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SYNTHESIS OF *C*-ARABINOFURANOSYL COMPOUNDS. PHOSPHONATE AND CARBOXYLATE ISOSTERES OF D-ARABINOSE 1,5-BISPHOSPHATE*

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ABSTRACT

Electrophile-mediated cyclization of 3,4,6-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol with *N*-bromosuccinimide yielded primarily 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-bromo-1-deoxy-D-glucitol (**10**). This apparently kinetically controlled reaction was of key importance in the successful synthesis of a phosphonate analog of β-D-arabinose 1,5-bisphosphate (**1**), namely, 2,5-anhydro-1-deoxy-1-phosphono-D-glucitol 6-phosphate (**4**), with high stereoselectivity. By contrast, condensation of the sodium salt of tetraethyl methylenediphosphonate and 2,3,5-tri-*O*-benzyl-D-arabinose (**7**) gave a phosphonate compound slightly enriched in the 2,5-anhydro-D-mannitol (α) isomer. In the Wittig–Michael reaction of stabilized phosphoranes with **7**, the α isomer preponderated. Since equilibration of methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-D-*glycero*-D-*galacto*- (**33**) and -D-*gulo*-heptonate (**34**) (5:1) resulted in a 1:1 α:β ratio, the preference for the 2,5-anhydro-D-mannitol (α) isomer probably reflects a kinetic bias. The carbomethoxy anomers were converted independently into the α and β carboxylate isosteres (**5** and **6**, respectively) of D-arabinose 1,5-diphosphate. Empirical force field calculations (MMP2) and n.m.r. experiments were conducted on the pairs of diastereomers **9** and **10**, and **33** and **34**. The calculations predict that the α and β anomers of each pair have similar energies, differing by only 2.1 kJ/mol. Compounds **4**, **5**, and **6** were evaluated for biological activity.

INTRODUCTION

Research into the synthesis and biological properties of *C*-glycosyl com-

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*A preliminary communication has been published (see ref. 8).
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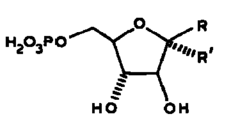
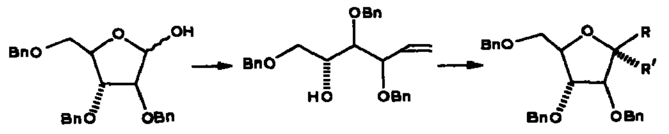


1 R = H, R' = OPO_3H_2
2 R = OPO_3H_2, R' = H
3 R = OPO_3H_2, R' = CH_2OH
4 R = $CH_2PO_3H_2$, R' = H
5 R = H, R' = CH_2CO_2H
6 R = CH_2CO_2H, R' = H



7

8

9 R = H, R' = CH_2Br
10 R = CH_2Br, R' = H
11 R = H, R' = CH_2HgBr
12 R = CH_2HgBr, R' = H

pounds has expanded over the last decade[1,2]. Our interest in this area arose out of a desire to obtain stable analogs of D-arabinose 1,5-bisphosphate[3] (**1**), the β anomer* of which (**2**) retains a significant portion of the biological activity of β-D-fructose 2,6-diphosphate[3,4] (**3**). Compounds **2** and **3** are activators of 6-phosphofructo-1-kinase (EC 2.7.1.11) and inhibitors of fructose 1,6-bisphosphatase (EC 3.1.3.11), important enzymes in the metabolism of D-glucose. Since the anomeric phosphate group in **2** and **3** is very prone to hydrolysis, we decided to synthesize the phosphonate and carboxylate analogs, **4–6**, as stable isosteres (for examples of the synthesis and use of phosphonates as phosphate isosteres, see refs. 5–8).

In our synthetic studies, we have prepared compounds highly or totally enriched in either *C*-β- or -α-D-arabinofuranosyl structures. Our preliminary communication[8] briefly described the synthesis of **4** in a stereoselective manner. Herein, we report the full details of this synthesis, as well as alternative approaches to the synthesis of **4** and the synthesis of the carboxylate isosteres **5** and **6**. Additionally, we have performed empirical-force-field (EFF) calculations and n.m.r. experiments on several of the *C*-D-arabinofuranosyl compounds.

RESULTS AND DISCUSSION

Phosphonate synthesis. — Condensation of the protected D-arabinose derivative **7** with 2.3 mol equiv. of methylenetriphenylphosphorane in oxolane (THF) gave the alkenol **8** in 68% yield[8]. Treatment of **8** with *N*-bromosuccinimide afforded, almost quantitatively, an 11:89 mixture of the α and β anomers **9** and **10**, respectively, which were not separable by t.l.c.[8,9]. As we have already reported[8], a similar cyclization of **8** with mercuric acetate[10] produced the mercurials **11** and **12** in an 11:89 ratio (after exchange to the bromide).

A related sequence, involving methylenetriphenylphosphorane and 2,3,4,6-tetra-*O*-benzyl-D-glucose, has been reported by Pougny *et al.*[10]. In their example,

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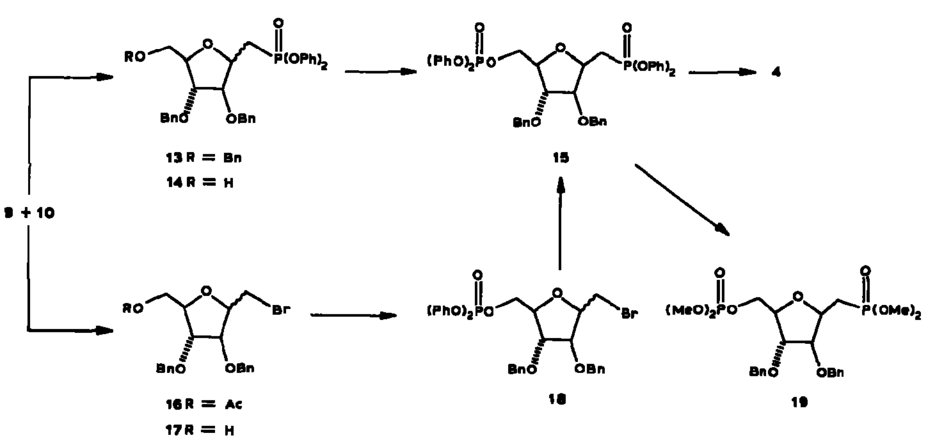
*Throughout the paper, the term "anomer" is used in the same context for *C*-glycosyl compounds as for carbohydrates. In the Experimental section where the 2,5-anhydro-D-hexitol nomenclature is used, the α and β anomers correspond to the D-*manno* and D-*gluco* epimers, respectively.

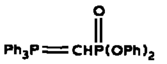


electrophile-mediated cyclization of a homologous alkenol with mercuric acetate led to a single (α) anomer. The importance of this result is that the cyclization proceeded in a manner *cis* to the proximal (originally allylic) benzyl ether substituent, an effect Pougny *et al.*[10] attributed to through-space coordination between the proximal benzyl ether and the electrophile[10,11]. We have suggested[8] that this stereoselectivity may be due to the through-bond *electronic* influence of the proximal benzyl ether, such as predicted by the "inside alkoxy" effect[12]. Several research groups have obtained similar stereochemical results for haloetherifications of allylic ethers and alcohols[13], as well as kinetic halolactonization reactions[14,15] (especially in the presence of allylic oxygen substituents).

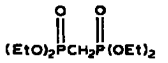
The 11:89 mixture of **9** and **10** was transformed into **4** as follows[8]. An Arbusov reaction with diphenylethyl phosphite[16,17] gave the diphenyl phosphonate **13**. On removal of the benzyl ether groups by catalytic hydrogenolysis with palladium and hydrogen or transfer hydrogenation, considerable decomposition took place. The diphenylphosphoryl ester group of the phosphonate may have cyclized onto the free adjacent hydroxyl group in a side-reaction following debenzylation, a problem observed previously in a related system[18]. Consequently, we sought to prepare alcohol **14** from **13**. Selective deprotection with a pyridine-poisoned catalyst[3] gave a low yield of **14**. Alternatively, we treated **13** carefully with one mol equiv. of iodotrimethylsilane[19] to furnish **14** in 25–40% yield. This compound was phosphorylated conventionally to give **15** which, fortunately, is a solid, and crystallization supplied material consisting solely of the β anomer (as determined by ^{13}C n.m.r. spectrometry[8,20]). The overall yield of **15** from the mixture of **9** and **10** was around an unacceptably low 10%. Thus, we developed an alternative synthesis in which the low-yielding, selective debenzylation step (*e.g.*, **13** to **14**) was performed first. Acid-catalyzed acetolysis[22] of an 11:89 mixture of **9** and **10** produced the monoacetate **16** in 86% yield. Deacetylation gave **17**, phosphorylation of which produced the phosphate **18**, also in high yield (60% from **16**). The Arbusov reaction proceeded in the same manner as mentioned earlier, giving desired **15** in ~40%

yield. By use of this route, the total yield of **15** from the mixture of **9** and **10** was ~20%.

