOEt and brine) and FC (AcOEt/acetone 2:3) afforded 1.91 g (79%) of **58**. R_f (AcOEt/acetone 2:3) = 0.19. $[\alpha]_D^{25}$ = −40° (c = 0.59, $CHCl_3$). IR ($CHCl_3$): 3535w, 2985s, 2932w, 2903w, 2866w, 1727s, 1260w, 1476w, 1450w, 1440w, 1404w, 1389m, 1382m, 1368w, 1295w, 1240s (br), 1202s, 1160m, 1152m, 1113m, 1050s, 1026s, 970s, 939m, 898w, 896w, 849w. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.98 (dd, J = 5.3, J(H, OH) = 8.2, H—C(4)); 4.80 (m, H—C(5) and H—C(6)); 4.24 (m, 2P(O—CH_2—CH$_3$)$_2$); 3.45 (ddd app. as br d, J(H,P) = 27.6, H—C(1)); 3.15 (m, H—C(2) and OH); 2.78 (m, H—C(7)); 1.84 (m, H—C(7)); 1.34 (m, 18H, O$_2$C(CH_3)$_2$ and 2P(OCH$_2$CH_3)$_2$). ^{13}C-NMR ($CDCl_3$): 207.34 (sd, J(C,P) = 17, C(3)); 108.91 (s, O$_2$C(CH$_3$)$_2$), 78.40 (d, C(4)); 72.95 (dd, J(C,P) = 2.0); 72.67 (dd, J(C,P) = 7.0); 63.08, 62.41, 61.84, 61.48 (4 td, J(C,P) = 6, 7, 7, 7, 2P(OCH$_2$CH$_3$)$_2$); 39.79 (d, C(2)); 38.86 (dd, J(C,P) = 137, C(7)); 27.45 (tdd, J(C,P) = 145, 11, C(7)); 25.82 (q, CH$_3$ acetal); 24.01 (q, CH$_3$ acetal); 16.22, 16.17 (2dq, J(C,P) = 7.0, 5.0, 2P(OCH$_2$CH$_3$)$_2$). ^{31}P-NMR ($CDCl_3$): 30.26 (s); 26.98 (s). CI-MS: 475 (5); 474 (23); 473 (100, [M + 1]$^+$); 397 (17). Anal. Calcd. for $C_{18}H_{34}O_{10}P_2$ (472.41): C, 45.76; H, 7.25; P, 13.11. Found: C, 45.50; H, 7.51; P, 12.92.

1D-(1/2,4,5,6)-1-(Diethylphosphonyl)-4-(diphenoxyphosphoryl)-2-(diethylphosphinylmethyl)-5,6-O-isopropylidene-4,5,6-trihydroxy-cyclohexan-3-one (**59**)

