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The Search for a Potentially Prebiotic Synthesis of Nucleotides via Arabinose-3-phosphate and Its Cyanamide Derivative

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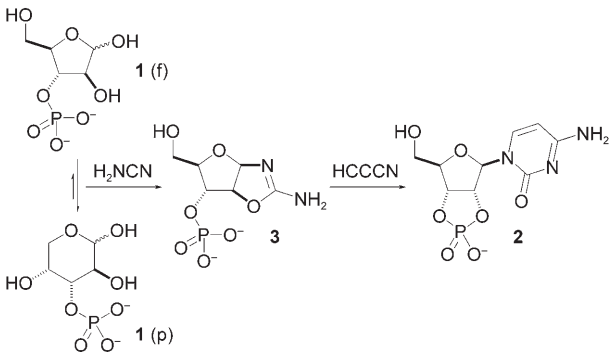
Abstract: For the RNA world hypothesis to be accepted, the constitutional self-assembly of RNA will have to be demonstrated. Conceptually, the simplest route to RNA involves nucleotide polymerisation. Activated pyrimidine nucleotides can be derived from arabinose-3-phosphate under potentially prebiotic conditions, but the prebiotic synthesis of this sugar phosphate has not hitherto been investigated. The results of synthetic approaches involving phosphorylation, phosphate migration and 2,3-C–C bond construction are described herein.

Keywords: aldol reaction · diastereoselectivity · nucleotides · phosphorylation · prebiotic · RNA

Introduction

As part of an ongoing investigation into the prebiotic origin of RNA, we recently showed that D-arabinose-3-phosphate (**1**) could be converted into β-D-cytidine-2′,3′-cyclic phosphate (**2**) by way of the aminooxazoline **3** (Scheme 1).[1] Being an activated nucleotide, **2** is a monomer with the potential to undergo polymerisation to RNA, and its synthesis by stepwise nucleobase assembly on a sugar–phosphate scaffold is etiologically noteworthy for a number of reasons: 1) It involves the selection of the furanose ring system from a starting material that exists predominantly in pyranose (p) forms, 2) the β-configuration at C(1′) is established, 3) inversion of configuration at C(2′) takes place and 4) the phosphate group is activated from a monoester to a diester. We recently showed that deactivation of **2**, by hydrolysis to the 2′- and 3′-monophosphates, can be reversed by the action of cyanoacetylene, the very reagent used in the second stage of nucleobase assembly.[2] This continuous reactivation was seen as strengthening the case for the involvement of nucleoside-2′,3′-cyclic phosphates, such as **2**, in the prebiogenesis of RNA. Our work on the potential constitutional self-assembly of RNA has been guided by the use of matrices that make clear the many possible routes to RNA from its constituent prebiotic feedstock molecules. By using a constitutional self-assembly matrix for pyrimidine RNA (Figure 1), we now sought to extend the sequence **1**→**3**→**2** such that **2** could be accessed from simple feedstock molecules.



Scheme 1. Stepwise pyrimidine nucleobase assembly on a sugar-phosphate template.

Pentose–phosphate derivatives can be produced by aldolisation of mono- or bis(glycolaldehyde) phosphate and formaldehyde,[3,4] or by direct phosphorylation of the free pentoses.[5,6] As the aldolisation route produces pentose-2,4-diphosphates, or 2,4-cyclic phosphates, and our target **1** is a pentose-3-phosphate, we first considered the direct phosphorylation route. Inoue et al. have investigated the phosphorylation of the D-aldopentoses with cyclotriphosphate **4** at high pH, and reported that D-arabinose gives α-D-arabinopyranose-1-triphosphate **5** in low yield (Scheme 2).[5] According to these authors, other phosphorylated products

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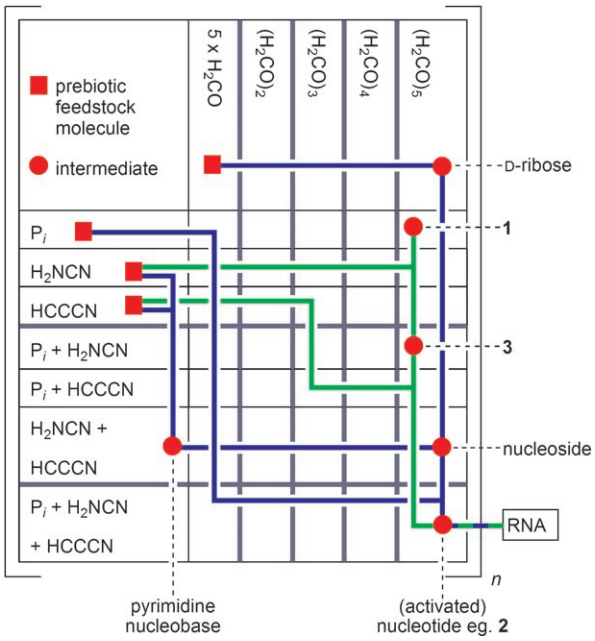
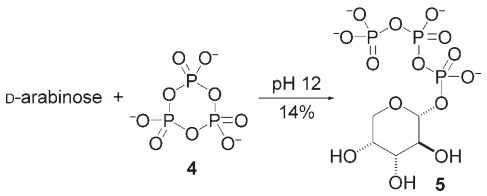
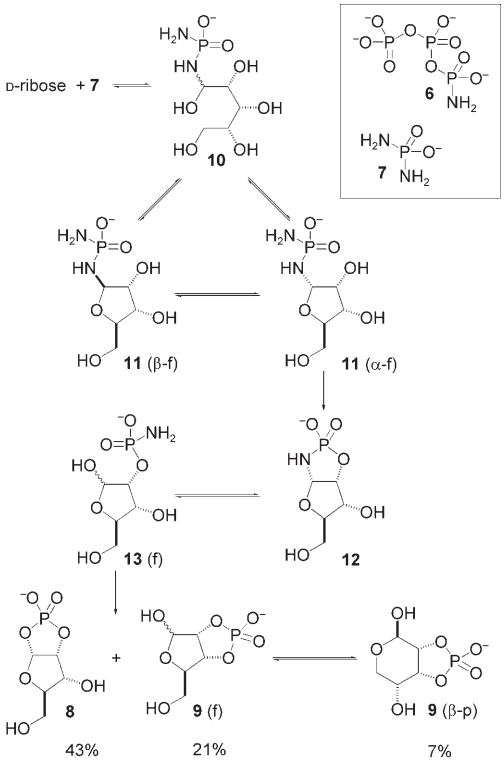


Figure 1. This constitutional self-assembly matrix makes clear the many potential routes to RNA from prebiotic feedstocks. The synthesis that has normally been assumed (blue lines) involves oxygenous chemistry from formaldehyde to ribose, and nitrogenous chemistry leading to nucleobases. Attachment of the nucleobases to ribose is followed by phosphorylation, activation and polymerisation. Despite extensive efforts, this route has not been experimentally demonstrated and this has prompted us to explore other routes suggested by the matrix, such as ones including the sequence **1**→**3**→**2** (green lines). For simplicity, only the assembly options for pyrimidine RNA are shown, but similar matrices can be constructed for assembly of purine RNA.



Scheme 2. Direct phosphorylation by using cyclotriphosphate.

were formed, suggesting low selectivity, but the nature of these byproducts could not be determined due to their low yield. Krishnamurthy et al. investigated the phosphorylation of the D-aldotetroses and D-ribose by amidotriphosphate (AmTP) **6** and diamidophosphate (DAP) **7** at neutral pH (Scheme 3).[6] AmTP[7] and DAP[8] can be produced by ammonolysis of **4** and are viewed as prebiotically plausible phosphorylating agents (or analogues thereof). By using either reagent, D-ribose was converted to the 1,2- and 2,3-cyclic phosphates **8** and **9**, respectively, with the latter existing in equilibrating β-pyranose and α- and β-furanose forms.[9,10] The chemistry was more efficient with DAP (**8**+**9**, 71%) than with AmTP (**8**+**9**, 29%), however, and this was ascribed to faster equilibration of intermediate adducts with the former reagent. In the case of AmTP, "exploratory experiments" suggested that the other three aldopentoses



Scheme 3. Intramolecular phosphorylation by transient tethering in the *ribo* series.

behave similarly to ribose.[6] The formation of **8** and **9** from D-ribose and **7** presumably proceeds via the acyclic adduct **10**. Dehydration of **10** and ring closure could give the monocyclic adduct **11** in either furanose or pyranose forms, but the former are expected to predominate, if kinetic control is operative, because closure to the furanose ring is faster.[11] The α-furanose form of **11** is then predisposed towards cyclisation, giving the phosphoramidate **12**, presumably by means of nucleophilic displacement of ammonia from an N-protonated form of **11** (α-f). Ring opening of **12** to **13**, via imine or oxonium ion intermediates, is then followed by recyclisation to a mixture of **8** and **9**. As the 1,2-cyclic phosphate is only formed in the furanose form **8**, it can be inferred that it results from closure of the α-furanose form of **13**. This suggests that **9** (f) is initially produced from furanose forms of **13**, and then equilibrates with **9** (p). Krishnamurthy et al. then went on to show that the mixture of **8** and **9** could be hydrolysed in a separate step, at low pH, to a mixture of D-ribose-2-phosphate and D-ribose-3-phosphate.[6] The formation of D-ribose-3-phosphate, albeit as the minor product, attracted our attention as it suggested that it might be possible to make the arabino-analogue **1** in a similar manner. Although the *trans*-2,3 stereochemistry of D-arabinose would prevent formation of D-arabinose-2,3-cyclic phosphate in furanose forms, it potentially allows the formation of this material in (strained) pyranose forms. We, therefore, decided both to investigate the phosphorylation of D-arabinose by using DAP **7**, and to try and identify the other

products observed by Inoue et al. in their phosphorylation of D-arabinose by using cyclotriphosphate **4**.[5] We also planned to study the possible interconversion of the various arabinose phosphates, and so decided to first use conventional synthesis to prepare standards for comparison.

Results and Discussion

Conventional synthesis of arabinose phosphates: Synthesis of D-arabinose-2-phosphate **14** started from benzyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside **15** (Scheme 4).[12] Phosphorylation of **15**, by using amidite chemistry, gave phosphate triester **16** in good yield. We had hoped to globally deprotect **16** to **14** by treatment with Me_3SiBr followed by aqueous acid workup, but these conditions left the anomeric benzyl protecting group in place in **17**, and subsequent hydrogenolysis was necessary to give **14**.

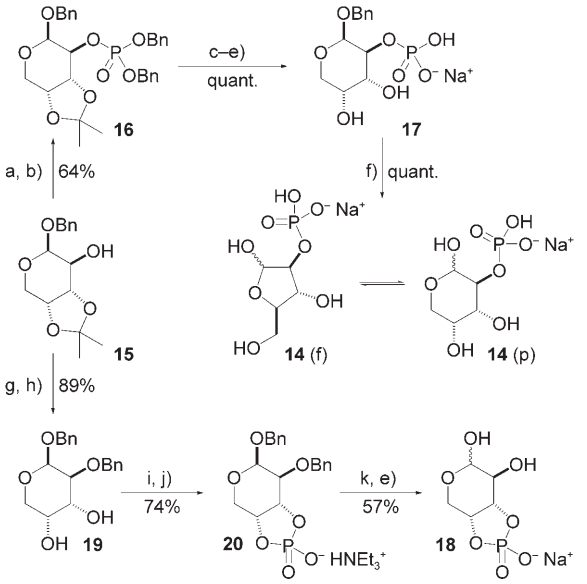
The synthesis of D-arabinose-3,4-cyclic phosphate **18** also commenced with **15**, and first involved protecting group manipulation to give the dibenzyl derivative **19**. Cyclophosphorylation of **19** by using the conditions of Pitsch et al.[10] gave the protected cyclic phosphate **20**, and hydrogenolysis of this material followed by ion-exchange gave **18**.

Our next target was arabinose-4-phosphate **21** (Scheme 5). This compound was synthesised in the L-series because in a related project we had need of xylose-4-phosphate **22**, and we envisaged that both L-**21** and D-**22** could be prepared from the L-arabinose derivative **23**.[12] In our subsequent investigation of the reaction of **21** with cyanamide, characterisation of the product was facilitated by comparison to the product formed from **22** and cyanamide, and, accordingly, the synthesis of **22** is also given herein.

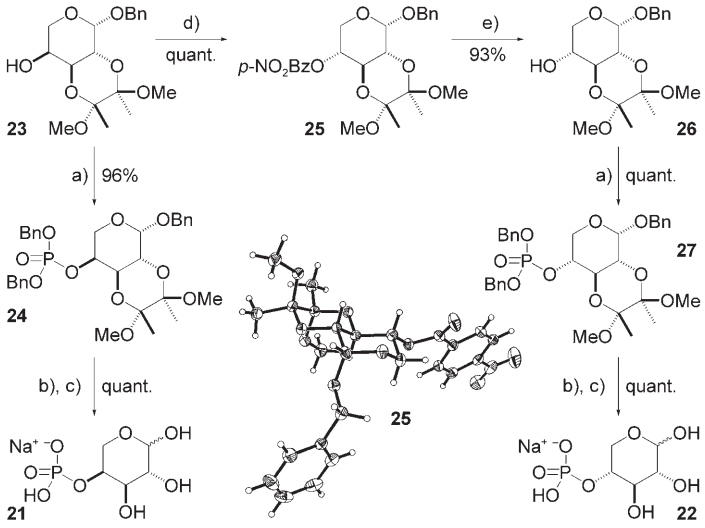
Phosphorylation of **23** by using tetrabenzylpyrophosphate[13] gave the fully protected phosphate **24**, which was deprotected by sequential hydrogenolysis and acidic hydrolysis to give, after neutralisation, **21**. Conversion of **23** into a D-xylose derivative was achieved through inversion at the 4-position by a Mitsunobu reaction whereupon the *para*-nitrobenzoate **25** was formed in quantitative yield. The inversion of stereochemistry associated with this reaction was proved by an X-ray crystallographic analysis of **25** (Scheme 5).[14] Ammonolysis of **25** then gave the alcohol **26** which was converted to **22**, by way of the protected phosphate **27**, by using the same chemistry employed for the conversion of **23** to **21**.