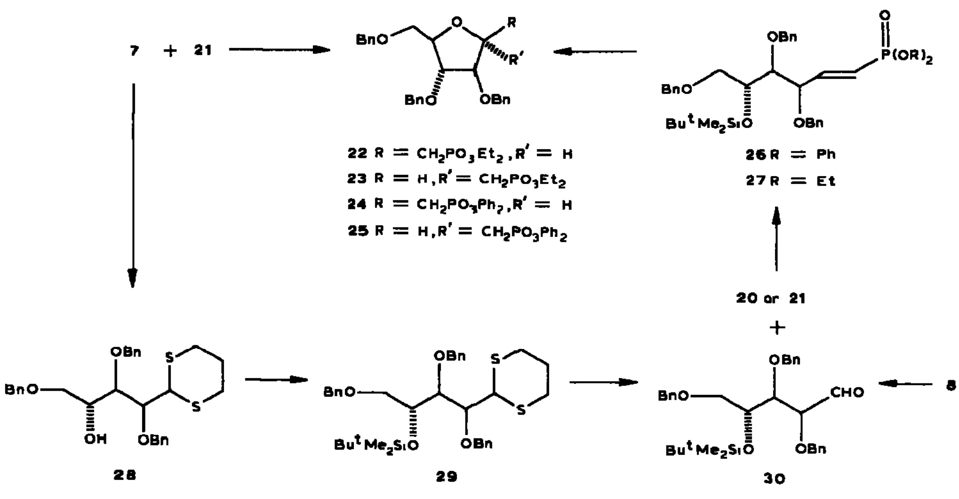
Deprotection of **15** proved to be more difficult than anticipated, thus, ironically, it was a major challenge in the synthesis. Lithium–ammonia reduction, which had been employed effectively by us in the synthesis of anomeric phosphates[3], resulted in extensive decomposition. Attempted hydrolysis of the phenyl phosphoryl esters also caused decomposition, and hydrogenolysis in the presence of platinum not only removed the four phenyl groups, but also led to monodebenzylation and reduction of one of the benzyl ether groups into a cyclohexylmethyl group. Initial debenzylation with 10% palladium-on-carbon proceeded slowly, and it appeared that cyclization to a *cis*-fused 1,2-oxaphospholane had again occurred, similar to the observation made in the hydrogenolysis of **13** (see above)[18]. Transfer hydrogenation (cyclohexene) went slowly as well, and the desired product was obtained in only a low yield (~10–20%). We explored the use of fluoride ion[23], which is a good nucleophile, for promoting phosphoryl ester hydrolysis. The phenyl esters were removed with cesium or tetrabutylammonium fluoride in oxolane, but all of the resultant fluorine–phosphorus bonds could not be efficiently hydrolyzed, possibly owing to the greater stability of the second P–F bond on each phosphorus atom[24]. However, conversion of **15** to the tetramethyl ester **19** in 65% yield was successfully achieved by use of cesium fluoride in refluxing methanol. The fluoride ion was essential, as **15** remained unchanged when heated in refluxing methanol. Compound **19** was stereochemically pure (β-D anomer) as shown by ^{13}C-n.m.r. spectroscopy. Hydrogenolysis of **19** with 10% palladium-on-carbon removed the


$Ph_3P{=}CH\overset{O}{\overset{\|}{P}}(OPh)_2$

20


$(EtO)_2\overset{O}{\overset{\|}{P}}CH_2\overset{O}{\overset{\|}{P}}(OEt)_2$

21



benzyl ethers, but proceeded with cyclization of the phosphonyl group onto the adjacent hydroxyl group (^{1}H-n.m.r. and mass spectral evidence). We had intended to transform **19** into **4** with iodotrimethylsilane[19]; however, this was preempted by the discovery of the following, three-step sequence to deprotect **15**. Treatment with 2.1 mol equiv. of tetramethylammonium hydroxide released two of the phenyl esters, presumably one from each phosphorus atom. At this point, the benzyl ethers were removed by hydrogenolysis without the problem of intramolecular cyclization, probably because the phosphonate group was protected as a monoanion. Finally, the phenyl esters were removed with hydrogen and platinum to give **4**, which was purified by selective precipitation as the disodium salt (34% overall yield from **15**).

We also investigated the preparation of phosphonate intermediates directly from **7**. Attempted condensation of the stabilized phosphorane[6,21] **20** with **7** in toluene at 110° or dimethyl sulfoxide at 50° resulted in no reaction. Condensation of **7** with tetraethyl methylenediphosphonate (**21**) under alkaline, two-phase conditions[7] was unsuccessful, as well. However, **7** reacted with the anion derived from the diphosphonate **21** in a homogeneous system to give **22** and **23** in ~50% yield with an α-to-β ratio of 2:1 (these anomers were inseparable by t.l.c.)[25].

In another approach to a phosphonate intermediate, **7** was treated with 1,3-propanedithiol in the presence of methanesulfonic acid to generate the alcohol **28** (40% yield), which was protected by treatment with *tert*-butylchlorodimethylsilane to give **29** (100% yield). Testing of various methods for removal of the dithiane residue led us to employ *N*-bromosuccinimide in aqueous acetonitrile at −10°; this gave the desired compound **30** in 50–99% yield. Unfortunately, on a large scale (70 mmol of **29**), the silylated aldehyde **30** was contaminated with a considerable proportion of **7**, which could not be readily separated. We suppose that **7** was regenerated by attack of a transient thionium ion*, formed during removal of the dithiane group, on the oxygen atom of the silyl ether, followed by desilylation and hydrolysis of the anomeric thiol. Alternatively, the alkenol **8** was protected with the *tert*-butyldimethylsilyl group and subjected to ozonolysis (using a dimethyl sulfide workup) to afford **30** in 70% yield. Reaction of **30** with the stabilized ylide **20** or diphosphonate **21** gave intermediates **26** or **27**, respectively, both in yields of ~20–40%. Treatment of **27** with fluoride ion gave **22** and **23** (~25%), enriched in the α-D anomer **23** (α:β ratio was 2:1). However, treatment of **26** with fluoride ion in oxolane or ethanol, or under a number of acidic conditions, led to decomposition without formation of **24** and **25**. Although these exploratory reactions were not optimized, they demonstrated the feasibility of other approaches to phosphonate isosteres of **2**. We elected to concentrate upon the electrophile-mediated cyclization of **8** (*viz.* **8** to **10**), because it led to the β-D configuration (**4**), thought[3] to be essential for biological activity**.