Chlorodiphenylphosphate (0.263 mL, 1.27 mmol, 341.2 mg) was added dropwise to **58** (220 mg, 0.423 mmol) in pyridine (1 mL) at 0° under Ar. The mixture was stirred for 80 min. Workup with CH_2Cl_2, saturated aqueous $CuSO_4$, saturated $NaHCO_3$, and brine. FC (SiO_2 containing 1% $NaHCO_3$, acetone/hexane 1:1) gave 232.5 mg of **59** (78%). R_f (acetone/hexane 3:2) = 0.59. IR ($CHCl_3$): 3037w, 2985s, 2932w, 2905w, 2868w, 1794w, 1744m, 1590m, 1487m, 1453w, 1441w, 1407w, 1382m, 1369w, 1283s, 1245s, 1182s, 1160s, 1126m, 1115m, 1092s, 1083s, 1043s, 1024s, 1012s, 968s, 902w, 850w. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.15 (m, 10 arom. H); 5.79 (dd, J(H,P) = 8.3, J = 5.5, H—C(4)); 4.78 (t, J = 6.0, 6.0, H—C(5)); 4.70 (quint, J = 5.9, ~3.0, ~3.0, H—C(6)); 4.08 (m, 2P(OCH_2CH$_3$)$_2$); 3.38 (ddd app. as br d, J(H,P) = 27.7, H—C(1)); 3.04 (m, H—C(2)); 2.69 (dddd, J(H,P) = 20.3, ~2.5, J = 15.5, ~2.5, H—C(7)) 1.86 (ddd app. as dt, J(H,P) = 15.6, J = 15.6, 11.3, H'—C(7)); 1.33 (m, O$_2$C(CH_3)$_2$ and 2P(OCH$_2$CH_3)$_2$). ^{13}C-NMR ($CDCl_3$): 199.9 (sd, J(C,P) = 14.3, C(3)); 150.3 (sd, J(C,P) = 8.2, arom. C—O—P); 150.1 (sd, J(C,P) = 7.2, arom. C—O—P); 129.3 (d, arom.); 125.1 (d, arom.); 120.2 (d, arom.); 120.1 (d, arom.); 109.4 (s, O$_2$C(CH$_3$)$_2$); 78.5 (dd, J(C,P) = 3.4); 77.2 (dd, J(C,P) = 4.5); 72.9 (dd, J(C,P) = 6.8); 63.1, 62.6, 61.8, 61.5 (4 td, J(C,P) = 6.9, 6.5, 6.8, 6.0, 2P(OCH$_2$CH$_3$)$_2$); 40.0 (d, C(2)); 37.8 (dd, J(C,P) = 138, C(1)); 27.3 (tdd, J(C,P) = 145.3, 10.7, C(7)); 25.8 (q, CH$_3$ acetal); 24.1 (q, CH$_3$ acetal); 16.1, 16.06, 16.02, 15.9 (4q, 2P(OCH$_2$CH$_3$)$_2$). ^{31}P-NMR: 29.6 (s); 25.9 (s); −12.2 (s).

1L-(1/2,3,4,5,6)-5,6^2-Anhydro-4-O-[(tert-butyl)-dimethylsilyl]-1-(diethylphosphonyl)-6-(ethylphosphinylmethyl)-2,3-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclohexane (**57**)

$NaBH_4$ (38.7 mg, 1.02 mmol) was added at 0° to a solution of **55** (50 mg, 0.085 mmol) in *i*-propanol (0.5 mL) under Ar. The solution was stirred for 1 h. The mixture was dissolved in AcOEt and excess $NaBH_4$ was destroyed with saturated aqueous NH_4Cl. Usual workup and FC afforded 29 mg (57.8%) of **57** as a white solid. An analytical sample was recrystallized in hexane giving white, thin needles. R_f (CH_2Cl_2/AcOEt/EtOH 10:10:3) = 0.33. Mp 155–156°. $[\alpha]_D^{25}$ = +13° (c = 1, $CHCl_3$). IR ($CHCl_3$): 3665w, 3410w (br), 2981s, 2949m, 2925m, 2900m, 2852m, 2465w, 1600w, 1469w, 1458w, 1442w, 1438w, 1409w, 1389m, 1381m, 1374m, 1361w, 1352w, 1327w, 1290w, 1240s, 1200s, 1161m, 1124m, 1094s, 1062s, 1046s, 1012s, 972s, 878s, 865s, 838m. ^{1}H-NMR (400 MHz, $CDCl_3$): '4.33 (dd, J = 4, 2, H—C(4)); 4.2 (m, 3POCH_2CH$_3$, H—C(2) and H—C(5)); 3.98 (ddd, J(H,P) = 2.7, J = 8, 4, H—C(3)); 2.95 (m, H—C(6)); 2.55 (m, H—C(1) and H—C(7)); 1.77 (ddd, J(H,P) = 18, J = 14, 12.5, H'—C(7)); 1.50 ((s, CH_3 acetal), 1.35 (m, 12H, CH_3 acetal and 3POCH$_2$CH_3); 0.92 (s, SiC(CH_3)$_3$); 0.1 (s, Si(CH_3)$_2$). ^{13}C-NMR ($CDCl_3$): 109.31 (s, O$_2$C(CH$_3$)$_2$); 75.80 (ddd, J(C,P) = 15.1, 8.6, C(5)); 73.69 (dd, J(C,P) = 14.2); 72.69 (dd, J(C,P) = 6.6); 70.12 (dd, J(C,P) = 3.0); 63.03, 62.25, 61.71 (3 td,