D-Arabinose-3-phosphate **1** was prepared by the route we have previously described.[15]

Potentially prebiotic phosphorylation of D-arabinose: We first investigated the phosphorylation of arabinose with DAP **7** according to the procedure of Krishnamurthy et al.[6] An aqueous solution of D-arabinose and **7** was stirred at room temperature over a period of days, with aliquots being taken at regular intervals for ^{1}H NMR spectroscopic analysis. During the phosphorylation, ammonia was released causing the pH to rise and slowing down the reaction.[6] To counter this, acidic ion-exchange resin was added periodically to neutralise the mixture. It was also necessary to add further portions of **7** to drive the reaction. By comparison with literature values for the chemical shift of the anomeric protons of products from the phosphorylation of D-ribose[6] and from analysis of coupling constants, it was possible to identify the different components of the reaction mixture by ^{1}H NMR spectroscopy (see Figure 2a, Scheme 6 and



Scheme 4. Conventional synthesis of D-arabinose-2-phosphate **14** and D-arabinose-3,4-cyclic phosphate **18**. a) $(BnO)_2PN(iPr)_2$, 1*H*-tetrazole, MeCN; b) *t*BuOOH, H_2O; c) Me_3SiBr, CH_2Cl_2; d) 1 M HCl; e) Na^+-Dowex-50, H_2O; f) H_2, Pd/C, THF/H_2O; g) NaH, BnBr, THF/DMF; h) 1 M HCl/THF 1:1; i) $POCl_3$, py.; j) Et_3N, H_2O; k) H_2, $Pd(OH)_2$/C, EtOH. py: pyridine.



Scheme 5. Conventional synthesis of L-arabinose-4-phosphate **21** and D-xylose-4-phosphate **22**. a) *t*BuOK, THF, RT→−40 °C, $(BnO)_2P(O)OP(O)(OBn)_2$; b) H_2, $Pd(OH)_2$/C, MeOH; c) 90% TFA, CH_2Cl_2 then pH→7 (NaOH aq.); d) pNO_2BzOH, Ph_3P, $iPrO_2CN{=}NCO_2iPr$, THF; e) NH_3, $MeOH/CH_2Cl_2$. TFA: trifluoroacetic acid.

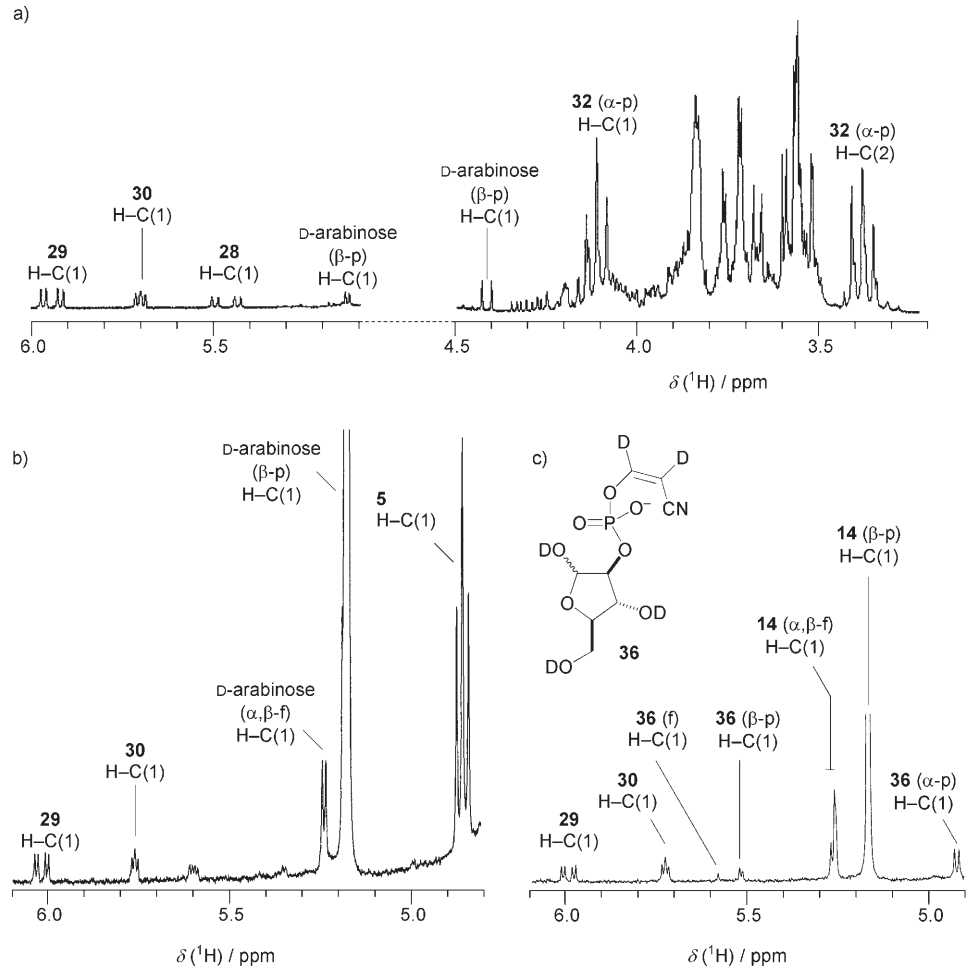
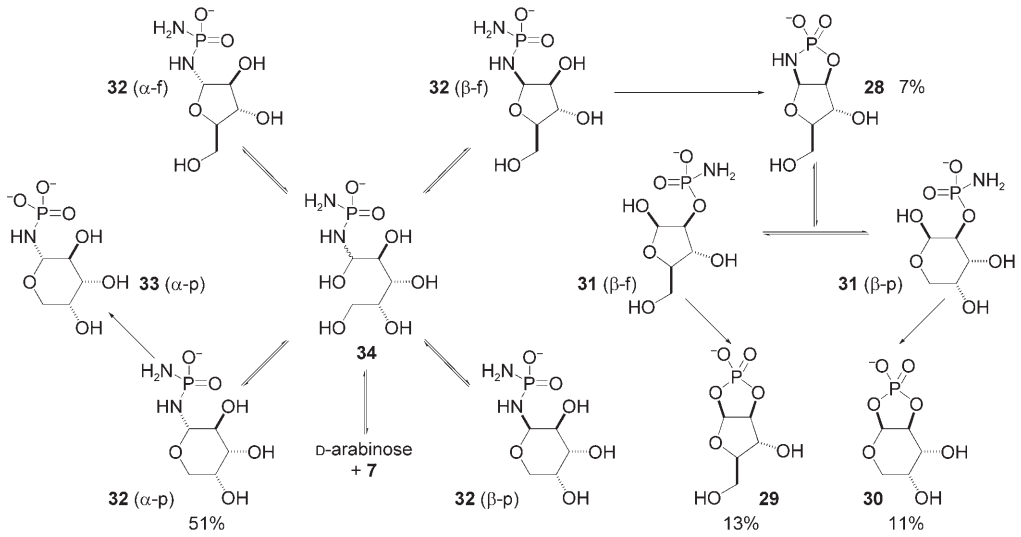


Figure 2. ^{1}H NMR analysis of the direct phosphorylation of arabinose and the attempted cyclisation of the 2-phosphate to the 2,3-cyclic phosphate. a) Products of reaction of arabinose and DAP **7**, b) products of reaction of arabinose and cyclotriphosphate **4**, and c) products of reaction of D-arabinose-2-phosphate **14** with cyanoacetylene in D_2O.

Table 1). The signals for the anomeric proton of the 1,2-cyclic phosphoramidate **28** and the furanose 1,2-cyclic phosphate **29** were identified by comparison to the corresponding signals of **12** and **8** in the *ribo* series. Relative to that series, there was also an additional downfield-shifted anomeric signal in the ^{1}H NMR spectrum. This signal showed a coupling to phosphorus, and we assign it to the pyranose form of the 1,2-cyclic phosphate **30** on the basis of the small value for $J_{1,2}$. The amount of **28** was seen to rise and then fall as **29** and **30** increased. This latter observation is also consistent with the structural assignment for **30**, as **29** is presumably formed from **28** via the 2-phosphoramidate **31**, and this compound is expected to exist in both furanose and pyranose forms, with one of the latter, **31** (β-p), setup to cyclise to **30**. The lack of such a pyranose-1,2-cyclic phosphate in the phosphorylation of D-ribose is presumably due to the increased propensity for D-ribose to exist in furanose forms.[11] The generation of 1,2-cyclic phosphates from D-arabinose was slower and less efficient than from D-ribose, and



Scheme 6. Intramolecular phosphorylation by transient tethering in the *arabino* series.

Table 1. Partial ^{1}H NMR spectroscopic data for the various species formed during the phosphorylation of D-arabinose by DAP **7**.

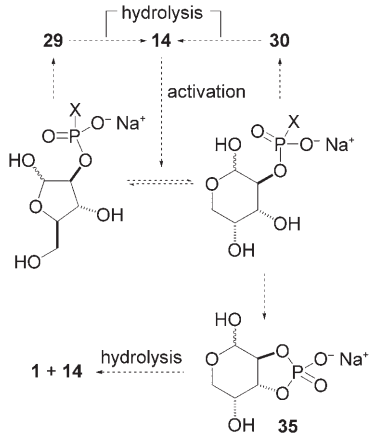
Compound	δ H–C(1) [ppm][a]	$J_{1,2}$ [Hz]	$J_{H\text{-}P}$ [Hz]
28	5.47	5.0	18.3
29	5.95	4.4	13.8
30	5.70	3.7	4.3
32 (α-p)	4.12	8.3	8.3

[a] Spectra were recorded in D_2O and the chemical shifts were found to be very pD dependent, those given here are taken from a single spectrum.

extensive accumulation of the α-pyranosyl adduct **32** (α-p) was also observed. This compound was identified by comparison of $J_{1,2}$ and $J_{H,P}$ to the corresponding coupling constants of **5**, and by its subsequent very slow conversion back to the starting sugar. We assume that this conversion proceeds by means of hydrolysis to the monoamidate adduct **33** (α-p), and, at the later stages of the reaction, we also observed low-intensity signals tentatively assigned to **33** (α-p), slightly upfield-shifted relative to **32** (α-p). The pyranose and furanose adducts **32** presumably all derive from the open-chain adducts **34**. The formation, persistence and then hydrolysis of the pyranose adducts **32** (α-p) and **33** (α-p) are presumably the major contributory factors to the inefficient phosphorylation of D-arabinose relative to D-ribose. Not only was the phosphorylation of D-arabinose found to be slow and inefficient, but the 2,3-cyclic phosphate (from which **1** might have been accessed by hydrolysis) was not detected. After 5 d, the reaction mixture comprised unreacted D-arabinose, **28** (7%), **29** (13%), **30** (11%) and **32** (α-p; 51%).

We next investigated the products formed in the phosphorylation of D-arabinose by using cyclotriphosphate **4** at high pH. Inoue et al. had found that the 1-triphosphate **5** was the major phosphorylated product,[5] and we were able to confirm these findings observing **5** in 15% yield (Figure 2b)). In addition to **5**, and by comparison to the products of phosphorylation by using DAP **7**, we were able to identify the 1,2-cyclic phosphates **29** and **30** as products of phosphorylation by using **4**. These latter compounds were both formed in very low yield (≈1–2%) along with an unidentified product characterised by a dd signal for H–C(1) at $\delta = 5.60$ ppm. As it can be assumed that **30** is derived by cyclisation of the β-anomer of **5**, and that **29** is derived by cyclisation of the β-furanose isomer of **5**, then it is reasonable to assume that the α-furanose isomer of **5** is also formed. Like **5** itself, the α-furanose isomer of **5** cannot undergo cyclisation, and so we tentatively assign the dd signal at $\delta = 5.60$ ppm to this latter species. Whatever the case, it is clear that the phosphorylation of D-arabinose by using **4** at high pH is inefficient. Furthermore, the 3-phosphate **1** is again not formed, so we were forced to consider less direct ways in which this compound could be produced under potentially prebiotic conditions.

Potential formation of D-arabinose-3-phosphate 1 by phosphate migration: As Krishnamurthy et al. showed that D-ribose-2-phosphate can be formed by hydrolysis of the 1,2-cyclic phosphate **8**,[6] it seems reasonable to assume that D-arabinose-2-phosphate **14** could be similarly formed from the 1,2-cyclic phosphates **29** and **30**. Thus, even though **29** and **30** are minor products in the phosphorylation of D-arabinose by **4** or **7**, there existed the possibility that the 3-phosphate **1** might be formed from the 2-phosphate **14** by phosphate migration. We had in mind a sequence whereby **14** was somehow cyclised to the 2,3-cyclic phosphate **35** which could then undergo hydrolysis to **1** and (back to) **14** (Scheme 7). Any success in demonstrating such a sequence—particularly if the hydrolysis of **35** showed selectivity for the formation of **1**—would then have been followed by a search for a more-efficient synthesis of **14** via **29** and **30**. At the outset, we were not particularly hopeful because the previously noted formation of the 1,2-cyclic phosphates **29** and **30** (eg. from **31** (β-f) and **31** (β-p) in the phosphorylation of D-arabinose with DAP **7** (Scheme 6)) suggested that any form of activation of **14** would result in cyclisation to the 1,2-cyclic phosphates rather than the 2,3-cyclic phosphate **35**. However, for the sake of completeness, and to more fully explore the RNA constitutional self-assembly matrix (Figure 1), we treated **14** with cyanoacetylene in an attempt to make **35**. In our earlier work using cyanoacetylene to (re)cyclise β-D-cytidine-2′(3′)-phosphates to **2**,[2] we had found that five to ten equivalents of this electrophile were required to obtain the highest yields of cyclised product. However, in the attempted cyclisation of **14** to **35**, we first conducted an experiment in D_2O by using two equivalents of cyanoacetylene and ^{1}H NMR spectroscopy to determine whether the reaction followed the desired course or not (Figure 2c). Had **35** been produced, we would have optimised conditions for its production, but, in the event, it was not, and the 1,2-cyclic phosphates **29** and **30** were detected instead. In addition to clear signals for the H–C(1) of **29** and **30**, small signals of similar appearance to the signals for H–C(1) of the various forms of residual **14**, but ≈0.3 ppm



Scheme 7. Potential formation of a 3-phosphate from a 2-phosphate by phosphate migration in the *arabino* series.

downfield-shifted were apparent. In previous work, we have shown that cyanoacetylene reacts with phosphate monoesters to give *Z* cyanovinyl adducts, so it seems reasonable to suggest that these additional H–C(1) signals are due to the various forms of **36**, the deuterated *Z*-cyanovinyl adduct of **14**. The cyanovinyl group of **36** is deuterated because, in D_2O, the proton of cyanoacetylene rapidly exchanges for a deuteron, and the incipient vinyl anion resulting from phosphate addition is quenched with a deuteron.[15] The cyclisation of the β-anomers of **36** to **29** and **30** confirms our earlier suspicion that any form of activation of the phosphate group of **14** will result in this mode of cyclisation.

