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Synthesis of Bis(glycoaldehyde) Phosphodiester and Mixed Glycoaldehyde-triose Phosphodiesters

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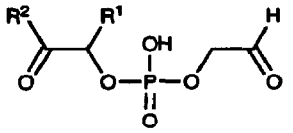
Abstract The syntheses of the potentially prebiotic compounds, bis(glycoaldehyde) phosphodiester **1**, dihydroxyacetonephosphoglycoaldehyde **2** and glyceraldehyde-2-phosphoglycoaldehyde **3** have been achieved.

Introduction

The recent discoveries that RNA has both catalytic potential[1] and the capacity to evolve *in vitro*[2] have added experimental weight to the theory of an 'RNA world'[3]. In the preceding paper we have presented a novel retrosynthetic analysis of the RNA polymer that suggests a potentially prebiotic synthesis involving aldol polymerisation chemistry, intramolecular redox transfer and ring closure *via* a mesomeric heterocyclic betaine intermediate. Our analysis suggests that bis(glycoaldehyde) phosphodiester **1** and simple glycoaldehyde-triose mixed phosphodiesters **2** and **3**, Fig. 1, might be important in the prebiogenesis of RNA.



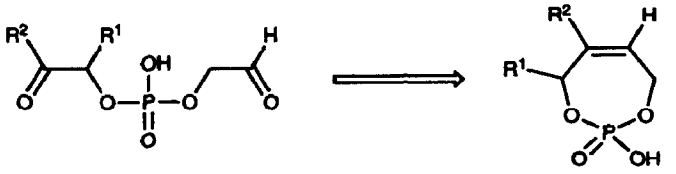
1 R^1=R^2=H
2 R^1=H, R^2=CH_2OH
3 R^1=CH_2OH, R^2=H

Fig. 1. Phosphodiester Targets

Accordingly we have initiated a programme aimed at synthesising such phosphodiesters and studying their behaviour in aqueous solution. In this paper we report efficient syntheses of bis(glycoaldehyde) phosphodiester **1**, dihydroxyacetonephosphoglycoaldehyde **2** and glyceraldehyde-2-phosphoglycoaldehyde **3**.

Results and discussion

It was envisaged that as the targets **1**, **2** and **3** all contain potentially reactive carbonyl groups that these groups should be introduced at the end of any synthetic scheme by ozonolysis. To avoid by-product formation in the ozonolysis we chose to synthesise appropriately substituted 7-membered cyclophosphodiesters which, upon ozonolysis, would generate both carbonyl groups from the same ring double bond, Fig. 2.



1 R^1=R^2=H
2 R^1=H, R^2=CH_2OH
3 R^1=CH_2OH, R^2=H

Fig. 2. Ozonolysis Disconnection

In the synthesis of **1**, Fig. 3[4], the appropriate cylophosphodiester **5** was easily generated by treatment of (Z)-2-butene-1,4-diol with phosphoryl chloride in the presence of triethylamine followed by hydrolysis of the resulting chlorophosphate **4** in aqueous THF. Ozonolysis in methanol followed by reductive work-up with dimethyl sulphide afforded bis(glycoaldehyde) phosphodiester **1**[5].

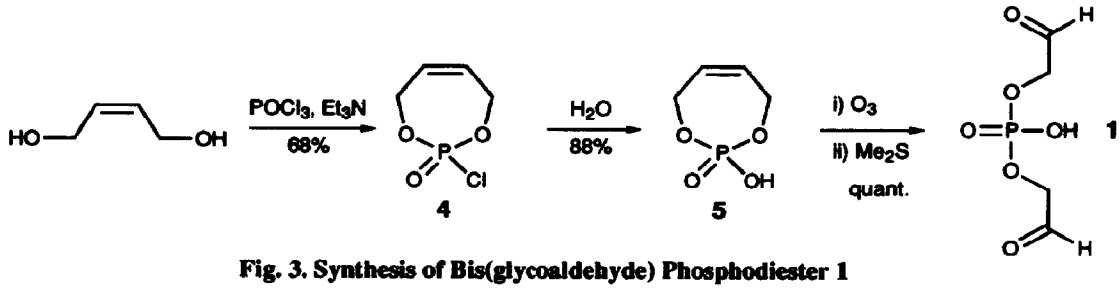


Fig. 3. Synthesis of Bis(glycoaldehyde) Phosphodiester 1

The syntheses of **2** and **3** required the preparation of selectively protected hydroxymethyl-2-butene-1,4-diols. *tert*-Butyldimethylsilyl was chosen as protecting group as it was envisaged that this group might be removed by the acid generated during hydrolysis of the appropriate chlorophosphate intermediate. The common cis 2-butene-1,4-diol moiety of the desired, selectively protected hydroxymethyl-2-butene-1,4-diols suggested a synthetic route based on some sort of furan oxidolysis/reduction procedure[6]. For the synthesis of **2**, (E)-2-*tert*-butyldimethylsilyloxymethyl-2-butene-1,4-diol **6** was conveniently prepared by Diels-Alder reaction of 3-*tert*-butyldimethylsilyloxymethyl-furan with singlet oxygen followed by reduction of the resultant ozonide equivalent with sodium borohydride, Fig. 4.