J(C,P) = 5.0, 6.5, 5.5, 3POCH$_2$CH$_3$); 42.22 (ddd, J(C,P) = 143.8, 16.9, C(1)); 32.61 (ddd, J(C,P) = 2, 2, C(6)); 27.20 (td, J(C,P) = 123.2, C(7)); 26.07 (q, SiC(CH$_3$)$_3$); 23.91 (q, CH$_3$ acetal); 17.85 (s, SiC(CH$_3$)$_3$); 16.38, 16.27, 16.20 (3dq, J(C,P) = 6.3, 6.9, 6.7, 3) (POCH$_2$CH$_3$); 16.24 (q, CH$_3$ acetal); −4.18 (q, SiCH$_3$); −4.95 (q, SiCH$_3$). ^{31}P-NMR ($CDCl_3$): 46.87 (s); 28.73 (s). CI-MS: 545 (11), 544 (34), 543 (100, [M + 1]$^+$). Anal. Calcd. for $C_{22}H_{44}O_9P_2Si$ (542.62): C, 48.70; H, 8.17; P, 11.42. Found: C, 48.47; H, 8.34; P, 11.25.

Diphenyl(2,3,4,6-tetra-O-benzyl)-α and β-D-glucopyranosyl) phosphine oxide **61** *and* **62**

A. Under N_2, 44 μl (25 mmol) $HPPh_2$ were added to a solution of 115 mg (0.20 mmol) **60** [30], in 2 mL degassed CH_2Cl_2 at 0°. After 6 h at room temperature, 1 mL of AcOH and 0.5 mL of 35% H_2O_2 were added. After 12 h, aqueous workup (5% $NaHCO_3$, CH_2Cl_2) and FC (toluene/AcOEt 7:3) gave 115 mg of a 55:45 mixture of **61** and **62**.

B. Under N_2, 450 μl (2.00 mmol) of Ph_2POMe and 350 μl (1.70 mmol) of TMSOTf were added to a solution of 880 mg (1.51 mmol) of **18** in 3 mL CH_2Cl_2 at 0°. After stirring the mixture for 6 h at room temperature, further 200 μl of Ph_2POMe and 150 μl of TMSOTf were added. The mixture was quenched after 2 days with 1 mL of saturated $NaHCO_3$ solution. Normal aqueous workup followed by FC (as above) gave 842 mg (76.9%) of a 86:14 mixture (by NMR) of **61** and **62**.

Data of **61**: Mp 141–142° (CH_2Cl_2/hexane). R_f 0.34 (toluene/AcOEt 7:3). $[\alpha]_D^{25}$ = +44.0° (c = 1.02, $CHCl_3$). IR (nujol): 3090w, 3060m, 3030m, 2950(sh); 2920s, 2850s, 1490w, 1460(sh), 1450m, 1440m, 1375m, 1365(sh); 1335w, 1240w, 1205w, 1170m, 1120m, 1090m, 1080m, 1070m, 1060m, 1040m, 1025m, 1005(sh), 995m, 980w, 950w, 920w, 900w, 850w, 760w, 735m, 7805s, 695s. ^{1}H-NMR (400 MHz, $CDCl_3$): 800–6.80 (m, 30 arom. H); 4.88–4.22 (4 AB, CH_2Ph), 4.91 (d, J = 5.9, H—C(1)); 4.61 (t, J = 7.3, H—C(3)); 4.17 (ddd, J = 5.9, 7.4, J(C,P) = 17.8, H—C(2)); 4.06 (m, H—C(5)); 3.68 (dd, J = 7.2, 9.7, H—C(4)); 3.52 (dd, J = 3.8, 10.7, H_A—C(6)); 3.21 (dd, J = 2.1, 10.7, H_B—C(6)). ^{13}C-NMR (50 MHz, $CDCl_3$): 138.42 (s); 138.38 (s); 137.95 (s); 137.46 (s); 134.67 (s); 132.78 (s); 131.80–130.80 (m); 128.60–127.40 (m); 80.76 (dd, J(C,P) = 2.5); 78.70 (d); 77.55 (d); 74.95 (d); 74.35 (t); 74.21 (dd, J(C,P) = 79.5, C(1)); 73.57 (t); 73.32 (t); 73.08 (t); 68.66 (t). ^{31}P-NMR (81 MHz, $CDCl_3$): 23.27. Anal. Calcd. for $C_{46}H_{45}O_6P$ (724.73): C, 76.23; H, 6.26; P, 4.27. Found: C, 76.12; H, 6.41; P, 4.15.