Unable to find a route from the 2-phosphate of arabinose to the 3-phosphate, but intrigued by the possibility of phosphate migration, we next considered a route to the 3-phosphate from the 4-phosphate. In pyranose forms of arabinose-4-phosphate, the 3′-OH is the only hydroxyl group available for cyclisation; furthermore, it is *cis*-configured relative to the 4-phosphate group. Before exploring potentially prebiotic routes to the 4-phosphate, we, therefore, decided to investigate the possible 4′- to 3′-phosphate migration experimentally by using material prepared by conventional synthesis. As mentioned previously, we prepared the 4-phosphate **21** in the L-series (Scheme 5), but as we planned to use ^{1}H NMR spectroscopy to monitor the potential conversion to the 3-phosphate via the 3,4-cyclic phosphate, it did not matter that our standard samples of the latter two compounds were prepared in the D-series. Encouraged by early experiments in which **21** was treated with a few equivalents of cyanoacetylene, and the 3,4-cyclic phosphate **18** appeared to be formed, we optimised the reaction, and found that when three equivalents were used, 60% conversion to L-**18** could be achieved (Figure 3a–c). Then, to our delight, we found that acidic hydrolysis of our synthetic standard of D-**18** proceeded quantitatively, and showed selectivity in favour of the 3-phosphate over the 4-phosphate, with **1** and D-**21** being formed in a 2:1 ratio (Figure 3c–f). Thus, if exposure to cyanoacetylene and subsequent hydrolysis can be deemed to be etiologically relevant, we have formally demonstrated the prebiotic conversion of arabinose-4-phosphate to the 3-phosphate in 40% overall yield, and, accordingly, we now sought a prebiotically plausible route to the 4-phosphate.

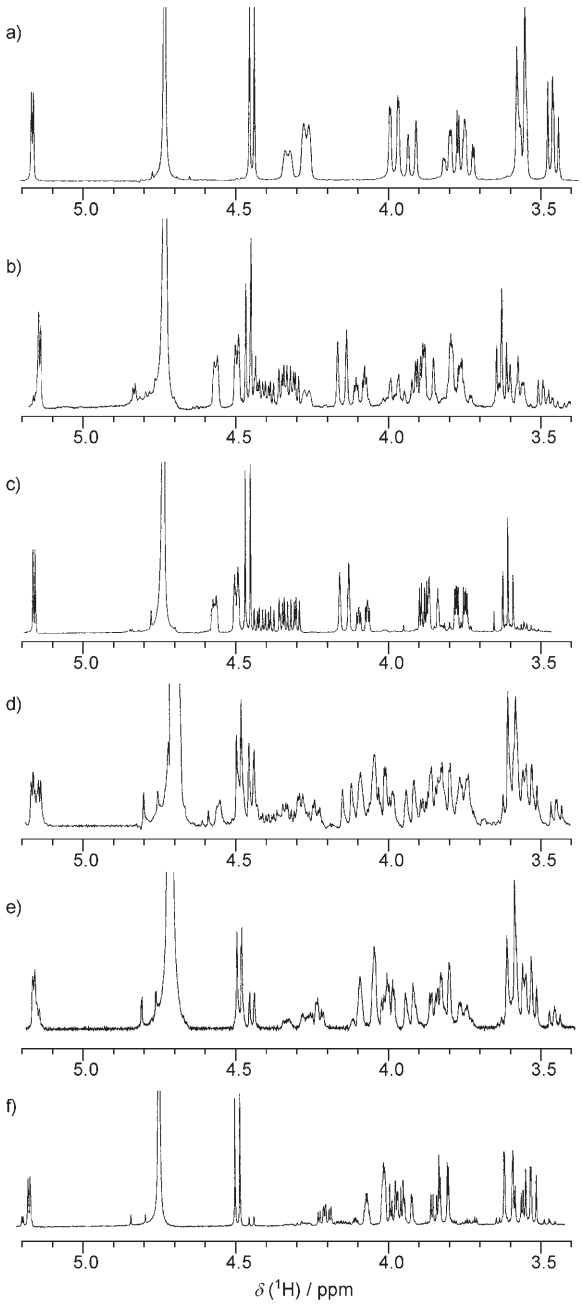
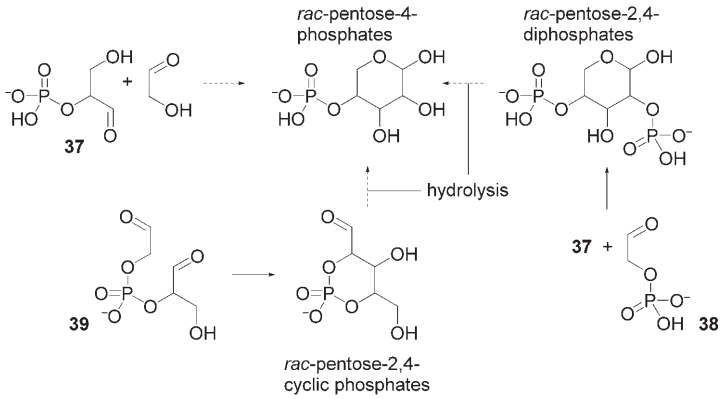


Figure 3. ^{1}H NMR spectroscopic analysis of the migration of the arabinose-4-phosphate to the 3-phosphate via the 3,4-cyclic phosphate. a) L-Arabinose-4-phosphate **21**, b) products of the reaction of **21** with cyanoacetylene in D_2O, c) authentic standard of D-arabinose-3,4-cyclic phosphate **18**, d) products of acid-catalysed hydrolysis of **18** in D_2O, e) as d) but spiked with an authentic standard of D-arabinose-3-phosphate **1**, and f) authentic standard of **1**.

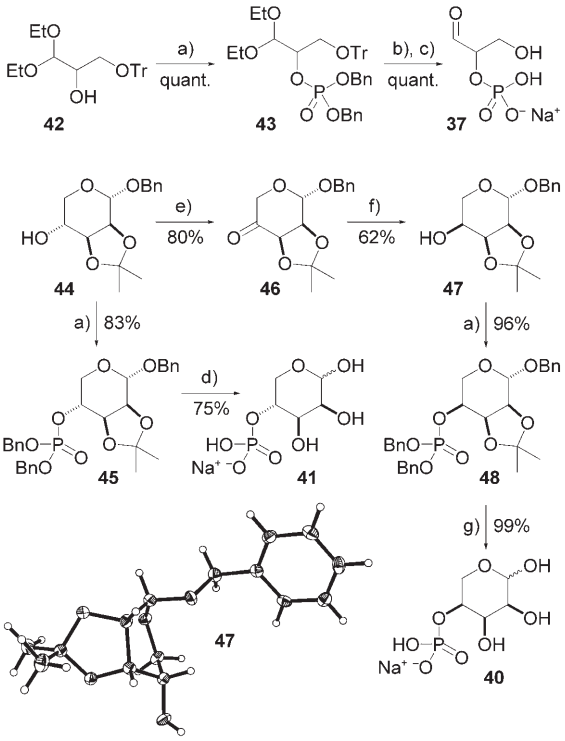
Potential formation of arabinose-4-phosphate, or derivatives thereof, by C(2)–C(3) bond-forming processes: Because arabinose-4-phosphate is not formed by direct phosphorylation of the free sugar, we initially considered several aldolisation routes to the (*rac*-)pentose-4-phosphates. Ostensibly, the simplest route involves the hetero-aldolisation of glycolaldehyde and glyceraldehyde-2-phosphate **37** with the former acting as donor, and the latter as acceptor (Scheme 8). Although this route looks simple on the face of it, it relies upon a specific hetero-aldolisation, and homo-aldolisation of either component, or the alternative hetero-aldolisation could not be ruled out a priori. Therefore, before evaluating this route experimentally, we also considered other options. The 4-phosphates could conceivably also be produced by hydrolysis of the 2,4-diphosphates which themselves have been shown to be accessible by hetero-aldolisation of glycolaldehyde phosphate **38** and **37**.[3] *rac*-Arabinose-2,4-diphosphate was a minor kinetic product of such an aldolisation, but the major component when the products were subsequently allowed to equilibrate under the same



Scheme 8. (Potential) aldolisation and hydrolysis routes to pentose-4-phosphates.

basic conditions of the reaction.[3] Despite this predisposed formation of arabinose-2,4-diphosphate, we did not pursue this route further because of the perceived difficulty of hydrolysing the 2-phosphate selectively. The (presumed) easier hydrolysis of cyclic phosphate diesters temporarily attracted our attention to arabinose-2,4-cyclic phosphate, but the intramolecular aldolisation of the acyclic diester **39**, from which this could derive, has been shown to give predominantly the *ribo*- and *xylo*-configured products.[4] With coupled aldolisation and hydrolysis routes to the 4-phosphate ruled out, we were forced to focus our attention on the first possible aldolisation route—the hetero-aldolisation of glycolaldehyde and glyceraldehyde-2-phosphate **37**. Investigation of this route demanded more conventional synthesis (Scheme 9). Firstly, we needed a synthesis of **37**, and, secondly, we decided to synthesise ribose- and lyxose-4-phosphates **40** and **41** so that, along with **21** and xylose-4-phosphate **22**, we would have ^{1}H NMR spectroscopic standards for all four pentose-4-phosphates.[16] We wanted a full set of standards of potential products in case the desired hetero-aldolisation was found to operate, but with a strong stereochemical selectivity against the *arabino*-configured product *rac*-**21**. Furthermore, there would have been other etiological implications had *rac*-**40** been produced selectively, and, anyway, we had in mind an additional use for **40** and **41** in a later part of this work.

Krishnamurthy et al. synthesised D-**37** by phosphorylation of D-glyceraldehyde by using **6**, but their procedure involved an ion-exchange chromatography step that limited scale up.[6] As enantiomeric purity of the product was unimportant for the applications we planned, we developed a route to racemic material by starting from the known acetal **42**. Phosphorylation by using tetrabenzylpyrophosphate gave the dibenzyl phosphate **43** which was deprotected to *rac*-**37** by hydrogenolysis, and acid hydrolysis. The hydrolysis was carried out in D_2O to enable convenient monitoring of reaction progress by ^{1}H NMR spectroscopy so that a slower subsequent acid-catalysed destruction of **37** could be avoided. We synthesised ribose-4-phosphate in the L-series, and lyxose-4-phosphate in the D-series from **44**, the D-enantiomer of a known L-lyxose derivative.[17] Phosphorylation of **44** by using tetrabenzylpyrophosphate gave protected D-lyxose-4-phosphate **45**. Hydrogenolytic debenzylation of **45** was followed by acid treatment to hydrolyse the acetal, and neutralisation and lyophilisation to give **41** as a sodium salt. An oxidation–reduction sequence—via ketone **46**—served to convert **44** to the L-ribose derivative **47**, the structure of which was confirmed by X-ray crystallography.[14] Phosphorylation of **47** then gave protected L-ribose-4-phosphate **48**. In this case, hydrogenolysis effected removal of the three benzyl protecting groups and the isopropylidene group, the latter presumably catalysed by the liberated monoalkyl phosphoric acid without the need for addition of exogenous acid. Finally, neutralisation with sodium hydroxide, and lyophiisation afforded L-**40** as a sodium salt.

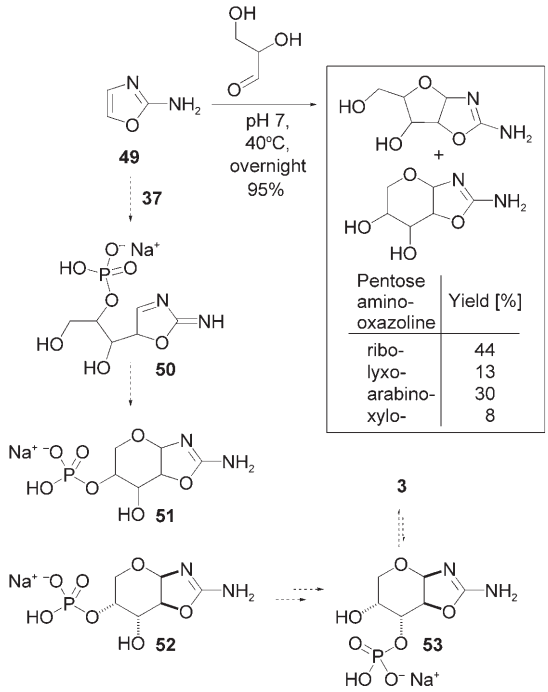


Scheme 9. Conventional synthesis of *rac*-glyceraldehyde-2-phosphate **37**, L-ribose-4-phosphate **40** and D-lyxose-4-phosphate **41**. a) *t*BuOK, THF, RT→−40 °C, $(BnO)_2P(O)OP(O)(OBn)_2$; b) H_2, Pd/C, dioxane/H_2O; c) D_2O, pD≈2.2, 50 °C, 2 d then H_2O pH→7 (NaOH aq.), d) H_2, Pd/C, MeOH then pH→1 (HCl aq.), 40 °C, 3 h then pH→7 (NaOH aq.); e) CrO_3, py, Ac_2O, CH_2Cl_2; f) $NaBH_4$, EtOH, 0 °C; g) H_2, Pd/C, MeOH then pH→7 (NaOH aq.).