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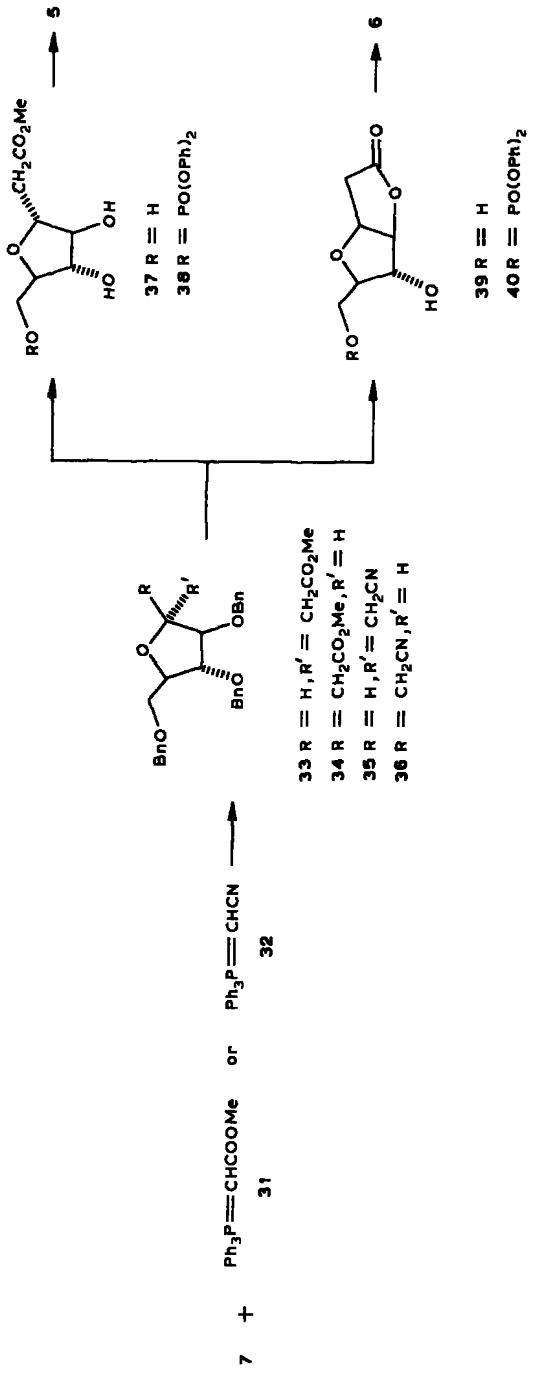
*For an example of this type of reaction, see ref. 26.

McClard *et al.*[25] have described the preparation of a mixture of **4 and its 2,5-anhydro-D-mannitol epimer. This mixture had a similar potency in activating phosphofructo-1-kinase, relative to that of our sample of **4**, but was a more effective inhibitor of fructose-1,6-bisphosphatase, suggesting that 2,5-anhydro-D-mannitol epimer may be a potent inhibitor of this latter enzyme.


7
+
$Ph_3P{=}CHCOOMe$
31
or
$Ph_3P{=}CHCN$
32
BnO
BnO
OBn
R
R'
33 R = H, R' = CH_2CO_2Me
34 R = CH_2CO_2Me, R' = H
35 R = H, R' = CH_2CN
36 R = CH_2CN, R' = H
RO
HO
OH
CH_2CO_2Me
37 R = H
38 R = $PO(OPh)_2$
5
RO
HO
O
39 R = H
40 R = $PO(OPh)_2$
6

Carboxylate synthesis. — The synthesis of **5** and **6** originated in the reaction of **7** with stabilized phosphorane **31**, in the manner of Ohrui *et al.*[20]. Refluxing 2 mol equiv. of **31** with **7** for 10 h produced a 9:1 mixture of **33** and **34**. Cyclization occurred spontaneously, since no open-chain alkenes were detected. In different experiments, the ratio of **33** to **34** varied from 9:1 to 5:1. This suggested that the thermodynamic ratio is different from 9:1. Indeed, equilibration[20] of a 5:1 mixture of **33** and **34** produced a final ratio of 1:1. Thus, there is no thermodynamic preference for either isomer of this pair of diastereomers. Treatment of **7** with phosphorane[27] **32** produced a mixture of nitriles **35** and **36** in a ratio of 2:1. This reaction also favors the α-D anomer (**35**), as in the reaction of **7** with **31**. Treatment of the mixture of **35** and **36** with base caused the facile elimination of benzyl alcohol, similar to some recently reported observations[28]. A 9:1 mixture of **33** and **34** was hydrogenolyzed to give a mixture of, preponderantly, methyl ester **37**, along with lactone **39**. The formation of lactone **39** from **34** supports the stereochemical assignment of **34**, which was based on ^{13}C-n.m.r. data*. Compounds **37** and **39** were easily separated by chromatography on silica gel, and each was selectively phosphorylated to give compounds **38** and **40**, respectively. A two-stage deprotection of **38** and **40** by use of platinum and hydrogen for the phenyl esters, and then basic hydrolysis of the carboxylic esters gave **5** and **6**, respectively, characterized as their trisodium salts.

Force-field calculations and n.m.r. experiments. — Since oxolane-ring systems are conformationally fluxional, it is not obvious *a priori* which (if any) tri-*O*-benzylarabinofuranosyl anomer is more thermodynamically stable, a point which might have relevance to the mechanistic analysis of the reactions discussed above. We conducted EFF calculations in order to address this question. Such calculations give information not only on the preferred conformation for a molecule, but also on alternative conformations that may be adopted. The degree to which various low-energy conformations contribute can be readily ascertained by inspection of the calculated energies (for a related study, see Burkert *et al.*[30]).

Force-field calculations for the bromomethyl compounds **9** and **10**, and esters **33** and **34**, were conducted with the MMP2 program developed by Burkert and Allinger[31]. Two low-energy conformations were found for both of the α anomers **9** and **33**, but only one reasonable conformation was obtained for the β anomers **10** and **34**. These conformations are displayed in Fig. 1, and the calculated energies, dihedral angles for the ring protons, and calculated vicinal, proton–proton coupling constants based on the dihedral angles, in Table I.

The energy minima were found after considerable analysis of possible ring conformations and conformational orientations accessible to the substituents (some details are mentioned in the Experimental section). The low-energy conformations generally have the majority of the ring substituents in a *pseudo*-equatorial orientation.

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*For the analogous formation of a *cis*-fused lactone, see ref. 29.

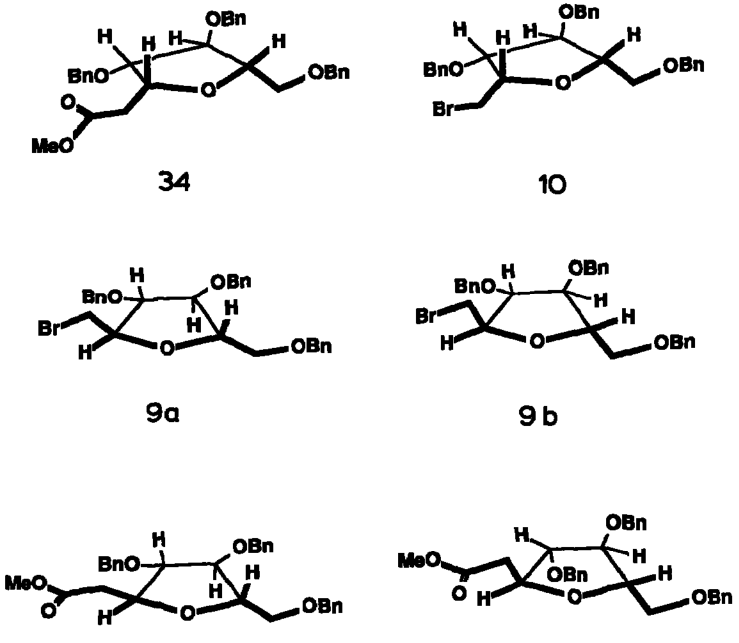

Fig. 1. Low-energy conformations for **9**, **10**, **33**, and **34** determined by MMP2 (L configurations shown).

TABLE I

ENERGIES, AND CALCULATED DIHEDRAL ANGLES AND VICINAL COUPLING CONSTANTS FOR EACH CONFORMATION OF **9**, **10**, **33**, AND **34**[a]

Structure	*MMP2 energy (kJ/mol)*	*Coupling constant (Hz)*[b] *and dihedral angle (degrees)*[c]		
		$J_{2,3}$ *or* $J_{3,4}$	$J_{3,4}$ *or* $J_{4,5}$	$J_{4,5}$ *or* $J_{5,6}$
9a	224.1	2.2 (110)	4.4 (131)	9.1 (153)
9b	221.3	3.4 (119)	6.2 (141)	10.0 (160)
10	219.2	3.4 (47)	0.8 (99)	4.0 (123)
33a	240.2	4.1 (123)	6.7 (144)	10.0 (161)
33b	247.3	0.7 (88)	0.9 (102)	5.0 (129)
34	238.1	3.6 (46)	0.8 (100)	4.1 (123)

[a] See Fig. 1. [b] Upper row, **9** and **10**; lower row, **33** and **34**. [c] Dihedral angle is given in parentheses.

The energy difference between the lowest-energy α and β conformations was only ~2.0 kJ/mol, with the β anomers being slightly preferred. This corresponds to only a 2:1 ratio of diastereomers at equilibrium, which is consistent with the lack of thermodynamic preference determined in the equilibration experiment on **33** and **34**.