Data of **62**: Mp 150–151° (CH_2Cl_2/hexane). R_f 0.27 (toluene/AcOEt 7:3). $[\alpha]_D^{25}$ = +14.7° (c = 1.04, $CHCl_3$). IR (nujol): 3060w, 3040w, 2920(br), 1500w, 1460m, 1440m, 1380m, 1360(sh), 1190w, 1180w, 1150, 1120w, 1095(br), 1075(sh), 1030w, 750w, 735w, 720w, 695m. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.00–7.00 (m, 30 arom. H); 4.90–4.25 (4 AB, CH_2Ph); 4.24 (dd, J = 10.1, J(1,P) = 2.5, H—C(1)); 3.97 (q, J = 9.6, H—C(2)); 3.78 (t, = 8.9, H—C(3)); 3.57 (m, H—C(4) and H—C(6)); 3.45 (m, H—C(5)). ^{13}C-NMR (50 MHz, $CDCl_3$): 138.32 (s); 138.23 (s); 137.93 (s); 137.87 (s); 132.07–131.20 (m); 129.84–127.30 (m); 87.43 (dd, J(C,P) = 12.9); 81.06 (dd, J(C,P) = 13.1); 78.26 (dd, J(C,P) = 89.7, C(1)); 75.06 (t); 74.71 (t); 73.29 (t); 68.93 (t). ^{31}P-NMR (81 MHz, $CDCl_3$): 21.96. Anal. Calcd. for $C_{46}H_{45}O_6P$ (724.73): C, 76.23; H, 6.26; P, 4.27. Found: C, 75.92; H, 6.42; P, 4.01.

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REFERENCES AND FOOTNOTES

[1] R. Engel, *Chem. Ber., 77,* 1977, 349.
[2] J. Thiem, B. Meyer, H. Paulsen, *Chem. Ber., 111,* 1978, 3325.
[3] M. Mikolajczyk, *Pure & Appl. Chem., 59,* 1987, 983.
[4] [a] B. Aebischer, A. Vasella, H. P. Weber, *Helv. Chim. Acta, 65,* 1982, 621; [b] D. Beer, A. Vasella, *Helv. Chim. Acta, 68,* 1985, 2254.
[5] Isosteric phosphonate analogues of aldose-1-phosphates and ulose-2-phosphates are known: [a] M. Chmielewski, J. N. BeMiller, D. P. Ceretti, *Carbohydr. Res., 97,* 1981, Cl; [b] F. Nicotra, L. Panza, F. Ronchetti, *Tetrahedron Lett., 25,* 1984, 5937; [c] R. B. Meyer, T. E. Stone, P. K. Jesthi, *J. Med. Chem., 27,* 1984, 1095; [d] B. E. Maryanoff, A. B. Reitz, S. O. Nortey, *Tetrahedron, 44,* 1988, 3093; [e] S. Ayral-Kaloustian, V. G. DeVries, M. B. Floyd Jr., *Abstr., B65,* XIVth Intern. Carbohydr. Symp. Stockholm, 14.-19.8.1988; [f] R. Meuwly, A. Vasella, *Helv. Chim. Acta, 69,* 1986, 751; [g] R. Julina, A. Vasella, *Helv. Chim. Acta, 68,* 1985, 819.
[6] R. Huber, A. Vasella, *Tetrahedron, 46,* 1990, 33.
[7] [a] G. A. Russell, J. Hershberger, *Chem. Commun.,* 1980, 216; [b] G. A. Russell, F. Ros, J. Hershberger, H. Tashtoush, *J. Org. Chem., 47,* 1982, 1480.
[8] K. A. Petrov, V. A. Chanzov, L. V. Pastukhova, W. N. Bogdanov, *Zh. Obshch. Khim., 46,* 1976, 1246.
[9] B. Aebischer, R. Meuwly, A. Vasella, *Helv. Chim. Acta, 67,* 1984, 2236.
[10] F. Baumberger, A. Vasella, *Helv. Chim. Acta, 60,* 1983, 2210.
[11] R. Meuwly, A. Vasella, *Helv. Chim. Acta, 67,* 1984, 1568.
[12] R. Meuwly, A. Vasella, *Helv. Chim. Acta, 68,* 1985, 997.
[13] [a] S. I. Al-Khalil, R. W. Bowman, *Tetrahedron Lett., 25,* 1984, 461; [b] W. R. Bowman, G. D. Richardson, *Tetrahedron Lett., 22,* 1981, 1551; [c] L. Eberson, S. S. Shaik, *J. Am. Chem. Soc., 112,* 1990, 4484.
[14] J. Thiem, M. Günther, H. Paulsen, *Chem. Ber., 108,* 1975, 2279.
[15] Such interactions have been postulated in other cases. See e.g. H. Kunz, P. Schmidt, *Liebigs Ann. Chem.,* 1982, 1245.