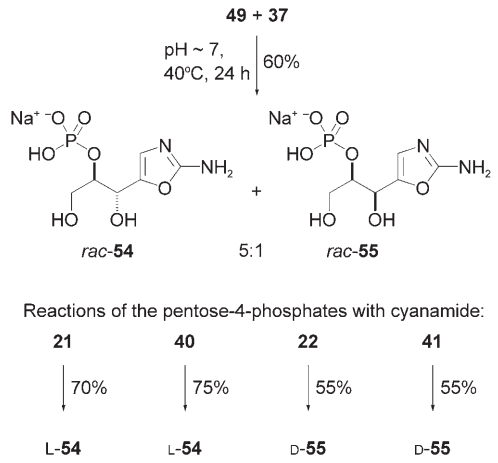
With standards of the four potential pentose-4-phosphate products in hand (albeit in enantiomerically pure rather than racemic form), we next investigated the aldol reaction of glycolaldehyde and **37**. When a 0.2 M solution in both glycolaldehyde and *rac*-**37** was incubated at pH 11 for 3 h at 60 °C, a complex mixture resulted. By ^{1}H NMR spectroscopic analysis, it was clear that a substantial amount of the initial **37** remained, but signals for residual glycolaldehyde were not apparent. Suspecting that glycolaldehyde had predominantly undergone homoaldolisation, and that **37** had

been largely unreactive under the conditions used, we subjected the two compounds to the same conditions individually. These experiments confirmed our suspicion—the glycolaldehyde was converted into a complex mixture of products whilst **37** was unchanged. We investigated several other aldol reaction conditions, but on no occasion found any evidence, by comparison of NMR spectra to those of the standards, for the synthesis of any of the pentose-4-phosphates. It can thus be concluded that whilst arabinose-3-phosphate **1** can be obtained from arabinose-4-phosphate **21** by phosphate migration, the 4-phosphate (and, indeed, any other pentose-4-phosphate) cannot be produced by a simple aldolisation process.

We recently showed that pentose aminooxazoline derivatives can be produced in an aldol-type reaction in which the 2′,3′-C–C bond is constructed (Scheme 10). The *ribo*-, *arabino*-, *xylo*- and *lyxo*-configured aminooxazolines exist in furanose forms, but the *lyxo*-configured derivative was shown to exist as an equilibrating mixture of furanose and pyranose forms. 2-Aminooxazole **49** functions as a glycolaldehyde enolate equivalent at neutral pH in this reaction, and adds to the carbonyl group of glyceraldehyde with good facial selectivity. As we have also recently found that **49** will add to glyceraldehyde-3-phosphate, we now wondered whether it would add to the 2-phosphate **37**. If such an addition took place, the resultant adducts **50** would be incapable of ring closure to furanose aminooxazoline derivatives, but there remained the possibility that the pyranose aminooxazolines **51** could form. If the phosphate of the arabinose derivative **52** could be induced to migrate from the 4′-position to the 3′-position—the successful conversion of **21** to **1** auguring well in this regard—then the resultant pyranose aminooxazoline **53** should be able to equilibrate with the furanose form **3**. The possibility of bypassing **1**, and forming **3** in this way was extremely appealing, and so we proceeded to treat **37** with **49** in the same way as we did with glyceraldehyde-3-phosphate. Upon examining the reaction products by ^{1}H NMR spectroscopy, it was apparent that both components of the reaction had been consumed, and a complex mixture had formed, but we were unable to detect any signals that we could attribute to pentose-4-phosphate aminooxazolines. Assuming that addition of **49** to **37** had taken place as envisaged, but that the adducts had not undergone cyclisation and had instead hydrated, we heated the reaction products in an attempt to bring about dehydration. Subsequent ^{1}H NMR spectroscopic analysis revealed that further reaction had taken place, but aminooxazolines had still not been formed, and instead signals consistent with two diastereoisomeric aminooxazoles presumed to be **54** and **55** (Scheme 11) were



Scheme 10. Potential formation of pentose-aminooxazoline-3′-phosphates by 2′,3′-C–C bond formation, giving the corresponding 4′-phosphates, and subsequent phosphate migration.



Scheme 11. Formation of pentose-aminooxazole-4′-phosphates.

observed. By integration of the signals assumed to be due to these aminooxazoles relative to signals for all other species present, it could be estimated that the two products were formed in a 5:1 ratio and a combined yield of 60%. To gain support for the assigned structures, and to determine the relative stereochemistry of the most abundant product, we next investigated the reaction of the pentose-4-phosphates **21**, **40**, **22** and **41** with cyanamide. Our reasoning was that **21** and **40** should give one of the diastereoisomeric aminooxazoles, and **22** and **41** should give the other. The aminooxazole products from these cyanamide reactions would presumably be enantiopure in contrast to the racemic products from the addition of **49** to **37**, but the NMR data would of course be comparable. In the event, it was found that aminooxazole products were formed in moderate to good yield by heating the pentose-4-phosphates with cyanamide in aqueous solution (Scheme 11). The major product **54** in the addition of **49** to **37** corresponded to the aminooxazole

product formed from **21** or **40** and cyanamide, and the minor product **55** corresponded to the aminooxazole formed from **22** or **41** and cyanamide. It thus appears that the pentose-4-phosphate aminooxazolines **51** (including **52**) are strained and unstable relative to the isomeric aminooxazoles **54** and **55**. In the reaction of **49** with **37**, it is not possible to say whether **54** derives from *arabino*- or *ribo*-configured initial addition products, or whether **55** derives from *xylo*- or *lyxo*-configured addition products because stereochemistry at C(2′) is lost in the subsequent conversion to aminooxazoles. However, the stereoselective formation of **54** in 50% yield in water at neutral pH is chemically noteworthy. From an etiological point of view, the successful construction of the 2′,3′-C–C bond in **54** is offset by the lack of opportunity the open chain structure affords for regioselective phosphate migration. If the phosphate could undergo migration to the 3′-position, then protonation at C(2′) would give an *arabino*- or *ribo*-configured intermediate with the potential to become the corresponding furanose aminooxazoline. In contrast to the demonstrated situation with the predominantly pyranose arabinose-4-phosphate **21**, and the presumed situation with the pyranose **52**, the open-chain structure of **54** suggests that if the phosphate were activated, both 3′,4′- and 4′,5′-cyclic phosphates would be formed. Furthermore, cyclisation would be expected to be slower than it was with **21** because of the bond rotation allowed by the open chain structure of **54**. We thus did not hold out much hope when we treated **54** with cyanoacetylene, and we were not surprised to observe a complex mixture of products by NMR spectroscopic analysis. We did not attempt to resolve this mixture or characterise any of its components and simply concluded that an efficient conversion to the 3′,4′-cyclic phosphate is not possible by using cyanoacetylene in this case.

Conclusion

The results described in this paper suggest that the previously reported conversion of arabinose-3-phosphate **1** to β-cytidine-2′,3′-cyclic phosphate **2** is not of direct etiological relevance. Direct phosphorylation of arabinose does not give **1**, neither can the 2-phosphate **14**, which is accessible, be converted to **1**. The 4-phosphate **21** can be efficiently converted to **1**, but direct formation of **21** is not possible, nor is formation by a 2′,3′-C–C bond construction process involving aldolisation of glycolaldehyde and glyceraldehyde-2-phosphate **37**. Formation of a cyanamide derivative of **21**, by addition of 2-aminooxazole **49** to **37**, is possible, but regioselective phosphate migration in this derivative is not possible. Thus, we have been able to solve the 4′- to 3′-phosphate migration or the 2′,3′-C–C bond construction problems, but not both in the same sequence. The stepwise assembly of pyrimidine nucleobases via aminooxazoline intermediates remains etiologically attractive, however, particularly as direct ribosylation of cytosine and uracil has not proved possible under prebiotically plausible conditions. The obligate 1′,2′-*cis*-relationship in the aminooxazoline intermediates means that stereochemical inversion at the 2′-position (from β-*arabino*-intermediates) or the 1′-position (from α-*ribo*-intermediates) is necessary. The fact that our previously demonstrated sequence involving 2′-inversion cannot be extended back to prebiotically plausible starting materials now makes further investigation of processes involving 1′-inversion an important objective.[18] Only when the constitutional self-assembly matrix for RNA has been fully explored (Figure 1) will it be possible to draw firm conclusions about the likelihood of a prebiotic origin of this nucleic acid.

Experimental Section

General: Reagents and solvents are from Fluka, Aldrich, and Lancaster. Petroleum ether (40–60) was used. TLC: Merck Kieselgel 60 F_{254}; detection by UV or by dipping plates in EtOH/anisaldehyde/concentrated H_2SO_4/AcOH 180:10:10:2 or 5% (w/v) ammonium molybdate in H_2SO_4 (1.0 M) followed by heating with a heat gun. Flash chromatography: Sorbisil C_{60} silica gel. M.p.: Sanyo Gallenkamp, uncorrected. FTIR: AT1 Mattson Genesis series spectrophotometer (KBr disc, Nujol mull, film or solution), $\tilde{\nu}$ in cm^{-1}. NMR: Varian INOVA 300E, Varian INOVA 400, Varian UNITY 500; δ in ppm, J in Hz, assignments by COSY, HMBC, HMQC (app.: apparent, br: broad). EIMS/CIMS: Micromass Trio 2000; ESIMS, APCIMS: Micromass Platform; HRMS: Thermofinnigan MAT95XP. HPLC: Gilson semi-preparative system: Rainin Dynamax-60 Å Si83-141-C, Rainin Dynamax-60 Å C_{18} 21.2 mm × 25 cm; Gilson 115 UV detector, 255 nm.

1-*O*-Benzyl-3,4-*O*-isopropylidene-β-D-arabinopyranoside-2-*O*-dibenzylphosphate (16): A sample of **15**[12] was dried over P_2O_5 overnight under high vacuum. A mixture of **15** (400 mg, 1.43 mmol), powdered dried 3 Å molecular sieves (600 mg) and $(BnO)_2PN(iPr)_2$ (0.94 mL, 2.86 mmol) in anhydrous MeCN (8 mL) was stirred at RT for 20 min under N_2. Then a solution of 1*H*-tetrazole in MeCN (0.45 M, 25.4 mL, 11.44 mmol) was added and the reaction mixture left to stir at RT. After 4 h, *t*BuOOH (70% (aq.), 6.5 mL, 4.60 mmol) was added and stirring was continued for a further 1 h. The mixture was then filtered through Celite and the filtrate concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), washed with $NaHCO_3$ (aq. saturated, 3 × 30 mL), then brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification first by flash chromatography (cyclohexane/EtOAc 8:2 then 7:3), and then by normal phase HPLC (hexane/EtOAc 1:1), gave **16** as a white solid (500 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (3H, s; Me), 1.53 (3H, s; Me), 3.98–4.08 (2H, m; $H_2C(5)$), 4.27 (1H, app. d; J = 5.3 Hz; H–C(4)), 4.39–4.48 (1H, m; H–C(3)), 4.50–4.58 (1H, m; H–C(2)), 4.52–4.75 (2H, AB q, J = 12.0 Hz; PhCH_2), 5.04 (d, J = 7.5 Hz; H–C(1)), 5.06–5.15 (4H, m; 2 × PhCH_2OP), 7.30–7.41 ppm (10H, m; Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 26.68 (Me), 28.35 (Me), 59.13 (PhCH_2), 69.37 (d, J = 5.4 Hz; PhCH_2OP), 69.73 (d, J = 5.7 Hz; PhCH_2OP), 70.10 (C(5)), 74.03 (C(4)), 74.34 (d, J = 6.6, C(3)), 76.57 (d, J = 5.9, C(2)), 96.56 (C(1)), 109.65 (Me$_2C$), 127.82–128.85, 136.06, 136.13, 136.16, 136.23, 137.26 ppm (Ar); ESIMS (pos., MeCN): m/z (%): 541 (10) $[M+H]^+$, 563 (100) $[M+Na]^+$.

Sodium 1-*O*-benzyl-β-D-arabinopyranoside-2-*O*-phosphate (17): Me_3SiBr (0.33 mL, 2.58 mmol) was added dropwise under N_2 to a stirred solution of **16** (348 mg, 0.64 mmol) in anhydrous CH_2Cl_2 (10 mL). After stirring for 1 h, the solution was concentrated, and the residue stirred in H_2O (6 mL, pH → 1) overnight. The pH was then adjusted to 6.5 by addition of a concentrated solution of NaOH aq., and the mixture was lyophilised to furnish **17** (205 mg, quant.). ^{1}H NMR (500 MHz, D_2O): δ = 3.40 (1H, ABX dd, J_{AB} = 12.6, J_{AX} = 1.8 Hz; H–C(5)), 3.64 (1H, ABX br d, J = 12.6 Hz; H–C(5′)), 3.71 (1H, dd, J = 10.2, 3.5 Hz; H–C(3)), 3.75 (1H, m; H–C(4)), 4.03 (1H, dt, J = 9.5, 3.7 Hz, H–C(2)), 4.39–4.48 (2H, AB q, J = 11.7 Hz; PhCH_2), 4.93 (1H, d, J = 3.9 Hz; H–C(1)), 7.14–7.25 ppm (5H,

m; Ar); ^{13}C NMR (125.7 MHz, D_2O): δ=62.61 (Ph*C*H$_2$), 69.12 (C(4)), 70.25 (C(5)), 71.03 (C(3)), 98.28 (d, J=26.5 Hz; C(1)), 128.56–129.02, 137.26 ppm (Ar); ^{31}P NMR (121.5 MHz, D_2O): δ=4.29 ppm (br s); ESIMS (neg., H_2O): m/z (%): 319 (100) $[M+H]^-$, 341 (5) $[M+Na]^-$; HR-ESIMS: (neg., H_2O): m/z: calcd for $C_{12}H_{16}O_8P$: 319.0588; found: 319.0588.