In-depth n.m.r. experiments were conducted on mixtures of **9** and **10**, and **33** and **34**. ^{13}C-N.m.r. was used to determine the relative orientation of the β and α anomers[20,21]. Additionally, the carbon resonances for **9** and **10** were assigned by a ^{13}C–^{1}H heteronuclear, shift-correlated, two-dimensional n.m.r. experiment[32]. The ^{1}H-chemical-shift assignments were based on a series of ^{13}C(^{1}H)-selective decoupling experiments and by two-dimensional, ^{1}H–^{1}H homonuclear decoupled spectroscopy, along with standard shift-correlated (COSY) spectroscopy. Some of

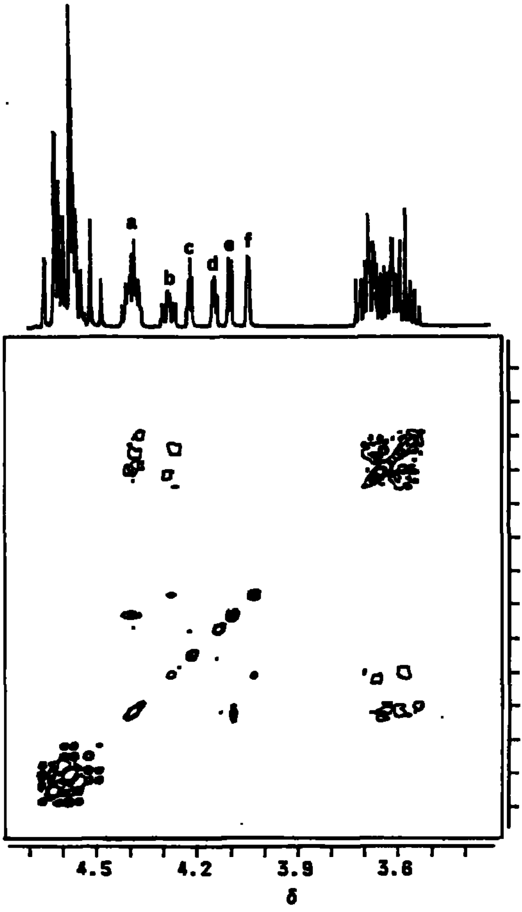

Fig. 2. A standard, one-dimensional spectrum (top) and a 2-D, *J*-correlated (COSY), ^{1}H-n.m.r. contour plot (bottom) of the aliphatic protons of **9** and **10** (9:11 mixture) obtained at 360 MHz. Assignments: a, H-2 and H-5 of **9** and H-2 of **10**; b, H-5 of **10**; c, H-3 of **9**; d, H-4 of **9**; e, H-3 of **10**; f, H-4 of **10**.

TABLE II

^{1}H-N.M.R. DATA FOR SELECTED PROTONS OF **9**, **10** AND **33**, **34**

Compound	*Chemical shifts (δ) and multiplicities*[a]								*Coupling constants (Hz)*[b]								
9, **10** **33**, **34**	*H-1a* *H-2a* *(dd)*	*H-1b* *H-2b* *(dd)*	*H-2* *H-3* *(ddd)*	*H-3* *H-4* *(dd)*	*H-4* *H-5* *(dd)*	*H-5* *H-6* *(ddd)*	*H-6a* *H-7a* *(dd)*	*H-6b* *H-7b* *(dd)*	$J_{1a,1b}$ $J_{2a,2b}$	$J_{1a,2}$ $J_{2a,3}$	$J_{1b,2}$ $J_{2b,3}$	$J_{2,3}$ $J_{3,4}$	$J_{3,4}$ $J_{4,5}$	$J_{3,5}$ $J_{4,6}$	$J_{4,5}$ $J_{5,6}$	$J_{5,6a}$ $J_{6,7a}$	$J_{5,6b}$ $J_{6,7b}$
9	3.54[c]	3.48[c]	4.36	4.16	4.09	4.36	3.62[d]	3.57[d]	[e]	[e]	[e]	2.8	2.2	0.5	3.3	[e]	[e]
10	3.61	3.54	4.37	4.04	3.98	4.23	3.63	3.52	[e]	5.9	8.0	3.7	0.9	0	2.5	6.0	6.8
33	3.50	3.56	4.22	4.02	3.90	4.48	2.65	2.63	12.0	6.1	6.1	3.2	[e]	[e]	[e]	[e]	[e]
34	3.47	3.56	4.06	3.92	3.97	4.44	2.74	2.74	12.0	6.2	6.2	3.1	[e]	[e]	[e]	[e]	[e]

[a] dd, Doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet. [b] ±0.1 Hz. [c,d] Assignments may be interchanged. [e] Values could not be determined because of overlapping resonances.

the coupling constants were undetermined because of overlap; nevertheless, most of the n.m.r. parameters could be determined. A 2-D, n.m.r. COSY experiment of a 9:11 mixture of **9** and **10** is plotted in Fig. 2. ^{1}H-N.m.r. data for these compounds are listed in Table II.

Several salient points can be discerned by inspection of the data in Table II. Comparison of the $J_{2,3}$ value of **9** and **10**, and the $J_{3,4}$ value for **33** and **34**, indicated only a very small difference (at most 1 Hz for **9** and **10**, and 0–0.3 Hz for **33** and **34**). Analysis of these chemical shifts or coupling constants could not have been used to assign relative stereochemistry. Because of small differences in n.m.r. chemical shifts and coupling constants, an attempt to assign the form of the oxolane ring based on these parameters may be fraught with error. Comparison of the coupling constants with those calculated from the MMP2 conformations, however, revealed a fairly close correlation (although the calculations represent gas-phase conditions and the n.m.r. experiments were conducted for deuteriochloroform solutions).

In conclusion, *C*-D-arabinofuranosyl compounds, selectively enriched in either the β or α anomer, were synthesized. The β configuration was obtained by electrophile-mediated cyclization of **8**, allowing for the preparation of the pure phosphonate anomer **4**. Wittig–Michael reactions of **7** with stabilized phosphoranes gave preponderantly the α anomer. The carbomethoxy derivatives **33** and **34** prepared in this manner, were transformed into carboxylates **5** and **6**, respectively. The biological activity of **4**–**6** was evaluated *in vitro*. For activation of phosphofructo-1-kinase, the concentrations for half-maximal activity were 31μM, >1mM, and >1mM, respectively. For inhibition of fructose-1,6-bisphosphatase, the IC$_{50}$ values were 173μM, >1mM, and >1mM, respectively. In comparison, **2** activated phosphofructo-1-kinase with a concentration for half-maximal activity of 1μM, and inhibited fructose-1,6-bisphosphatase with an IC$_{50}$ of 3.4μM. Thus, carboxylate isosteres **5** and **6** are inactive, whereas phosphonate **4** retains a significant portion of the activity of **2**. We are continuing to investigate electrophile-promoted cyclizations of **8**, and related compounds, to further define the diastereoselectivity.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas Hoover apparatus and are corrected. T.l.c. analysis was conducted on Whatman MK6F 200-μ silica gel plates. ^{1}H-N.m.r. spectra were recorded with either a Varian EM-360 (60 MHz), Varian EM-390 (90 MHz), or Bruker AM-360WB (360 MHz) spectrometer, as indicated. ^{13}C-N.m.r. spectra were recorded with a JEOL FX-60Q spectrometer operating at 15.0 MHz, or a Bruker AM-360WB spectrometer at 90.6 MHz where so noted. Where anomer ratios are reported for ^{1}H- and ^{13}C-n.m.r. experiments, integrations were obtained under quantitative conditions. Tetramethylsilane was used as an internal standard, except when D_2O was the solvent, in which case the spectra were referenced to external 1,4-dioxane. Elemental analyses were performed primarily by Galbraith Laboratories (Knoxville, TN). Chemical-ionization mass spectra (c.i.m.s.) were recorded with a Finnigan 3300–6100 system with methane as the reagent gas, except where indicated otherwise. The starting material, 3,5-di-*O*-benzyl-D-arabinose[33] (**7**), was purchased from Pfanstiehl Laboratories (Waukegan, IL).