[16] M. M. Vaghefi, R. J. Bernacki, N. K. Dalley, B. E. Wilson, R. K. Robins, *J. Med. Chem., 30,* 1987, 1383.
[17] These authors postulate a double inversion of configuration for the formation of **28** from α-D **18** but did not comment on the formation of **29** from **21**. At a higher temperature, preferred axial attack of $P(OMe)_3$ and relatively rapid dealkylation by excess TMSOTf may explain the formation of **28** and **29** in a satisfactory way.
[18] H. Paulsen, *Angew. Chem., 94,* 1982, 184.
[19] A. Dessinges, A. Vasella, *Carbohydr. Res., 174,* 1988, 47.
[20] J. Preiss, *Trends Biochem. Sci., 9,* 1984, 24; C. Cseke, A. Balogh, J. H. Wong, B. B. Buchanan, M. Stitt, B. Herzog, H. W. Heldt, *Trends Biochem. Sci., 3,* 1984, 533 and lit. quoted there.
[21] R. Meuwly, A. Vasella, *Helv. Chim. Acta, 69,* 1986, 751.
[22] M. Stitt, A. Vasella, *FEBS Letters, 228,* 1988, 60.
[23] K. Briner, A. Vasella, *Helv. Chim. Acta, 70,* 1987, 1341.
[24] R. R. Schmidt, *Angew. Chem., 98,* 1986, 213.
[25] D. Scholz, K. Bednarik, W. Neruda, E. Janzek, H. Loibner, K. Briner, A. Vasella, unpublished work.
[26] A. Vasella, K. Wallimann, *Helv. Chim. Acta,* in press.
[27] E. Behrman, *Carbohydr. Res., 36,* 1974, 231.
[28] [a] S. Mirza, L.-P. Molleyres, A. Vasella, *Helv. Chim. Acta, 68,* 1985, 988; [b] K. T. Douglas, S. Shinkai, *Angew. Chem. int. edn., 24,* 1985, 31.
[29] H. Chimura, H. Nakamura, T. Takita, T. Takenchi, H. Umezawa, K. Kato, S. Saito, T. Tomisawa, Y. Iitaka, *J. Antib., 28,* 1975, 743.
[30] K. Briner, A. Vasella, *Helv. Chim. Acta, 72,* 1989, 1371.
[31] A. Vasella, K. Briner, N. Soundararajan, M. S. Platz, unpublished work.
[32] X. Du, K. Fan, J. L. Goodman, M. A. Kesselmayer, K. Krogh-Jespersen, J. A. La Villa, R. A. Moss, Sh. Shen, R. S. Sheridan, *J. Am. Chem. Soc., 112,* 1990, 1920.
[33] K. Briner, A. Vasella, unpublished work.
[34] For similar reactions, see M. Mikolajczyk, P. Graczyk, M. W. Wieczorek, G. Bujacz, Y. T. Struchkov, M. Y. Antipin, *J. Org. Chem., 53,* 1988, 3609 and lit. cit.
[35] [a] E. Juaristi, N. A. López-Núñez, R. S. Glass, A. Petsom, R. O. Hutchins, J. P. Stercho, *J. Org. Chem., 51,* 1986, 1357; [b] E. Juaristi, A. Glores-Vela, V. A. Labastida, *J. Org. Chem., 54,* 1989, 5191.