Sodium D-arabinose-2-phosphate (14): Pd/C (10% Pd, 100 mg) was added to a solution of **17** (195 mg, 0.61 mmol) in H_2O/THF (1:1, 14 mL). After degassing (N_2), the mixture was stirred under H_2 overnight at RT. Filtration through Celite and lyophilisation of the filtrate afforded **14** (167 mg, quant.) as a white solid. ^{1}H NMR (300 MHz, D_2O): δ=3.61–3.80 (2H, m; H−C(4), H−C(5)), 3.84–4.17 (3H, m; H−C(2), H−C(3), H−C(5′)), 4.54 (0.47H, d, J=7.4 Hz; H−C(1) (α-p)), 5.26 (0.43H, d, J=3.4 Hz; H−C(1) (β-p)), 5.35 ppm (0.1H, 2×app.s; H−C(1) (f)); ^{13}C NMR (75.4 MHz, D_2O): δ=62.45, 66.19, 68.21, 71.45, 72.80, 74.92 (C(2), C(3), C(4), C(5) (α, β)), 92.33 (d, J=5.3 Hz; C(1) (β-p)), 96.66 ppm (d, J=5.4 Hz; C(1) (α-p)); ^{31}P NMR (121.5 MHz, D_2O): δ=3.82 (s), 4.46 ppm (s); ESIMS (neg., H_2O): m/z (%): 229 (100) $[M+H]^-$; ESIMS (pos., H_2O): m/z: 253 (35) $[M+Na+2H]^+$, 275 (25) $[M+2Na+H]^+$, 297 (100) $[M+3Na]^+$; HR-ESIMS (neg., H_2O): m/z: calcd for $C_5H_{10}O_8P$: 229.0119; found: 229.0124.

1,2-Di-*O*-benzyl-β-D-arabinopyranoside (19): NaH (60% in oil, 429 mg) was added to a stirred solution of **15** (2.00 g, 7.14 mmol) in anhydrous THF (10 mL), and stirring was then continued for 30 min at RT. A solution of $PhCH_2Br$ (1.20 mL, 9.99 mmol) in anhydrous DMF (5 mL) was then added dropwise, and the mixture was stirred at RT overnight. The reaction was quenched with AcOH then concentrated in vacuo. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ aq. and then brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (cyclohexane/EtOAc 95:5 then 90:10) gave 1,2-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-arabinopyranoside (2.36 g, 90%) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.43 (3H, s; Me), 1.50 (3H, s; Me), 3.61 (1H, dd, J=7.8, 3.4 Hz; H−C(2)), 3.95–4.07 (2H, m; $H_2C(5)$), 4.28 (1H, app.d, J=5.3 Hz; H−C(4)), 4.46 (1H, dd, J=7.8, 5.8 Hz; H−C(3)), 4.59–4.80 (2H, AB q, J=12.4 Hz; $PhCH_2OC(2)$), 4.70–4.80 (2H, AB q, J=12.6 Hz; $PhCH_2OC(1)$), 4.93 (1H, d, J=3.4 Hz; H−C(1)), 7.33–7.47 ppm (10H, m; Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=24.30 (Me), 27.42 (Me), 57.52 ($PhCH_2$), 67.62 ($PhCH_2$), 70.56 (C(5)), 72.14 (C(4)), 74.09 (C(3)), 75.50 (C(2)), 94.39 (C(1)), 107.18 (Me_2C), 126.08–126.94, 136.03, 137.02 ppm (Ar); ESIMS (pos., MeOH): m/z (%): 393 (100) $[M+Na]^+$; HR-ESIMS (pos., MeOH): m/z: calcd for $C_{22}H_{26}O_5Na$: 393.1672; found: 393.1667. To a solution of this compound (2 g, 5.41 mmol) in THF (20 mL) was added a solution of 1M HCl. The mixture was stirred at 30°C overnight, then concentrated in vacuo to give **19** (1.71 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.76 (1H, ABX dd, J_{AB}=12.6, J_{AX}=1.9 Hz; H−C(5)), 3.78 (1H, dd, J=9.5, 3.6 Hz; H−C(2)), 3.91 (1H, ABX br d, J_{AB}=12.6 Hz; H−C(5′)), 4.05 (1H, m; H−C(4)), 4.12 (1H, dd, J=9.5, 3.3 Hz; H−C(3)), 4.52–4.77 (2H, AB q, J=12.1 Hz; $PhCH_2OC(1)$), 4.54–4.60 (2H, AB q, J=11.5 Hz; $PhCH_2OC(2)$), 5.00 (1H, d, J=3.3 Hz; H−C(1)), 7.30–7.45 ppm (10H, m; Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=62.32 ($PhCH_2$), 68.77 (C(4)), 69.17 (C(3)), 69.41 (C(5)), 72.52 (C(2)), 95.66 (C(1)), 128.15–128.92, 137.51, 138.05 ppm (Ar); ESIMS (pos., MeOH): m/z (%): 353 (100) $[M+Na]^+$; HR-ESIMS (pos., MeOH): m/z: calcd for $C_{19}H_{22}O_5Na$: 353.1359; found: 353.1365.

Triethylammonium 1,2-di-*O*-benzyl-β-D-arabinopyranoside-3,4-cyclic phosphate (20): A sample of **19** was dried over P_2O_5 overnight under high vacuum. To a stirred solution of **19** (1.00 g, 3.03 mmol) in anhydrous pyridine (7.6 mL) was added $POCl_3$ (0.565 mL, 6.06 mmol), and stirring was then continued at 25°C overnight. A mixture of Et_3N (6 mL) and H_2O (6 mL) was added, and the resultant mixture was stirred at 25°C for 1 h before being concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH 8:2, 1% Et_3N), and then by reverse-phase HPLC (H_2O for 15 min, then MeCN/H_2O 1:1), followed by lyophilisation gave **20** as a white powder (755 mg, 56%). ^{1}H NMR (500 MHz, CD_3OD): δ=1.23 (t, J=7.0 Hz; $N(CH_2CH_3)_3$), 3.06 (q, J=7.0 Hz; $N(CH_2CH_3)_3$), 3.88–3.94 (2H, AB q, J=13.7 Hz; $H_2C(5)$), 4.03 (1H, dd, J=8.4, 3.3 Hz; H−C(2)), 4.44–4.67 (2H, AB q, J=12.1 Hz; $PhCH_2OC(1)$), 4.47–4.57 (2H, m; H−C(3), H−C(4)), 4.62–4.76 (2H, AB q, J=11.7 Hz; $PhCH_2OC(2)$), 4.89 (1H, d, J=3.1 Hz; H−C(1)), 7.25–7.38 ppm (10H, m; Ar); ^{13}C NMR (75.4 MHz, CD_3OD): δ=59.41 (C(5)), 69.24, 73.02 ($PhCH_2$), 74.70 (C(4)), 77.34 (C(3)), 77.35 (C(2)), 96.19 (C(1)), 127.54–128.28, 137.51, 137.78 ppm (Ar); ^{31}P NMR (121.5 MHz, CD_3OD): δ=17.96 ppm (s); ESIMS (neg., MeOH): m/z (%): 391 (100) $[M]^-$; HR-ESIMS (neg., MeOH): m/z: calcd for $C_{19}H_{20}O_7P$: 391.0952; found: 391.0953.

Sodium D-arabinose-3,4-cyclic phosphate (18): $Pd(OH)_2$ (20% on C, 40 mg) was added to a solution of **20** (85 mg, 0.19 mmol) in EtOH (10 mL). After degassing (N_2), the mixture was stirred under H_2 for 2 d at RT. Filtration through Celite, treatment with Na^+-Dowex-50 resin and lyophilisation of the filtrate gave **18** (37 mg, 82%) as a white powder. ^{1}H NMR (500 MHz, D_2O): δ=3.64 (0.6H, app.t, J=8.2 Hz; H−C(2) (α)), 3.79 (0.6H, ddd, J=14.5, 4.1, 2.2 Hz; H−C(5) (α)), 3.88 (0.4H, d, J=14.2 Hz; H−C(5) (β)), 3.92 (0.4H, dd, J=8.4, 3.6 Hz; H−C(2) (β)), 4.11 (0.4H, dt, J=14.2, 3.2 Hz; H−C(5′) (β)), 4.17 (0.6H, d, J=14.5 Hz; H−C(5′) (α)), 4.31–4.38 (0.6H, m; H−C(3) (α)), 4.39–4.46 (0.4H, m; H−C(3) (β)), 4.48 (0.6H, d, J=8.5 Hz; H−C(1) (α)), 4.50–4.53 (0.6H, m; H−C(4) (α)), 4.57–4.60 (0.4H, m; H−C(4) (β)), 5.17 ppm (0.4H, d, J=3.5 Hz; H−C(1) (β)); ^{13}C NMR (75.4 MHz, D_2O): δ=58.73, 63.50, 64.00 (C(5) (α, β)), 69.14 (C(2) (β)), 73.01 (C(2) (α)), 74.48, 74.66 (C(4) (α, β)), 77.13 (C(3) (β)), 79.94 (C(3) (α)), 92.03 (C(1) (β)), 95.44 (C(1) (α)); ^{1}H-decoupled ^{31}P NMR (161.9 MHz, D_2O): δ=15.75 (s); ESIMS (pos., H_2O): m/z: 235 (15) $[M+Na+H]^+$, 257 (10) $[M+2Na]^+$; HR-ESIMS (pos., H_2O): m/z: calcd for $C_5H_8O_7Na_2P$: 256.9798; found: 256.9795.

1-*O*-Benzyl-2,3-(2,3-dimethoxybut-2,3-diyl)-β-L-arabinopyranoside-4-*O*-dibenzylphosphate (24): A solution of *t*BuOK in THF (1M, 0.94 mL) was added dropwise at RT to a solution of **23** (1.52 g, 4.28 mmol) in anhydrous THF (30 mL) under N_2. After 20 min, the solution was cooled to −40°C before addition of a solution of $((BnO)_2P(O))_2O$ (3.46 g, 6.42 mmol) in anhydrous THF (8 mL). After 20 min at −40°C, the solution was allowed to warm to 0°C for 1 h, then for 2 h at RT before AcOH (0.2 mL) was added. After concentration in vacuo, the residue was diluted with EtOAc, washed with H_2O and brine and then dried (Na_2SO_4). Purification by flash chromatography (cyclohexane/EtOAc 4:1 then 7:3) afforded **24** (2.82 g, quant.) as a colourless oil. R_f=0.53 (cyclohexane/EtOAc 1:1); $[\alpha]_D^{24}$=+33 (c=0.7 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.22 (3H, s; Me), 1.32 (3H, s; Me), 3.19 (3H, s; OMe), 3.26 (3H, s; OMe), 3.71 (1H, ABX dd, J_{AB}=13.1, J_{AX}=1.7 Hz; H−C(5)), 3.83 (1H, ABX d, J_{AB}=13.1 Hz; H−C(5′)), 4.20 (2H, m; H−C(2), H−C(3)), 4.71–4.76 (2H, AB q, J=12.6 Hz; $PhCH_2OC$), 4.76 (1H, m; H−C(4)), 4.97 (1H, d, J=3.1 Hz; H−C(1)), 5.08 (1H, ABX dd, J_{AB}=11.8, J_{AX}=7.5 Hz; $PhCH_2OP$), 5.11 (1H, ABX dd, J_{AB}=11.8, J_{BX}=7.2 Hz; $PhCH_2OP$), 5.18 (1H, ABX dd, J_{AB}=12.0, J_{AX}=6.2 Hz; $PhCH_2OP$), 5.23 (1H, ABX dd, J_{AB}=12.0, J_{BX}=6.4 Hz; $PhCH_2OP$), 7.28–7.42 ppm (15H, m; Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=17.73 (Me), 17.75 (Me), 47.84 (OMe), 48.07 (O−Me), 62.71 (C(5)), 64.47 (C(2)), 65.17 (C(3)), 69.13 ($PhCH_2OP$), 69.25 ($PhCH_2OP$), 69.57 ($PhCH_2OC$), 74.55 (C(4)), 96.83 (C(1)), 99.96 (*C*−OMe), 100.10 (*C*−OMe), 127.60, 127.69, 127.86, 127.89, 128.16, 128.28, 128.34, 128.41, 128.46, 137.50 ppm (Ar); ^{1}H-decoupled ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=−4.01 ppm (s); elemental analysis calcd (%) for $C_{32}H_{39}O_{10}P$: C 62.53, H 6.40, P 5.04; found: C 62.33, H 6.60, P 5.24; APCIMS (pos., MeOH): m/z (%): 583 (100) $[M-CH_3O]^+$, 638 (15) $[M+H+Na]^+$; HR-ESIMS (pos., MeOH): m/z: calcd for $C_{32}H_{39}O_{10}NaP$: 637.2173; found: 637.2173.