*3,4,6-Tri-O-benzyl-1,2-dideoxy-*D-arabino*-hex-1-enitol* (**8**). — To methyltriphenylphosphonium bromide (200 g, 0.56 mol) under Ar was added M lithium hexamethyldisilazanide (600 mL) in oxolane *via* a cannula. After being stirred for 30 min, the solution had a deep-red color and only a small amount of residual solid remained. Compound **7** (100 g, 0.24 mol), suspended in oxolane (30 mL), was added causing a precipitate to form ($Ph_3PCH_3^+ \cdot Br^-$). After 15 min, water was slowly added and the product was extracted into ether, washed with water (4 ×), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Purification by preparative l.c. (Waters Prep 500; silica gel; 3:22 ethylacetate–hexane) gave a yellow oil (67.8 g) that was homogeneous by t.l.c. (68%), $[\alpha]_D^{22}$ +4.2° (*c* 1.5, methanol); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.8 (d, *J* 5 Hz, OH), 3.6 (m, 2 H), 3.8–4.1 (m, 3 H), 4.4–4.7 (m, 6 H, CH_2Ph), 5.1–5.4 (m, 2 H), 5.6–6.1 (m, 1 H), and 7.2 (s, 15 H); the peak at δ 2.8 disappeared upon treatment with D_2O; ^{13}C(^{1}H)-n.m.r. ($CDCl_3$): δ 70.2, 70.5, 70.8, 73.2, 73.9, 80.0, 80.4, 118.7, 127–129 (15 C), 135.0, and 138.0 (3 C).

Anal. Calc. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.67; H, 7.40.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-bromo-1-deoxy-*D*-mannitol* (**9**) *and 2,5-anhydro-3,4,6-tri-O-benzyl-1-bromo-1-deoxy-*D*-glucitol* (**10**). — To a solution of **8** (1 g, 2.4 mmol) in dichloromethane (3 mL) at 0° was added *N*-bromosuccinimide (446 mg, 2.5 mmol). After 15 min, t.l.c. showed complete conversion to a faster-moving spot. Succinimide was filtered off and the solvent was removed to give a near quantitative yield of a mixture of **9** and **10**, contaminated by a little succinimide. Analytically pure material was obtained by chromatography of a small portion on silica gel (7:3 ethyl acetate–hexane). The ratio of epimers was determined by integration of the signals for the protons at C-3 and C-4 of **9** and **10**, and determined to be 11:89, respectively (see Table I for ^{1}H-n.m.r. data). ^{13}C(^{1}H)-N.m.r. ($CDCl_3$; 90.6 MHz): δ 28.24 (C-1, **10**), 32.33 (C-1, **9**), 70.12 (C-6, **9** or **10**), 70.16 (C-6, **9** or **10**), 81.28 (C-2, **10**), 82.69 (C-2, **9**), 82.21 (C-3, **10**), 82.83 (C-5, **9**), 83.14 (C-4, **10**), 83.45 (C-5, **10**), 84.68 (C-4, **9**), 85.33 (C-3, **9**), 127.8 (9 C), 128.4 (6 C), 137.6 (2 C), and 138.0.

Anal. Calc. for $C_{27}H_{29}BrO_4$: C, 65.19; H, 5.88; Br, 16.06. Found: C, 65.10; H, 5.90; Br, 16.13.

*2,5-Anhydro-3,4-di-O-benzyl-1-deoxy-1-diphenoxyphosphinoyl-*D*-mannitol and 2,5-anhydro-3,4-di-O-benzyl-1-deoxy-1-diphenoxyphosphinoyl-*D*-glucitol* (**14**). — A solution of **9** and **10** (11:89 ratio; 1.0 g, 2.0 mmol) and ethyl diphenyl phosphite[17] (2.1 g, 8 mmol) was heated for 2 d at 160°. The product was purified by chromatography (dry silica gel column; 3:7 ethyl acetate–hexane) to give **13** (750 mg; of undetermined configuration; 57%); ^{1}H-n.m.r. ($CDCl_3$; 60 MHz): δ 2.55 (centered multiplet, apparent d of d, 2 H), 3.5–4.5 (m, 10 H), and 7.1 (m, 25 H);

c.i.m.s.: *m/z* 651 (MH$^+$). To a solution of **13** (8.3 g, 12.8 mmol) in dichloromethane (20 mL) was added iodotrimethylsilane (1.73 mL, 12.1 mmol) at 0° under N_2. The solution was allowed to warm to ambient temperature, and then stirred for 18 h. Water was added, the product was extracted into ether, and the solution washed with water twice, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by chromatography (Waters Prep-500 l.c.; 2:3 ethyl acetate–hexane) to give unreacted **13** (1.1 g), along with **14** (2.5 g), clear oil. The unreacted **13** that was recovered was a 17:3 mixture of the 2,5-anhydro-D-mannitol to the 2,5-anhydro-D-glucitol epimers. Thus, it appeared that iodotrimethylsilane had selectively deprotected the 2,5-anhydro-D-glucitol derivative; ^{1}H-n.m.r. ($CDCl_3$; 60 MHz): δ 2.52 (centered multiplet, apparent d of d, *J* 7, 19 Hz), 3.5–4.3 (m, 6 H), 4.5 (m, 4 H), and 7.1–7.3 (m, 10 H); c.i.m.s.: *m/z* 561 (MH$^+$).

*2,5-Anhydro-3,4-di-O-benzyl-1-bromo-1-deoxy-*D*-mannitol diphenyl 6-phosphate and 2,5-anhydro-3,4-di-O-benzyl-1-bromo-1-deoxy-*D*-glucitol diphenyl 6-phosphate* (**18**). — A 1% solution of H_2SO_4 in acetic anhydride (16 mL) was added dropwise to a solution of an 11:89 mixture of **9** and **10** in acetic anhydride (70 mL). The mixture was stirred for 1 h, cold water was added, and the product was extracted into dichloromethane (2 × 100 mL). The combined organic extracts were washed with 5% $NaHCO_3$, NaCl solution, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography (Waters Prep 500 l.c.; 1:6 ethyl acetate–hexane) to give **16** (13.6 g, 86%), of undetermined configuration; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 1.9 (s, 3 H), 3.5 (m, 2 H), 3.6–4.5 (m, 10 H), and 7.2 (m, 10 H). To a mixture of **16** (13.6 g) in methanol (150 mL) was added 18% aq. NaOH (26 mL) at 35°. After being stirred for 5 min, the solution was concentrated and the product was extracted into dichloromethane, washed with water (2 × 30 mL), NaCl solution, dried ($MgSO_4$), and evaporated to give **17** (10.9 g, 92%) as a colorless syrup; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.1 (t, 1 H), 3.4–3.9 (m, 4 H), 3.95–4.35 (m, 5 H), 4.4–4.6 (m, 4 H), and 7.1–7.3 (m, 10 H). To a cooled solution of **17** (10.7 g, 26 mmol) in pyridine (50 mL) was added dropwise a solution of diphenyl phosphorochloridate (7.7 g, 29 mmol) in dichloromethane (5 mL) at 5°. The mixture was stirred for 45 min at ambient temperature, treated with water, and extracted into dichloromethane. The combined organic extracts were washed with M HCl and an NaCl solution, then dried ($MgSO_4$), and evaporated. The residue was purified by chromatography (Waters Prep 500 l.c.; 1:3 ethyl acetate–hexane) to give **18** (11.3 g, 67%), colorless syrup; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 3.9–4.1 (m, 2 H), 4.2–4.6 (m, 7 H), and 7.1–7.6 (m, 2 H).

Anal. Calc. for $C_{32}H_{32}BrOP$: C, 60.10; H, 5.10. Found: C, 60.29; H, 5.10.

*2,5-Anhydro-3,4-O-benzyl-1-deoxy-1-diphenoxyphosphinoyl-*D*-glucitol diphenyl 6-phosphate* (**15**). — *From* **14**. A solution of **14** (3.3 g, 5.9 mmol) in pyridine (30 mL) was treated with diphenyl phosphorochloridate (1.22 mL, 6.2 mmol) at 0°. The solution was allowed to warm to ambient temperature and stirred overnight. The product was extracted into ether, washed with water thrice, dried ($MgSO_4$), filtered, and concentrated. Azeotropic evaporation of the remaining pyridine (with toluene), treatment with activated charcoal (in ether), and crystallization from ether–hexane gave **15** (3.8 g, 81%), m.p. 72–73.5°; $[\alpha]_D^{23}$ +16.7° (*c* 1.5, methanol); ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 2.55 (centered multiplet, apparent d of d of d, 2 H, *J* 2, 6, 16 Hz), 3.96 (d, 1 H, *J* ~1 Hz), 4.02 (d, 1 H, *J* 3.4 Hz), 4.35–4.5 (m, 4 H), 4.6 (m, 6 H), and 7.1–7.35 (m, 30 H); ^{13}C(^{1}H)-n.m.r. (90.6 MHz, $CDCl_3$): δ 26.15 (d, $J_{C,P}$ 142.0 Hz), 68.15 (d, $J_{C,P}$ 6.2 Hz), 71.74, 72.02, 76.4, 82.00 (d, $J_{C,P}$ 8.5 Hz), 82.55 (d, $J_{C,P}$ 5.8 Hz), 82.98, 120.05 (d, 8 C, $J_{C,P}$ 2.7 Hz), 120.62 (d, 8 C, $J_{C,P}$ 2.4 Hz), 125–130 (14 C, arom.), 137.39 (d, 2 C, $J_{C,P}$ 3.5 Hz), and 150.2–150.5 (4 C).

Anal. Calc. for $C_{44}H_{42}O_{10}P_2$: C, 66.66; H, 5.34; P, 7.81. Found: C, 66.38; H, 5.44; P, 7.89.

From **18**. A suspension of **18** (10.8 g, 17 mmol) and ethyl diphenyl phosphite (20 g, 76 mmol) was stirred for 16 h at 178°. The product was purified by chromatography (Waters Prep-500 l.c.; 1:2 ethyl acetate–hexane) to give a waxy solid (5.2 g, 39%), which was recrystallized from ether–hexane, m.p. 72–73°.

*2,5-Anhydro-3,4-di-O-benzyl-1-deoxy-1-dimethoxyphosphinoyl-*D*-glucitol dimethyl 6-phosphate* (**19**). — A solution of **15** (1.98 g, 2.5 mmol) in methanol (70 mL) was treated with CsF (1.5 g, 10 mmol) at reflux for 15 h, and then evaporated. The residue was purified on silica gel (97:3 ethyl acetate–methanol) to give a yellow oil (**19**) that was homogeneous by t.l.c. (887 mg, 65%). Refluxing **15** in methanol for 15 h in the absence of fluoride resulted in no reaction. Substitution of tetrabutylammonium fluoride (commercial M solution in oxolane) for CsF gave a comparable yield of **19** (63%); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.18 (dd, 2 H, $J_{H,P}$ 7, 19 Hz), 3.5 (d, 12 H, $J_{H,P}$ 11 Hz), 3.7–4.1 (m, 6 H), 4.3–4.4 (m, 4 H), and 7.2 (s, 10 H); ^{13}C(^{1}H)-n.m.r. ($CDCl_3$): δ 24.8 (d, $J_{C,P}$ 141.6 Hz), 52.6 (d, $J_{C,P}$ 4.9 Hz, 2 C), 54.3 (d, $J_{C,P}$ 5.9 Hz, 2 C), 67.1 (d, $J_{C,P}$ 5.9 Hz), 70–73 (2 C), 76.4, 81.9, 82.4, 82.8, 127–130 (10 C), and 137.4 (2 C); c.i.m.s.: *m/z* 545 (MH^+).

Anal. Calc. for $C_{24}H_{34}O_{10}P_2 \cdot 0.25\ H_2O$: C, 52.51; H, 6.33; P, 11.28; H_2O, 0.82. Found: C, 52.71; H, 6.41; P, 11.23; H_2O, 1.16.

*Dilithium 2,5-anhydro-1-deoxy-1-phosphono-*D*-glucitol 6-phosphate hydrate* (**4**). — A stirred solution of **15** (1.0 g) in oxolane (5 mL) was treated with 10% tetrabutylammonium hydroxide in oxolane (10 mL). After 24 h, the solution was acidified to a pH of ~2 with M HCl, and the product was extracted into chloroform (6 vol.). The solution was dried ($MgSO_4$), filtered, and evaporated to give a clear oil (900 mg); ^{1}H-n.m.r. (90 MHz) indicated the absence of any tetrabutylammonium groups; c.i.m.s.: *m/z* 641 (MH^+). This material was dissolved in 3:7 2,2-dimethylpropanol–water (30 mL) and shaken with 10% Pd–C (2.05 g) under H_2 (0.34 MPa). After 24 h, additional water (10 mL) was added along with PtO_2 (2.5 g). The solution was shaken under H_2 (0.34 MPa) for another day, and then filtered; the catalyst was washed with water (40 mL). The filtrate was partially concentrated (to ~20 mL) and then lyophilized. The resultant white solid was redissolved in water (2 mL) and treated with M NaOH until pH 5.0 was reached. Treatment with methanol caused a flocculent precipitate to form (168 mg, 34%), m.p. >250° (dec); $[\alpha]_D^{20}$ +24.5° (*c* 2.1, water); ^{1}H-n.m.r. (360 MHz, D_2O): δ 1.73 (centered multiplet, apparent t, *J* ~7 Hz, PCH_a), 1.78 (centered multiplet, apparent t, *J* ~7 Hz, PCH_b), 3.6–3.78 (m, 3 H), 3.82 (d, *J* 2.4 Hz), 3.87 (d, *J* 2.5 Hz), and 3.9–4.06 (m, 1 H); $^{13}C(^1H)$-n.m.r. (D_2O): δ 27.9 (d, $J_{C,P}$ 130.9 Hz), 64.8 (d, $J_{C,P}$ 4.9 Hz), 77.9 (d, $J_{C,P}$ 5.8 Hz), 78.1, 78.5, and 83.6 (d, $J_{C,P}$ 7.8 Hz).

Anal. Calc. for $C_6H_{12}Na_2O_{10}P_2 \cdot 0.1\ CH_3OH \cdot 1.2\ H_2O$: C, 19.44; H, 3.96; H_2O, 5.74. Found: C, 19.43; H, 4.35; H_2O, 5.43.

The analyses for P and Na deviated from the calculated values. Considering the amorphous, hygroscopic nature of the compound, the structural assignment was based largely on the n.m.r. spectra, which had no unassigned resonances.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-diethoxyphosphinoyl-*D*-glucitol* (**22**) *and 2,5-anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-diethoxyphosphinoyl-*D*-mannitol* (**23**). — To a solution of **7** (420 mg, 1 mmol) and **21** (516 mg, 2 mmol) in oxolane (1 mL) was added M lithium bis(trimethylsilyl)amide in oxolane (1.1 mL). After stirring for 5 h at ambient temperature, little reaction was observed by t.l.c., so the solution was heated for 4 h at 40–50°. Additional molar equiv. of base and **21** were added (1.0 mL of M lithium bis(trimethylsilyl)amide in oxolane and 260 mg of **21**), and the solution was stirred for 4 d at ambient temperature. The solution was treated with water, and the product was extracted into dichloromethane, washed with water (2 ×), dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel (3:2 ethyl acetate–chloroform) to give **22** and **23** (290 mg, 50%); ^1H-n.m.r. (90 MHz, $CDCl_3$): δ 1.2 (m, 6 H), 2.2 (apparent d of d, *J* 7.18 Hz), 3.5 (m, 2 H), 3.7–4.3 (m, 10 H), 4.3–4.5 (m, 6 H), and 7.2 (s, 15 H); $^{13}C(^1H)$-n.m.r. ($CDCl_3$): δ 16.4 (d, 2 C, $J_{C,P}$ 5.9 Hz), 25.9 (d, 0.37 C, $J_{C,P}$ 141.6 Hz), 30.2 (d, 0.63 C, $J_{C,P}$ 137.7 Hz), 61–62 (m, 2 C), 70–74.5 (m, 4 C), 75–88 (4 C), 127–130 (m, 15 C), 137.9, 138.1, and 138.3; c.i.m.s. (NH_3): *m/z* 555 (MH^+, 90% of base peak), and 556 (MH^+ + 1, 30% of base peak).