Sodium L-arabinose-4-phosphate (21): A solution of **24** (1.11 g, 1.80 mmol) in MeOH (15 mL) that contained $Pd(OH)_2$ (180 mg, 0.09 mmol) was frozen, degassed and thawed three times. The mixture was then stirred under H_2 at RT overnight. Filtration through Celite, followed by concentration in vacuo afforded 2,3(2,3-dimethoxybut-2,3-diyl)-β-L-arabinopyranoside-4-phosphoric acid as a colourless foam (660 mg, quant.). $[\alpha]_D^{12}$=−19 (c=1.0 in MeOH). The α/β ratio was 7:3 in CD_3OD according to ^{1}H NMR spectroscopic integration. ^{1}H NMR (500 MHz, CD_3OD): δ=1.26 (3H, s; Me), 1.29 (3H, s; Me), 3.23 (3H, s; OMe), 3.25 (3H, s; OMe), 3.67 (0.3H, d, J=13.2 Hz; H−C(5) (β)), 3.73 (0.3H, dd, J=10.4, 7.8 Hz; H−C(2) (β)), 3.83 (1H, m; H−C(3) (β), H−C(5) (α)), 3.99 (0.7H, d, J=13.2 Hz; H−C(5) (α)), 4.09 (1.7H, m; H−C(5) (β), H−C(2) (α), H−C(3) (α)), 4.34 (0.3H, br d, J=7.3 Hz; H−C(4) (β)), 4.39

(0.7H, br d, $J=6.9$ Hz, H–C(4) (α)), 4.65 (0.3H, d, $J=7.9$ Hz; H–C(1) (β)), 5.23 ppm (0.7H, d, $J=3.5$ Hz; H–C(1) (α)); ^{13}C NMR (125.7 MHz, CD_3OD): $\delta=18.08$ (Me), 18.10 (Me), 18.16 (Me), 18.18 (Me), 48.33 (OMe), 48.40 (OMe), 48.47 (OMe), 48.49 (OMe), 62.95 (C(5) (β)), 65.73 (C(5) (α)), 66.88 (C(2) (β)), 67.22 (C(2) (α)), 69.58 (C(3) (β)), 70.08 (C(3) (α)), 74.05 (C(4) (β)), 74.83 (C(4) (α)), 92.73 (C(1) (α)), 96.80 (C(1) (β)), 101.08 ((*C*–OMe) (α)), 101.36 ((*C*–OMe) (α)), 101.40 ((*C*–OMe) (β)), 101.47 ppm ((*C*–OMe) (β)); ^{31}P NMR (161.9 MHz, CD_3OD): $\delta=3.36$ ppm (s); ESIMS (neg., MeOH): *m/z* (%): 325 (15) $[M-H_2O-H]^-$, 343 (100) $[M-H]^-$; HR-ESIMS (neg., MeOH): calcd for $C_{11}H_{20}O_{10}P$: 343.0805; found: 343.0800. To a solution of this compound (124 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) was added TFA (90%, aq., 0.25 mL) at RT and the mixture was left for 24 h. After separation of a white syrup, the yellow organic phase was removed. The white syrup was triturated with CH_2Cl_2 (5 mL) and dried in vacuo to give the free acid form of **21** (88 mg) which was dissolved in D_2O and neutralised with NaOD solution The resultant solution was lyophilised to afford **21** as a white powder (114 mg, quant.). The α/β ratio was 2:1 in D_2O according to ^{1}H NMR spectroscopic integration. ^{1}H NMR (500 MHz, D_2O): $\delta=3.54$ (0.66H, dd, $J=9.7$, 7.8 Hz; H–C(2) (α)), 3.63 (0.66H, m; H–C(3) (α)), 3.64 (0.66H, d, $J=13.4$ Hz; H_{eq}–C(5) (α)), 3.81 (0.33H, dd, $J=12.9$, 3.0 Hz; H–C(2) (β)), 3.87 (0.66H, m; H–C(5) (β)), 4.00 (0.33H, dd, $J=12.7$, 1.0 Hz; H–C(3) (β)), 4.05 (0.66H, dd, $J=13.1$, 2.2 Hz; H_{ax}–C(5) (α)), 4.33 (0.66H, m; H–C(4) (α)), 4.39 (0.33H, m; H–C(4) (β)), 4.51 (0.66H, d, $J=7.7$ Hz; H–C(1) (α)), 5.22 ppm (0.33H, d, $J=3.3$ Hz; H–C(1) (β)); ^{13}C NMR (125.7 MHz, D_2O): $\delta=61.84$ (C(2) (α)), 65.50 (C(5) (α)), 68.57 (C(3) (β)), 68.91 (C(5) (β)), 72.20 (C(2) (β)), 72.40 (C(4) (α)), 72.72 (C(4) (β)), 92.72 (C(1) (β)), 96.87 ppm (C(1) (α)); ^{31}P NMR (161.9 MHz, D_2O): $\delta=0.80$ (s), 1.67 ppm (s); ESIMS (neg., H_2O): *m/z* (%): 229 (100) $[M-2Na+H]^-$; HR-ESIMS (neg., H_2O): *m/z*: calcd for $C_5H_{10}O_8P$: 229.0119; found: 229.0115.

1-*O*-Benzyl-2,3-(2,3-dimethoxybut-2,3-diyl)-4-(4-nitrobenzoyl)-α-D-xylopyranoside (25): Compound **23** (727 mg, 2.05 mmol), PPh_3 (1.61 g, 6.15 mmol) and 4-nitrobenzoic acid (1.03 g, 6.15 mmol) were stirred in anhydrous THF (10 mL) under N_2 at RT. (iPrOC(O)N)$_2$ (1.21 mL, 6.15 mmol) was added dropwise and the resultant solution stirred at RT. After 2 d. The solution was concentrated in vacuo and the resulting yellow oil was purified by flash chromatography (cyclohexane/EtOAc 85:15) to give the product as a white powder. Recrystallisation from CH_2Cl_2/heptane gave **25** as yellow orthorhombic crystals (1.03 g, quant.). $R_f=0.64$ (cyclohexane/EtOAc 7:3); m.p. 171–173 °C; $[\alpha]_D^{25}=-83$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.27$ (3H, s; Me), 1.35 (3H, s; Me), 3.25 (3H, s; OMe), 3.30 (3H, s; OMe), 3.65 (1H, *t*, $J=10.7$ Hz; H_{ax}–C(5)), 3.87 (1H, dd, $J=10.2$, 3.6 Hz; H–C(2)), 3.94 (1H, dd, $J=10.8$, 5.8 Hz; H_{eq}–C(5)), 4.39 (1H, *t*, $J=10.0$ Hz; H–C(3)), 4.71–4.80 (2H, AB q, $J=12.5$ Hz; PhCH_2O), 4.93 (1H, d, $J=3.6$ Hz; H–C(1)), 5.20 (1H, dt, $J=10.3$, 5.8 Hz; H–C(4)), 7.30 (1H, *t*, $J=7.3$ Hz; Ar), 7.36 (2H, *t*, $J=7.4$ Hz; Ar), 7.43 (2H, d, $J=7.3$ Hz; Ar), 8.17 (2H, d, $J=8.9$ Hz; Ar), 8.29 ppm (2H, d, $J=8.9$ Hz; Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta=17.58$ (Me), 17.71 (Me), 47.70 (OMe), 47.93 (OMe), 59.16 (C(5)), 66.56 (C(3)), 68.27 (C(2)), 69.46 (PhCH_2), 70.58 (C(4)), 96.04 (C(1)), 99.61 (MeO–*C*), 99.94 (MeO–*C*), 123.51, 123.57, 127.67, 127.88, 128.28, 128.79, 130.72, 135.09, 137.19, 150.58 (Ar), 163.72 ppm (C=O); IR (film, CH_2Cl_2): $\tilde{\nu}=$ 1732 (CO), 1529, 1350 cm^{-1} (N=O); elemental analysis calcd (%) for $C_{25}H_{29}O_{10}N$: C 59.64, H 5.81, N 2.78; found: C 59.87, H 5.91, N 2.75; APCIMS (neg., MeOH): *m/z* (%): 503 (50) $[M]^-$, 504 (100) $[M+H]^-$.

1-*O*-Benzyl-2,3-(2,3-dimethoxybut-2,3-diyl)-α-D-xylopyranoside (26): A methanolic NH_3 solution (saturated, 60 mL) was added to a solution of **25** (8.12 g, 16.12 mmol) in CH_2Cl_2 (25 mL) and the resultant mixture was kept at 60 °C overnight After concentration in vacuo, the resulting yellow powder (10 g) was purified by flash chromatography (EtOAc/cyclohexane 1:3) to afford **26** (5.35 g, 93%) as a yellow-glassy syrup. $R_f=0.25$ (cyclohexane/EtOAc 7:3); $[\alpha]_D^{21}=-27$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.33$ (3H, s; Me), 1.35 (3H, s; Me), 3.24 (3H, s; OMe), 3.30 (3H, s; OMe), 3.57 (1H, app.t, $J=10.7$ Hz; H_{ax}–C(5)), 3.67 (1H, app.t, $J=5.4$ Hz; H_{eq}–C(5)), 3.70 (1H, dd, $J=10.3$, 3.6 Hz; H–C(2)), 3.85 (1H, dt, $J=9.9$, 5.7 Hz; H–C(4)), 4.04 (1H, dd, $J=10.2$, 9.3 Hz; H–C(3)), 4.67–4.77 (2H, AB q, $J=12.5$ Hz; PhCH_2O), 4.86 (1H, d, $J=3.6$ Hz; H–C(1)), 7.29 (1H, t, $J=7.5$ Hz; Ar), 7.27 (2H, t, $J=7.5$ Hz; Ar), 7.35 ppm (2H, d, $J=7.4$ Hz; Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta=17.64$ (Me), 17.78 (Me), 47.82 (OMe), 47.89 (OMe), 62.11 (C(5)), 67.98 (C(2)), 68.14 (C(4)), 69.08 (PhCH_2), 69.93 (C(3)), 96.10 (C(1)), 99.43 (MeO–*C*), 99.84 (MeO–*C*), 127.53, 127.90, 128.23, 137.37 ppm (Ar); IR (film, CH_2Cl_2): $\tilde{\nu}=3469$–3399 cm^{-1} (br OH); CIMS (pos., MeOH): *m/z* (%): 372 (60) $[M+NH_4]^+$; HR-CIMS (pos., MeOH): *m/z*: calcd for $C_{18}H_{30}O_7N$: 372.2017; found: 372.2020.

1-*O*-Benzyl-2,3-(2,3-dimethoxybut-2,3-diyl)-α-D-xylopyranoside-4-*O*-dibenzylphosphate (27): Synthesised from **26** (130 mg, 0.37 mmol) by the same procedure as **24** was from **23**. Purification by flash chromatography (PhMe/EtOAc 4:1) afforded **27** as a colourless oil (230 mg, quant.). $R_f=$ 0.60 (cyclohexane/EtOAc 1:1); $[\alpha]_D^{21}=-20$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.24$ (3H, s; Me), 1.32 (3H, s; Me), 3.23 (3H, s; OMe), 3.27 (3H, s; OMe), 3.58 (1H, t, $J=10.8$ Hz; H_{ax}–C(5)), 3.73 (1H, dd, $J=11.1$, 5.5 Hz; H_{eq}–C(5)), 3.74 (1H, dd, $J=10.1$, 3.6 Hz; H–C(2)), 4.12 (1H, t, $J=9.8$ Hz; H–C(3)), 4.40 (1H, m; H–C(4)), 4.60–4.75 (2H, AB q, $J=12.2$ Hz; PhCH_2OC), 4.88 (1H, d, $J=3.5$ Hz; H–C(1)), 5.13 (4H, m; PhCH_2OP), 7.30–7.42 ppm (15H, m; Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta=17.57$ (Me), 17.69 (Me), 47.78 (OMe), 47.90 (OMe), 60.43 (C(5)), 67.76 (C(3)), 68.09 (C(2)), 69.12 (PhCH_2), 69.25, 69.29 (PhCH_2OP), 72.98 (C(4)), 95.76 (C(1)), 99.51 (*C*–OMe), 99.88 (*C*–OMe), 127.62, 127.69, 127.88, 128.01, 128.27, 128.40, 128.50, 135.66, 135.75, 137.18 ppm (Ar); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta=-1.26$ ppm (sextet, $J=7.3$ Hz); APCIMS (pos., MeOH): *m/z* (%): 583 (20) $[M-CH_3O]^+$, 637 (85) $[M+Na]^+$; HR-ESIMS (pos., MeOH): *m/z*: calcd for $C_{32}H_{39}O_{10}NaP$: 637.2173; found: 637.2175.

Sodium D-xylose-4-phosphate (22): A solution of **27** (709 mg, 1.15 mmol) in MeOH (10 mL) that contained $Pd(OH)_2$ (40 mg, 0.06 mmol) was frozen, degassed and thawed twice. The mixture was then stirred under H_2 at RT overnight. Filtration through Celite followed by concentration in vacuo afforded the ketal, 2,3-(2,3-dimethoxybut-2,3-diyl)-α-D-xylopyranoside-4-phosphoric acid, and fully deprotected material in a 4:1 ratio as a colourless foam. Data for the ketal: ^{1}H NMR (500 MHz, CD_3OD): $\delta=$ 1.27 (1.5H, s; Me), 1.28 (1.5H, s; Me), 1.29 (3H, 2×s; 2×Me), 3.24 (1.5H, s; OMe), 3.27 (1.5H, s; OMe), 3.28 (1.5H, s; OMe), 3.29 (1.5H, s; OMe), 3.38 (0.5H; H–C(2) (β) partially obscured), 3.41 (0.5H, dd, $J=$ 11.7, 9.8 Hz; H–C(5) (β)), 3.63 (0.5H, dd, $J=10.1$, 3.8 Hz; H–C(2) (α)), 3.73 (0.5H, app.t, $J=9.7$ Hz; H–C(3) (β)), 3.81 (1H, m; H–C(5) (α)), 4.06 (0.5H, app.t, $J=9.6$ Hz; H–C(3) (α)), 4.12 (0.5H, dd, $J=11.7$, 5.4 Hz; H–C(5) (β)), 4.23 (1H, m; H–C(4) (α,β)), 4.60 (0.5H, d, $J=$ 7.9 Hz; H–C(1) (β)), 5.05 ppm (0.5H, d, $J=3.5$ Hz; H–C(1) (α)); ^{13}C NMR (75.4 MHz, CD_3OD): $\delta=17.95$ (Me), 18.05 (Me), 47.36 (OMe), 48.24 (OMe), 48.31 (OMe), 48.36 (OMe), 61.63 (C(5)), 68.92–70.04 (overlapping C(2), C(3)), 71.91 (C(2)), 72.46 (C(4)), 101.08 (C(1) (β)), 101.36 ppm (C(1) (α)); ^{31}P NMR (161.9 MHz, CD_3OD): $\delta=2.30$ (d, $J=$ 8.6 Hz, (β)), 2.36 (d, $J=8.6$ Hz, (α)); ESIMS (neg., MeOH): *m/z*: 343 (100) $[M-H]^-$; HR-ESIMS (neg., MeOH): *m/z*: calcd for $C_{11}H_{20}O_{10}P$: 343.0800; found: 343.0802. To a solution of all of this mixture in CH_2Cl_2 (5 mL) was added TFA (90%, aq., 0.25 mL). The mixture was left at RT for 24 h. After separation of a white syrup, the yellow organic phase was removed. The white syrup was triturated with CH_2Cl_2 (5 mL) and dried in vacuo. The residue was dissolved in D_2O and neutralised with NaOD solution, and the resultant solution lyophilised to afford **22** as a white powder (295 mg, 96%). $[\alpha]_D^{24}=+30$ ($c=1.1$ in H_2O). The α/β ratio was 1:2 in D_2O according to ^{1}H NMR spectroscopic integration. ^{1}H NMR (500 MHz, D_2O): $\delta=3.27$ (0.66H, dd, $J=9.0$, 8.0 Hz; H–C(2) (β)), 3.34 (0.66H, dd, $J=11.2$, 10.6 Hz; H_{ax}–C(5) (β)), 3.56 (0.66H, t, $J=9.1$ Hz; H–C(3) (β)), 3.57 (0.33H, dd, $J=9.2$, 3.2 Hz; H–C(2) (α)), 3.70 (0.33H, t, $J=10.9$ Hz; H_{ax}–C(5) (α)), 3.76 (0.33H, t, $J=9.1$ Hz; H–C(3) (α)), 3.81 (0.33H, dd, $J=11.3$, 5.6 Hz; H_{eq}–C(5) (α)), 3.97 (1H, m, H–C(4) (α,β)), 4.05 (0.66H, dd, $J=11.4$, 5.6 Hz; H_{eq}–C(5) (β)), 4.57 (0.66H, d, $J=$ 7.9 Hz; H–C(1) (β)), 5.16 ppm (0.33H, d, $J=3.7$ Hz; H–C(1) (α)); ^{13}C NMR (125.7 MHz, D_2O): $\delta=58.88$ (C(5) (α)), 64.16 (C(5) (β)), 71.05 (C(2) (α)), 71.85 (C(4) (α, β)), 72.14 (C(3) (α)), 73.64 (C(2) (β)), 75.30 (C(3) (β)), 91.70 (C(1) (α)), 96.17 ppm (C(1)(β)); ^{31}P NMR (161.9 MHz, D_2O): $\delta=3.87$ ppm (s, (α)), 4.01 (s, (β)); ESIMS (neg., H_2O): *m/z* (%): 229 (100) $[M-2Na+H]^-$; HR-ESIMS (pos., H_2O): *m/z*: calcd $C_5H_{10}O_8Na_2P$: 274.9903; found: 274.9904.

Reaction of sodium D-arabinose-2-phosphate (14) with cyanoacetylene: A solution of **14** (30 mg, 0.11 mmol) in D_2O (0.6 mL) at pD 7 was prepared. A solution of cyanoacetylene in D_2O (1 M, 0.22 mL, 0.22 mmol, 2 equiv) was then added, and the resultant mixture was allowed to stand at RT. The reaction was monitored by ^{1}H NMR spectroscopy with the spectra being recorded after 1 h, 5 h, 1 d and 4 d.

Reaction of sodium L-arabinose-4-phosphate (21) with cyanoacetylene: A solution of cyanoacetylene in D_2O (1 M, 0.21 mL, 0.21 mmol, 3 equiv), was added to a solution of **21** (18 mg, 0.07 mmol) in D_2O (0.5 mL; final pD 6.49). After 20 h at 60 °C, the solution was lyophilised to give a red powder (22 mg) which was redissolved in D_2O. ^{1}H NMR spectroscopic analysis showed 60 % conversion to the 3,4-cyclic-phosphate **18** (Figure 3).

Hydrolysis of sodium D-arabinose-3,4-cyclic phosphate (18): A solution of **18** (10.5 mg, 0.043 mmol) in D_2O (1 mL) was prepared and the pD adjusted to 2 with a solution of DCl. The volume was then adjusted to 1.5 mL with D_2O. The mixture was kept at RT, and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. After 4 d, the starting material was observed to have been consumed. Spiking of the ^{1}H NMR spectroscopic sample with authentic standards of D-arabinose-3-phosphate (**1**) and L-arabinose-4-phosphate (**21**) enabled the hydrolysis products to be identified as **1** and **21** in a ratio of 0.67:0.33 (Figure 3).

2-Dibenzylphosphoryl-3-triphenylmethylglyceraldehyde diethyl acetal (42): A solution of *t*BuOK (473 mg, 4.22 mmol) in THF (9 mL) was added dropwise at RT to a solution of **41**[19] (1.23 g, 3.01 mmol) in anhydrous THF (15 mL) under N_2. After stirring for 20 min, the solution was cooled to −40 °C and a solution of $((BnO)_2P(O))_2O$ (2.60 g, 4.83 mmol) in anhydrous THF (6 mL) was added. After 40 min at −40 °C, the solution was allowed to warm to 0 °C and stirred for 1 h then at RT for a further 3 h. NH_4Cl aq. (50 % saturated, 15 mL) and EtOAc (15 mL) were added to the mixture. The aqueous phase was extracted with EtOAc (2× 10 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ aq. (50 % saturated, 20 mL), H_2O (20 mL) and brine (20 mL), and was then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc 4:1) afforded **42** as a colourless oil (1.99 g, 99 %). R_f = 0.26 (petroleum ether/EtOAc 7:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (3H, t, J = 7.1 Hz; Me), 1.18 (3H, t, J = 6.9 Hz; Me), 3.34 (1H, dd, J = 10.6, 5.2 Hz; H−C(3)), 3.50 (1H, qd, J = 9.1, 7.1 Hz; CH_2CH_3), 3.53–3.61 (2H, m; CH_2CH_3, H−C(3)), 3.64 (1H, qd, J = 9.1, 7.1 Hz; CH_2CH_3), 3.73 (1H, qd, J = 9.1, 7.1 Hz; CH_2CH_3), 4.62 (1H, m; H−C(2)), 4.81 (1H, d, J = 5.7 Hz; H−C(1)), 5.04 (2H, ABX dt, J_{AB} = 12.0, J_{AX} = J_{BX} = 7.3 Hz; PhCH_2OP), 5.10 (2H, ABX dt, J_{AB} = 12.0, J_{AX} = J_{BX} = 7.3 Hz; PhCH_2OP), 7.20–7.37 (19H, m; Ar), 7.46–7.51 ppm (6H, m; Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.05 (Me), 15.17 (Me), 62.74 (OCH_2CH_3), 62.76, 62.79 (C(3)), 63.67 (OCH_2CH_3), 68.98 (2 PhCH_2OP), 77.78 (C(2)), 86.67 (CPh_3), 100.81 (C(1)), 126.93, 127.67, 127.72, 127.76, 128.18, 128.37, 127.38, 128.71, 135.95, 136.04, 143.64 ppm (Ar); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = −0.41 ppm (sextet, J = 8.5 Hz); elemental analysis calcd for $C_{40}H_{43}O_7P$: C 72.06, H 6.50, P 4.65; found: C 72.02, H 6.70, P 4.43; ESIMS (pos., MeOH): m/z (%): 684 (20) $[M+NH_4]^+$, 689 (100) $[M+Na]^+$, 690 (40) $[M+Na+H]^+$; HR-ESIMS (pos., MeOH): m/z: calcd for $C_{40}H_{43}O_7NaP$: 689.2639; found: 689.2639.

Sodium glyceraldehyde-2-phosphate (37): A solution of **42** (829 mg, 1.24 mmol) in dioxane/H_2O (2:1, 15 mL) that contains Pd/C (5 % Pd, 66 mg) was frozen, degassed and thawed three times before being stirred under H_2 at RT overnight. H_2O (5 mL) was then added and the mixture was filtered through Celite. After rinsing the Celite with dioxane/H_2O (1:1, 40 mL), the combined filtrates were lyophilised. CH_2Cl_2 (10 mL) and H_2O (5 mL) were added to the lyophilisate, and the resulting mixture shaken to effect dissolution of solids. After separation, the organic phase was extracted with H_2O (3×10 mL) and the combined aqueous phases were washed with CH_2Cl_2 (2×10 mL). The aqueous phase was then lyophilised and the resulting colourless oil (276 mg) was dissolved in D_2O (2.7 mL) and filtered through a 0.2 μm filter. The pD was adjusted to 2.2 (NaOD) and the solution was then warmed at 50 °C for 2 d. The hydrolysis was monitored by ^{1}H NMR spectroscopic analysis. After complete hydrolysis of the acetal, the pD was adjusted to ≈6 (NaOD) and the solution lyophilised to afford glyceraldehyde-2-phosphate **37** as the sodium salt (244 mg, 94 %). ^{1}H NMR (500 MHz, D_2O): δ = 3.64 (2H, m; H−C(3)), 3.96 (1H, m; H−C(2)), 4.94 ppm (1H, d, J = 3.8 Hz; H−C(1)); ^{13}C NMR (75.4 MHz, D_2O): δ = 61.64 (C(3)), 77.25 (C(2)), 89.48 ppm (C(1)); ^{1}H-decoupled ^{31}P NMR (161.9 MHz, D_2O): δ = 5.30 ppm (s); ESIMS (neg., H_2O): m/z (%): 169 (100) $[M]^-$; HR-ESIMS (neg., H_2O): m/z: calcd for $C_3H_6O_6P$: 168.9907; found: 168.9910.

1-*O*-Benzyl-2,3-*O*-isopropylidene-α-D-lyxopyranoside-4-*O*-dibenzylphosphate (45): A solution of *t*BuOK (274 mg, 2.45 mmol) in THF (5 mL) was added dropwise at RT to a solution of **44** (489 mg, 1.75 mmol) in anhydrous THF (15 mL) under N_2. After 20 min, the solution was cooled to −40 °C before a solution of $((BnO)_2P(O))_2O$ (1.50 g, 2.79 mmol) in anhydrous THF (5 mL) was added. After 40 min at −40 °C, the solution was allowed to warm to 0 °C for 1 h and then RT for 4 h. NH_4Cl (aq., 50 % saturated, 10 mL) was added, and the mixture was extracted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (15 mL) and the combined organic phases were washed with $NaHCO_3$ aq. (50 % saturated, 15 mL), H_2O (10 mL) and brine (20 mL). The resulting mixture was dried ($MgSO_4$) before filtration and the concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (petroleum ether/EtOAc 3:1) to afford **45** (779 mg, 83 %) as a colourless oil. R_f = 0.66 (petroleum ether/EtOAc 3:2); $[\alpha]_D^{24}$ = +26 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (3H, s; Me), 1.42 (3H, s; Me), 3.68 (1H, ABX q, J_{AB} = 11.4, J_{AX} = 8.8 Hz; H_{ax}−C(5)), 3.74 (1H, ABX q, J_{AB} = 11.6, J_{BX} = 4.7 Hz; H_{eq}−C(5)), 4.14 (1H, dd, J = 5.4, 1.9 Hz; H−C(2)), 4.22 (1H, app. t, J = 5.8 Hz; H−C(3)), 4.49 (1H, m; H−C(4)), 4.55–4.77 (2H, AB q, J = 11.8 Hz; PhCH_2OC), 4.91 (1H, d, J = 1.9 Hz; H−C(1)), 5.07 (2H, d, J = 7.5 Hz; PhCH_2OP), 5.09 (2H, dd, J = 7.8, 3.3 Hz; PhCH_2OP), 7.31–7.39 ppm (15H, m; Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.27 (Me), 27.74 (Me), 59.46 (C(5)), 69.30 (PhCH_2OP), 69.35 (PhCH_2OC), 69.50 (PhCH_2OP), 75.35 (C(4)), 75.71 (C(2)), 75.77 (C(3)), 96.84 (C(1)), 109.72 (Me_2C), 127.89, 127.95, 127.98, 128.47, 128.50, 128.51, 135.61, 135.67, 135.72, 136.74 ppm (Ar); ^{1}H-decoupled ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = −3.32 ppm (s); elemental analysis calcd (%) for $C_{29}H_{33}O_8P$: C 64.44, H 6.15, P 5.73; found: C 64.23, H 6.43, P 5.75; ESIMS (pos., MeOH): m/z (%): 563 (100) $[M+Na]^+$, 564 (40) $[M+H+Na]^+$; HR-ESIMS (pos., MeOH): m/z: calcd for $C_{29}H_{33}O_8NaP$: 563.1805; found: 563.1809.

Sodium D-lyxose-4-phosphate (41): A solution of **45** (323 mg, 0.60 mmol) in MeOH (10 mL) with Pd/C (5 % Pd, 32 mg) was frozen, degassed and thawed. The mixture was then stirred under H_2 at RT overnight. After this time, the mixture was filtered through Celite and the plug was rinsed with MeOH (5 mL). The pH was adjusted to 1 with HCl aq. and the solution was warmed for 3 h at 40 °C. After neutralization to pH ≈ 6 (NaOH), the solution was partially concentrated in vacuo then lyophilised to afford **41** as a white powder (124 mg, 75 %). The β/α ratio was 3:1 in D_2O according to ^{1}H NMR spectroscopic integration. ^{1}H NMR (300 MHz, D_2O): δ = 3.29 (0.25H, dd, J = 12.0, 8.3 Hz; H−C(5) (α)), 3.42 (0.75H, dd, J = 5.8, 3.2 Hz; H−C(2) (β)), 3.69 (0.25H, m; H−C(3) (α)), 3.70 (0.75H, dd, J = 12.3, 5.0 Hz; H−C(5) (β)), 3.81 (0.75H, dd, J = 12.3, 2.8 Hz; H−C(5) (β)), 3.82 (0.25H, m; H−C(2) (α)), 3.94 (0.75H, dd, J = 5.7, 3.5 Hz; H−C(3) (β)), 3.99 (0.25H, dd, J = 12.6, 4.4 Hz; H−C(5) (α)), 4.13 (1H, m; H−C(4) (α), H−C(4) (β)), 4.79 (0.25H, d, J = 1.6 Hz; H−C(1) (α)), 4.81 ppm (0.75H, d, J = 6.0 Hz; H−C(1) (β)); ^{13}C NMR (500 MHz, D_2O): δ = 61.14 (C(5) (α)), 62.28 (C(5) (β)), 68.89 (C(2) (α)), 69.49 (C(3) (β)), 69.70 (C(2) (β)), 69.78 (C(3) (α)), 72.32 (C(4) (β)), 73.37 (C(4) (α)), 92.70 (C(1) (α)), 93.36 ppm (C(1) (β)); ^{1}H-decoupled ^{31}P NMR (161.9 MHz, D_2O): δ = −3.32 ppm (s); ESIMS (neg., H_2O): 229 (90) $[M-H]^-$; HR-ESIMS (neg., H_2O): calcd for $C_5H_{10}O_8P$: 229.0119; found: 229.0112.