*2,3,5-Tri-O-benzyl-4-O-(*tert*-butyldimethylsilyl)-*D*-arabinose ethylene dithioacetal* (**29**). — A mixture of **7** (60 g, 0.14 mol), 1,3-propanedithiol (55.6 g, 0.52 mol), and methanesulfonic acid (15 mL) in benzene (500 mL) was stirred for 2 h. The solution was then washed with 3M NaOH and NaCl solution, dried (Na_2SO_4), filtered, and evaporated to give a pale-yellow syrup, **28**, pure by t.l.c. (72.3 g, 99%); c.i.m.s.: *m/z* 511 (M + 1). A mixture of crude **28** (8.05 g, 0.016 mol), *tert*-butylchlorodimethylsilane (6.75 g, 0.045 mol), and imidazole (8.19 g, 0.12 mol) in *N,N*-dimethylformamide (30 mL) was stirred under N_2 for 4 h at 60°. The mixture was poured into water and extracted into dichloromethane (2 × 50 mL). The combined organic layers were washed once with NaCl solution, dried (Na_2SO_4), filtered, and concentrated to give **29** as a colorless syrup (8.9 g, 89%), pure by t.l.c.; ^1H-n.m.r. (90 MHz, $CDCl_3$): δ 0.2 (s, 6 H), 0.9 (s, 9 H), 1.8–2.2 (m, 3 H), 2.9 (m, 4 H), 4.5–4.8 (m, 6 H), and 7.3 (m, 15 H); c.i.m.s.: *m/z* 625 (M + 1).

*2,3,5-Tri-O-benzyl-4-O-(*tert*-butyldimethylsilyl)-aldehydo-*D*-arabinose* (**30**). — A solution of dithiane **29** (1.6 g, 2.6 mmol) in acetonitrile (17 mL) was added dropwise to a solution of *N*-bromosuccinimide (3.6 g, 20 mmol) in 80% aqueous acetonitrile (35 mL) at −10°. After being stirred for 5 min, the mixture was poured into saturated aqueous $Na_2S_2O_3$ and extracted twice with ether (2 × 25 mL). The combined extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated to give **30** as a pale-yellow syrup (near quantitative yield), pure by t.l.c.; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.0 (m, 6 H), 0.8 (m, 9 H), 3.2–4.1 (m, 5 H), 4.3–4.6 (m, 6 H), and 7.1 (m, 15 H).

A mixture of the *aldehydo* sugar **30** (0.37 g, 0.69 mmol) and phosphorane **20** (1.2 g, 2.4 mmol) in benzene (5 mL) was refluxed under N_2 for 18 h. The solution was evaporated to a syrup which was purified by chromatography on preparative t.l.c. (1:1 ethyl acetate–hexane) to give **26** (0.33 g, 31%) pale-yellow syrup, pure by t.l.c.; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.0 (s, 6 H), 0.8 (s, 9 H), 3.3–4.25 (m, 5 H), 4.3–4.6 (m, 6 H), 6.1–6.8 (m, 2 H), and 7–7.4 (m, 15 H); ^{1}H-n.m.r. (360 MHz, $CDCl_3$) revealed a similar pattern in the vinylic region [δ peak centered at 6.25 (H-1), ~7.1 (H-2)] to that observed for **27**, supporting the *E* stereochemical assignment; the signal for H-2 was obscured under the aromatic proton signals; c.i.m.s.: *m/z* 765 (M + 1).

A M solution of lithium bis(trimethylsilyl)amide in oxolane (2.7 mL) was added to a solution of tetraethyl methylenediphosphonate (**21**; 0.7 g, 2.4 mmol) in oxolane (5 mL) under N_2. A solution of the *aldehydo* sugar **30** (0.48 g, 0.88 mmol) in oxolane (5 mL) was added, and it was stirred for 18 h at ambient temperature, poured into water, and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed once with an NaCl solution, dried (Na_2SO_4), filtered, and concentrated to give a pale-yellow syrup, which was purified by chromatography on preparative t.l.c. plates (1:1 ethyl acetate–hexane) to give pure **27**, (0.18 g, 31%), oil, pure by t.l.c.; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.1 (s, 6 H), 0.9 (s, 9 H), 1.3 (t, 6 H), 3.4–3.8 (m, 3 H), 4.0 (t, 4 H), 4.1–4.3 (m, 2 H), 4.3–4.6 (m, 6 H), 5.6–6.1 (m, 1 H), 6.3–6.8 (m, 1 H), and 7.3 (m, 15 H); ^{1}H-n.m.r. (360 MHz, $CDCl_3$; vinylic region): δ 6.01 (ddd, $J_{H,P}$ 21.1, $J_{1,2}$ 17.3, $J_{1,3}$ 1.4 Hz, H-1), and 6.82 (ddd, $J_{H,P}$ 22.5, $J_{1,2}$ 17.3, $J_{2,3}$ 5.5 Hz, H-2); this supports the *E* configurational assignment for **27**.

A mixture of **27** (65 mg, 97 mmol) in oxolane (2 mL) was treated with M tetrabutylammonium fluoride in oxolane (15 mL), and stirred under N_2 for 2 h. The solution was then poured into 3M NaOH and extracted into ethyl acetate (2 × 5 mL). The combined organic extracts were washed with NaCl solution, dried (Na_2SO_4), filtered, and concentrated to a syrup which was purified by chromatography on a preparative t.l.c. plate (4:1 ethyl acetate–hexane) to give **22** and **23** (13.3 mg, 25%), whose ^{1}H-n.m.r. spectrum was identical with that described above.

*Mixture of methyl 3,6-anhydro-4,5,7-tri-O-benzyl-2-deoxy-*D-glycero-D-galacto-*heptonate* (**33**) *and methyl 3,6-anhydro-4,5,7-tri-O-benzyl-2-deoxy-*D-glycero-D-gulo-*heptonate* (**34**). — A mixture of **7** (20 g, 48 mmol) and **31** (26 g, 77 mmol) was refluxed in acetonitrile (200 mL) for 24 h. The solution was evaporated and the residue purified by chromatography (dry silica gel column; 1:6 ethyl acetate–hexane) to give a mixture of **33** and **34** (20 g, 88%), colorless syrup; $[\alpha]_D^{23}$ +21.4° (*c* 0.52, methanol); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.6 (d, 2 H), 3.5 (m, 2

H), 3.7 (s, 3 H), 3.75–4.4 (m, 4 H), 4.5 (m, 6 H), and 7.2 (m, 15 H); $^{13}C(^1H)$-n.m.r. ($CDCl_3$): δ 34.1 (CH_2CO_2, **34**, ~0.11 C), 38.1 (CH_2CO_2, **33**, ~0.89 C), 51.6, 82.1, 82.9, 85.0, 86.6, 127–129 (15 C, arom.), 137.7 (3 C), 138.0, and 171.0.

Anal. Calc. for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77. Found: C, 72.87; H, 6.71.

Equilibration of **33** *and* **34**. — A solution of a 5:1 mixture of **33** and **34** (125 mg) in methanol (0.5 mL) was treated with 25% sodium methoxide in methanol[20,21] (28 μL). After 18 h, water was added, the product was extracted into ether, and the extract washed with water, dried ($MgSO_4$), filtered, and evaporated; ^{13}C-n.m.r. showed a 1:1 ratio of **33** and **34** by inspection of their respective C-2 resonances at δ 38.0 and 34.1, respectively. Similar treatment of **33** and **34** for 6 d also resulted in a 1:1 ratio.

*Mixture of 3,6-anhydro-4,5,7-tri-O-benzyl-2-deoxy-*D-glycero-D-galacto-*heptononitrile* (**35**) *and 3,6-anhydro-4,5,7-tri-O-benzyl-2-deoxy-*D-glycero-D-gulo-*heptononitrile* (**36**). — A suspension of **7** (6.0 g, 14.3 mmol) and **32** (ref. 27; 5.0 g, 16.7 mmol) in acetonitrile (80 mL) was heated under reflux for 2 d. The yellow solution was cooled and filtered, and the filtrate concentrated. The residue was chromatographed (flash chromatography on silica gel; 3:7 ethyl acetate–hexane) to give a 67:33 mixture of **35** and **36** (5.51 g, 87%); ^1H-n.m.r. (90 MHz, $CDCl_3$): δ 2.6 (centered multiplet, apparent t, 2 H), 3.52 (d, 2 H, *J* 5 Hz), 3.9–4.45 (m, 4 H), 4.5 (s, 6 H), and 7.3 (s, 15 H); $^{13}C(^1H)$-n.m.r. ($CDCl_3$): δ 18.3 (C-2, **36**, 0.32 C), 22.0 (C-2, **35**, 0.68 C), 68–74 (4 C), 78–86 (4 C), 116.9, 127–129 (15 C), 137.5, 137.6, and 138.1.