1-*O*-Benzyl-2,3-isopropylidene-β-L-erythropent-4-ulose (46): A mixture of CrO_3 (3.82 g, 38.18 mmol), anhydrous pyridine (6.10 mL, 76.37 mmol) and anhydrous CH_2Cl_2 (130 mL) was stirred for 15 min under N_2 at RT. A solution of **44** (2.67 g, 9.54 mmol) in anhydrous CH_2Cl_2 (6 mL) was added immediately followed by Ac_2O (3.6 mL, 38.18 mmol). After 30 min, EtOAc (100 mL) was added and the mixture was then poured into PhMe (100 mL) and filtered through a short pad of silica gel, which was then rinsed with EtOAc (2×100 mL). The combined filtrates were concentrated in vacuo, and the residue co-evaporated with PhMe

(50 mL) to give **46** as a yellow oil (2.52 g, 95%) which could be used without further purification. An analytical sample was prepared in the following way: the ketone was dissolved in EtOAc (30 mL) and washed with $CuSO_4$ aq.(saturated, 2×50 mL) and brine (20 mL). The mixture was dried ($MgSO_4$), filtered and then concentrated in vacuo to give a pale-yellow solid (2.12 g, 80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.38 (3H, s; Me), 1.52 (3H, s; Me), 4.17–4.24 (2H, AB q, J=16.7 Hz; $H_2C(5)$), 4.43–4.50 (2H, m; H–C(3), H–C(2)), 4.59–4.80 (2H, AB q, J=11.9 Hz; OCH_2Ph), 4.99 (1H, d, J=1.5; H–C(1)), 7.32–7.39 ppm (5H, m; Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=25.31 (Me), 26.66 (Me), 65.87 (C(5)), 70.03 (OCH_2Ph), 75.26 (C(3)), 77.68 (C(2)), 96.42 (C(1)), 111.87 (Me_2C), 128.08, 128.24, 128.59, 136.17 (Ar), 203.14 ppm (C(4)); IR (film, CH_2Cl_2): $\tilde{\nu}$=1743 cm^{-1} (CO); ESIMS (neg., MeOH): m/z (%): 277 (100) $[M-H]^-$; HR-ESIMS (neg., MeOH): m/z: calcd for $C_{15}H_{17}O_5$: 277.1081; found: 277.1089.

1-*O*-Benzyl-2,3-isopropylidene-β-L-ribopyranose (47): $NaBH_4$ (686 mg, 18.14 mmol) was added in portions to a solution of **46** (2.52 g, 9.07 mmol) in EtOH (20 mL) at 0°C. After stirring for 1 h, the mixture was allowed to warm to RT for 5 h and was then quenched with NH_4Cl aq. (50% saturated, 20 mL). After addition of EtOAc (10 mL) and separation, the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), and were then dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a colourless oil (2.06 g). Crystallization (petroleum ether/Et_2O) gave white monoclinic crystals (1.51 g, 62%). R_f=0.55 (petroleum ether/EtOAc 3:2); m.p. 60–64°C; $[\alpha]_D^{26}$=+105 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.38 (3H, s; Me), 1.50 (3H, s; Me), 3.63 (1H, dd, J=11.4, 7.9 Hz; H_{eq}–C(5)), 3.86 (1H, dd, J=11.0, 4.4 Hz, H_{ax}–C(5)), 4.06 (1H, dt, J=7.9, 4.4 Hz, H–C(4)), 4.16 (1H, dd, J=6.5, 3.3 Hz; H–C(2)), 4.62 (1H, dd, J=6.3, 4.4 Hz; H–C(3)), 4.58–4.81 (2H, AB q, J=11.8 Hz; PhCH_2O), 4.79 (1H, d, J=3.2 Hz; H–C(1)), 7.31 (1H, m; Ar), 7.36 ppm (4H, m; Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=25.29 (Me), 26.54 (Me), 62.34 (C(5)), 64.20 (C(4)), 69.73 (PhCH_2O), 72.92 (C(3)), 75.01 (C(2)), 97.61 (C(1)), 109.94 (Me_2C), 127.88, 128.08, 128.44, 137.07 ppm (Ar); IR (film, CH_2Cl_2): $\tilde{\nu}$=3446 cm^{-1} (OH); elemental analysis calcd (%) for $C_{15}H_{20}O_5$: C 64.27, H 7.19; found: C 64.30, H 7.12; CIMS (pos., MeOH): m/z: 298 $[M+NH_4]^+$; HR-CIMS (pos., MeOH): m/z: calcd for $C_{15}H_{24}O_5N$: 298.1649; found: 298.1646.

1-*O*-Benzyl-2,3-*O*-isopropylidene-β-L-ribopyranoside-4-*O*-dibenzylphosphate (48): Procedure as for **45**. By starting from **47** (762 mg, 2.72 mmol), **48** (1.40 g, 96%) was obtained as a white oil. R_f=0.66 (petroleum ether/EtOAc 3:2); $[\alpha]_D^{21}$=+58 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.31 (3H, s; Me), 1.45 (3H, s; Me), 3.77 (2H, m; H–C(5)), 4.07 (1H, dd, J=6.3, 3.8 Hz; H–C(2)), 4.47 (1H, dd, J=6.3, 3.8 Hz; H–C(3)), 4.62 (1H, d, J=3.8 Hz; H–C(1)), 4.70 (2H, AB q, J=12.1 Hz; PhCH_2OC), 4.83 (1H, m; H–C(4)), 5.07 (2H, m; PhCH_2OP), 7.34 ppm (15H, m; Ar); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=25.52 (Me), 26.61 (Me), 60.40 (C(5)), 69.48 (PhCH_2OP), 69.86 (PhCH_2OC), 69.96 (C(4)), 72.40 (C(3)), 75.80 (C(2)), 98.18 (C(1)), 127.93, 127.96, 128.02, 128.07, 128.47, 128.53, 128.59, 128.61, 128.64 ppm (Ar); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=−1.59 (sextet, J=20.1 Hz); elemental analysis calcd (%) for $C_{29}H_{33}O_8P$: C 64.44, H 6.15, P 5.73; found: C 64.42, H 6.24, P 5.76; ESIMS (pos., MeOH): m/z (%): 563 (100) $[M+Na]^+$, 564 (30) $[M+Na+H]^+$; HR-ESIMS (pos., MeOH): m/z: calcd for $C_{29}H_{39}O_8P$: 541.1986; found: 541.1983.

Sodium L-ribose-4-phosphate (40): A solution of **48** (1.13 g, 2.08 mmol) in MeOH (20 mL) that contained Pd/C (209 mg, 0.21 mmol) was stirred under H_2 at RT overnight. The mixture was then filtered through Celite and the plug was rinsed with MeOH (5 mL). H_2O (5 mL) was added before the solution was neutralised to pH≈6 (NaOH). The solution was partially concentrated in vacuo, and was then lyophilised to afford **40** as a white powder (571 mg, quant.). The β/α ratio was 2:1 in D_2O according to ^{1}H NMR spectroscopic integration. ^{1}H NMR (500 MHz, D_2O): δ=3.42 (0.66H, dd, J=6.8, 3.0 Hz; H–C(2) (β)), 3.57 (0.33H, dd, J=12.2, 2.9 Hz; H–C(5) (α)), 3.68 (0.66H, dd, J=11.5, 4.4 Hz; H–C(5) (β)), 3.69 (0.33H, m; H–C(2) (α)), 3.82 (0.66H, dd, J=11.5, 4.6 Hz; H–C(5) (β)), 3.93 (0.33H, m; H–C(3) (α)), 3.97 (0.33H, dd, J=12.5, 5.5 Hz; H–C(5) (α)), 4.11 (0.66H, m; H–C(4) (β)), 4.16 (0.66H, m; H–C(3) (β)), 4.78 (0.33H, d, J=2.0 Hz; H–C(1) (α)), 4.82 ppm (0.66H, d, J=6.9 Hz; H–C(1) (β)); ^{13}C NMR (125.7 MHz, D_2O): δ=60.72 (C(5)), 67.53 (C(3)), 68.42 (C(2)), 69.38 (C(4)), 91.91 (C(1) (α)), 92.26 ppm (C(1) (β)); ^{31}P NMR (161.9 MHz, D_2O): δ=0.41 (d, J=8.6 Hz; (β)), 0.76 ppm (d, J=8.6 Hz; (α)); ESIMS (neg., H_2O): m/z (%): 229 (100) $[M]^-$; HR-ESIMS (neg., H_2O): m/z: calcd for $C_5H_{10}O_8P$: 229.0119; found: 229.0115.

Attempted aldol reaction of sodium glyceraldehyde-2-phosphate (37) with glycolaldehyde: Compound **37** (20 mg, 0.10 mmol) and glycolaldehyde (5.6 mg, 0.10 mmol) were dissolved in H_2O (0.5 mL) and the pH was adjusted to ≈11 (NaOH). The resultant solution was heated at 50°C for 3 h and was then cooled to RT, adjusted to pH ≈7 (HCl), and lyophilized. The resulting residue was dissolved in D_2O and analysed by ^{1}H NMR spectroscopy.

In control experiments, **37**, glycolaldehyde, threose, and erythrose were separately subjected to the same reaction conditions.

Reaction of 2-aminooxazole (49) with sodium glyceraldehyde-2-phosphate (37): Compound **37** (40 mg, 0.19 mmol) and **49** (16 mg, 0.19 mmol) were dissolved in D_2O (0.75 mL) and the pD was adjusted to 7.2 (NaOD). The solution was then heated to 40°C and occasionally monitored by ^{1}H NMR spectroscopic analysis. According to integration of the signals at δ=4.65–4.72 and 3.45–3.60 ppm, the ratio of *rac*-**54**/*rac*-**55** was 5:1 after 24 h.

Reaction of the pentose-4-phosphate sodium salts with cyanamide: Cyanamide was added to a solution of the pentose-4-phosphate sodium salt in D_2O/H_2O, and the pD/pH was adjusted to a value near neutrality (NaOD/NaOH). After heating, the reaction was cooled down and analysed by ^{1}H NMR spectroscopy either directly or after lyophilisation and (re)dissolution in D_2O.

Data for L-***54*** *as prepared from* ***21***: Conditions: **21** (35 mg, 0.15 mmol) and cyanamide (16 mg, 0.38 mmol) in H_2O (0.8 mL), pH 7, 28 h at 60°C, followed by lyophilisation and dissolution in D_2O. Yield: ≈30% residual **21** + ≈70% L-**54**; ^{1}H NMR (500 MHz, D_2O): δ=3.61 (1H, br d, J=2.5 Hz; H–C(5)), 3.62 (1H, br d, J=4.5 Hz; H–C(5)), 4.32 (1H, m; H–C(4)), 4.72 (1H, d, J=3.5 Hz; H–C(3)), 6.69 ppm (1H, s; H–C(1)); ^{13}C NMR (100.6 MHz, D_2O): δ=61.76 (C(5)), 68.78 (C(3)), 75.63 (C(4)), 122.85 (C(1)), 143.38 (C(2)), 161.31 ppm (C(6)); ^{31}P NMR (161.9 MHz, D_2O): δ=4.39 ppm (d, J=8.0 Hz); ESIMS (neg., H_2O): m/z (%): 253 (30) $[M]^-$; HR-ESI-MS (neg., H_2O): calcd for $C_6H_{10}N_2O_7P$: 253.0231; found: 253.0234.

Data for L-***54*** *as prepared from* ***40***: Conditions: **40** (20.5 mg, 0.07 mmol) and cyanamide (6.2 mg, 0.15 mmol) in D_2O (0.75 mL), pD 7.2, 20 h at 60°C, followed by lyophilisation and redissolution in D_2O. Yield: ≈25% residual **40** and ≈75% L-**54**; ^{1}H NMR (300 MHz, D_2O): δ=3.54 (1H, br d, J=1.5 Hz; H–C(5)), 3.55 (1H, br d, J=2.2 Hz; H–C(5)), 4.25 (1H, m; H–C(4)), 4.66 (1H, d, J=3.9 Hz; H–C(3)), 6.63 ppm (1H, s; H–C(1)); ^{13}C NMR (100.6 MHz, D_2O): δ=62.04 (C(5)), 69.69 (C(3)), 75.99 (C(4)), 120.14 (C(1)), 143.69 (C(2)), 163.05 ppm (C(6)); ^{31}P NMR (161.9 MHz, D_2O): δ=1.47 ppm (br s); ESIMS (neg., H_2O): 253 (50) $[M]^-$; HR-ESIMS (neg., H_2O): calcd for $C_6H_{10}N_2O_7P$: 253.0231; found: 253.0219.

Data for D-***55*** *as prepared from* ***22***: Conditions: **22** (30 mg, 0.13 mmol) and cyanamide (11 mg, 0.26 mmol) in H_2O (0.8 mL), pH 7.4, 38 h at 60°C, followed by lyophilisation and dissolution in D_2O. Yield: ≈14% residual **22** and ≈56% D-**55**; ^{1}H NMR (500 MHz, D_2O): δ=3.48 (1H, dd, J=12.3, 5.1 Hz; H–C(5)), 3.65 (1H, dd, J=12.3, 3.2 Hz; H–C(5)), 4.34 (1H, tdd, J=8.2, 5.0, 3.2 Hz; H–C(4)), 4.71 (1H, d, J=8.1 Hz; H–C(3)), 6.75 ppm (1H, s; H–C(1)); ^{13}C NMR (125.7 MHz, D_2O): δ=62.07 (C(5)), 65.73 (C(3)), 75.69 (C(4)), 123.56 (C(1)), 142.77 (C(2)), 161.60 ppm (C(6)); ^{31}P NMR (121.5 MHz, D_2O): δ=5.08 ppm (d, J=8.4 Hz); ESIMS (neg., H_2O): 253 (100) $[M]^-$; IR (solid): $\tilde{\nu}$=1636 cm^{-1} (C=N); HR-ESIMS (neg., H_2O): m/z: calcd for $C_6H_{10}N_2O_7P$: 253.0231; found: 253.0235.

Data for D-***55*** *as prepared from* ***41***: Conditions: **41** (24.4 mg, 0.10 mmol) and cyanamide (8.9 mg, 0.21 mmol) in D_2O (0.75 mL), pD 6.9, 50 h at 60°C. Yield: ≈40% D-**55**; ^{1}H NMR (300 MHz, D_2O): δ=3.44 (1H, dd, J=12.3, 5.0 Hz; H–C(5)), 3.60 (1H, dd, J=12.3, 2.8 Hz; H–C(5)), 4.29

(1H, m; H−C(4)), 4.67 (1H, d, J = 7.9 Hz; H−C(3)), 6.70 ppm (1H, s; H−C(1)).

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