Anal. Calc. for $C_{28}H_{29}NO_4$: C, 75.83; H, 6.59; N, 3.16. Found: C, 75.57; H, 6.63; N, 3.08.

*Methyl 3,6-anhydro-2-deoxy-*D-glycero-D-galacto-*heptonate* (**37**) *and 3,6-anhydro-2-deoxy-*D-glycero-D-gulo-*heptono-1,4-lactone* (**39**). — A 9:1 mixture of **33** and **34** (24 g, 50 mmol) in ethanol (600 mL) was shaken with 10% Pd–C (7.9 g) under 0.34 MPa of H_2 for 18 h. The solution was filtered and the filtrate concentrated. The residue was chromatographed (Waters Prep 500 l.c.; 6:1 ethyl acetate–hexane) to give **37** (5.3 g, 51%) and **39** (1.3 g, 15%), colorless syrups, R_F (6:1 ethyl acetate–hexane) 0.21 (**37**) and 0.25 (**39**); ^1H-n.m.r. (90 MHz, D_2O) for **37**: δ 2.6–2.8 (m, 2 H), 3.5–3.7 (m, 2 H), 3.7 (s, 3 H), and 3.8–4.4 (m, 4 H); for **39**: δ 2.9–3.1 (m, 2 H), 3.5–3.85 (m, 2 H), 3.9–4.5 (m, 2 H), and 5.0–5.2 (m, 2 H, H-3,4); c.i.m.s. (**37**): *m/z* 175 (MH^+).

*Trisodium 3,6-anhydro-2-deoxy-*D-glycero-D-galacto-*heptonate 7-phosphate tetrahydrate* (**5**). — A solution of diphenyl phosphorochloridate (5.9 g, 22 mmol) in toluene (10 mL) was added dropwise to a solution of **37** (4.6 g, 22 mmol) in pyridine (30 mL) at −30°. The mixture was stirred for 4.5 h at 0°, treated with cold water, and extracted into dichloromethane (2 × 50 mL). The combined organic extracts were washed with water and NaCl solution, then dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a dry silica gel column (4:1 ethyl acetate–hexane) to give **38** (4.98 g, 52%), colorless syrup; ^1H-n.m.r. (90 MHz, $CDCl_3$): δ 2.5 (d, 2 H), 3.6 (s, 3 H), 3.9–4.4 (m, 8 H), and 7.2 (m, 10 H); $^{13}C(^1H)$-n.m.r.

($CDCl_3$): δ 38.1 (CH_2CO_2), 51.8, 68.3 ($J_{C,P}$ 5.9 Hz), 77.8, 80.6, 80.9, 81.8, 120.2 (4 C), 125.5 (2 C), 129.8 (4 C), and 150.2 (d, 2 C, $J_{C,P}$ 6.8 Hz); c.i.m.s.: *m/z* 439 (MH^+).

A solution of **38** (4.85 g, 11 mmol) in methanol (100 mL) was shaken with PtO_2 (2.0 g) under H_2 (0.34 MPa) for 1.5 h. The suspension was filtered, and the filtrate concentrated and treated with aq. NaOH (1.27 g in 20 mL of water). After 4 h, the solution was lyophilized to furnish **5** (3.5 g, 76%), white foam, $[\alpha]_D^{25}$ +17° (*c* 1.5, water); ^1H-n.m.r. (90 MHz, D_2O): δ 2.6 (d, 2 H), and 3.8–4.6 (m, 6 H); $^{13}C(^1H)$-n.m.r. (D_2O): δ 41.1 (CH_2CO_2), 63.7 (d, $J_{C,P}$ 3.9 Hz), 76.8, 79.9, 80.1, 81.5 (d, $J_{C,P}$ 7.9 Hz), and 179.2.

Anal. Calc. for $C_7H_{10}Na_3O_9P \cdot 3.8\,H_2O$: C, 20.68; H, 4.36; Na, 16.96; P, 7.61; H_2O, 16.83. Found: C, 20.99; H, 4.42; Na, 16.59; P, 7.90; H_2O, 15.80.

*Trisodium 3,6-anhydro-2-deoxy-*D-glycero-D-gulo-*heptonate 7-phosphate tetrahydrate* (**6**). — A solution of diphenyl phosphorochloridate (1.69 g, 6.3 mmol) in toluene (2 mL) was added dropwise to a solution of **39** (1.0 g, 5.7 mmol) in pyridine (10 mL) at −30°, followed by addition of 4-(dimethylamino)pyridine (50 mg). The mixture was stirred for 5 h at 0°, treated with cold water, and the product extracted into dichloromethane. The organic layer was washed with water and an NaCl solution, then dried (Na_2SO_4), filtered, and concentrated. The beige residue was chromatographed (dry column of silica gel; 4:1 ethyl acetate–hexane) to afford **40** (0.60 g, 28%) colorless syrup; ^1H-n.m.r. (90 MHz, $CDCl_3$): δ 2.8 (m, 2 H), 3.8–4.6 (m, 5 H), 4.8 (m, 2 H, H-3,4), and 7.1–7.5 (m, 10 H).

A solution of **40** (0.6 g) in methanol (20 mL) was shaken with PtO_2 (0.32 g) under H_2 (0.34 MPa) for 2.5 h. The solution was filtered and the filtrate concentrated. The residue was treated with aq. NaOH (0.15 g in 5 mL of water) for 1.5 h. The solution was lyophilized to give **6** (0.41 g, 18%, from **39**), crisp foam, $[\alpha]_D^{25}$ +13.6° (*c* 0.90, water); ^1H-n.m.r. (90 MHz, D_2O): δ 2.6 (d, 2 H) and 3.8–4.6 (m, 6 H); $^{13}C(^1H)$-n.m.r. (D_2O): 36.6 (CH_2CO_2), 63.9 (d, *J* 4.9 Hz), 77.6, 78.8, 78.9, 84.0 (d, $J_{C,P}$ 8.8 Hz), and 179.2.

Anal. Calc. for $C_7H_{10}Na_3O_9P \cdot 3.8\,H_2O$: C, 20.68; H, 4.36; Na, 16.96; P, 7.61; H_2O, 16.33. Found: c, 20.99; H, 4.42; Na, 16.59; P, 7.90; H_2O, 15.80.

2-D N.m.r. experiments[32]. — The 2-D n.m.r. spectra were recorded with a Bruker AM-360WB instrument using standard Bruker software. The COSY-2D, ^1H-n.m.r. experiments were performed in a 5-mm probe, at a concentration of 15 mg/0.5 mL, using a 90° pulse, 6.9 μs, a 3.03-s recycle time, and 16 acquisitions per data set. For **9** and **10**, a spectral width of 1700.0 Hz in F_1 and F_2 was used with a 512W × 256W transform, and for **33** and **34**, a spectral width of 1501.5 Hz in F_1 and F_2 with a 2K × 1K transform. The data were processed with a sine-bell, window function, and diagonally symmetrized.

The ^{13}C–^1H, COSY-2D n.m.r. experiment was performed on a 150 mg/2.0 mL solution of **9** and **10** in a 10-mm probe using a 90° pulse, 16 μs for ^{13}C, and a 90° pulse, 43 μs for ^1H on the decoupler coil of a VPS broadband-probe head. A 3.06-s recycle time with 64 acquisitions per data set and a spectral width of 8928.6

Hz in F_2 and 1700.6 Hz in F_1 were utilized. A 1K × 512W transform and a sine-bell window function was used in processing.

EFF calculations. — Energy minimizations were performed with the MMP2 force field[31]. In order to insure against obtaining false minima due to unfavorable side-chain rotamers, the full spectrum of rotations (360° in 10° increments) was separately examined for each of the following bonds (for **9**, **10** and **33**, **34**, respectively): C-5/6, C-6/7; C-6/7, O; C-4/5, O; C-3/4, O; all of the $PhCH_2$, O bonds; and the two single bonds to C-1 of **33**, **34**. After placing each of the key bonds in its locally minimized form, the molecule was then subjected to a full structure–energy minimization procedure.

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