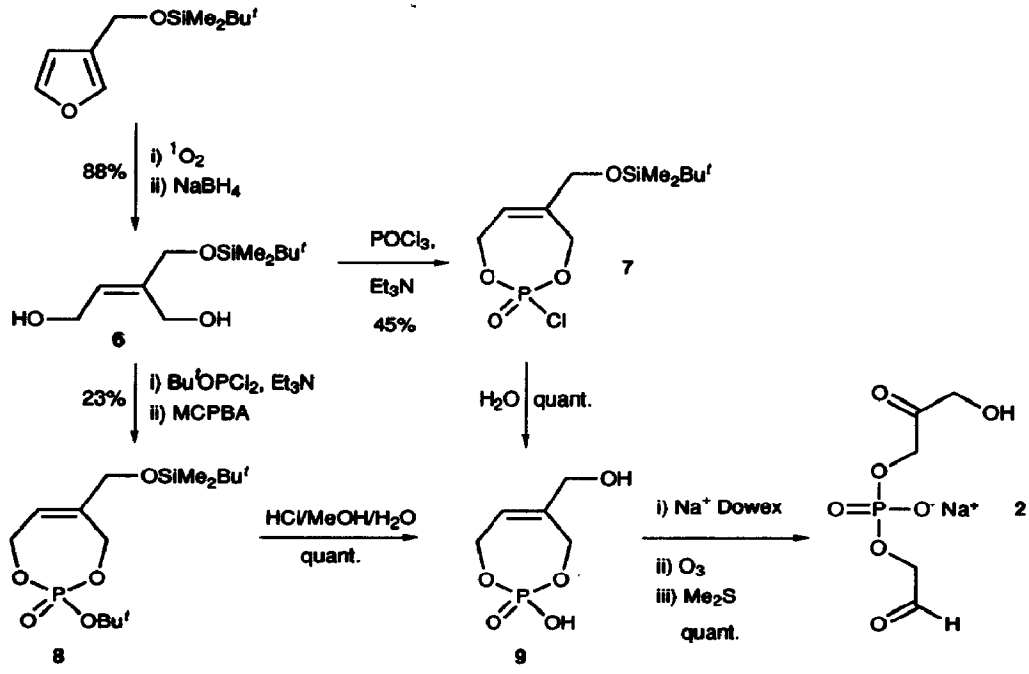


Fig. 4. Synthesis of Dihydroxyacetonephosphoglycoaldehyde 2

Phosphorylation with phosphoryl chloride and triethylamine proceeded satisfactorily but the chlorophosphate **7** thus obtained proved difficult to purify and this route was temporarily abandoned and a less direct route was explored. Phosphitylation of **6** with *tert*-butyloxyphosphodichloridite followed by oxidation with *meta*-chloroperbenzoic acid gave the easily purifiable phosphotriester **8** in acceptable yield. Deprotection of both the phosphoryl and hydroxyl groups was then cleanly effected by treatment with methanolic HCl. Ozonolysis of the cyclic phosphodiester **9** as its sodium salt[7] in methanol followed by reductive work-up with dimethyl sulphide then afforded the linear phosphodiester **2**. At this point we discovered that the chlorophosphate **7** could be purified by careful chromotography on alumina. Hydrolysis of **7** with concommitant desilylation proceeded extremely cleanly to give the cyclic phosphodiester **9** identical with that prepared by the longer, fully protected route. This 'deprotected' route thus constitutes the method of choice for the synthesis of **2**.

The synthesis of **3** parallels that of **2**, the starting point being the isomeric 2-*tert*-butyldimethylsilyloxymethyl-furan, Fig. 5.

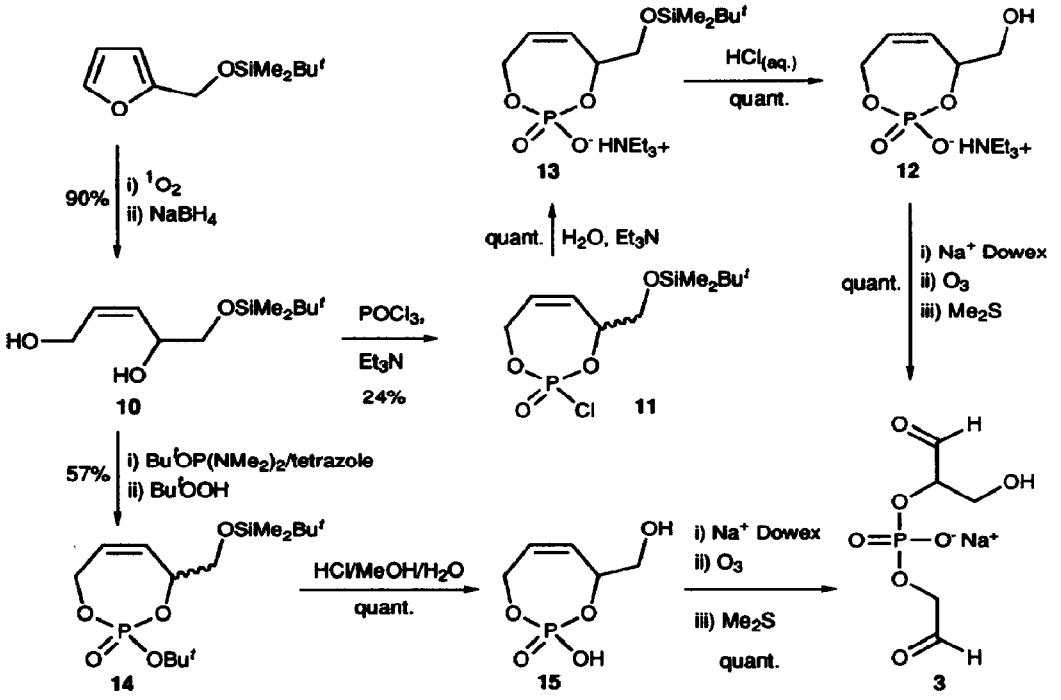


Fig. 5. Synthesis of Glyceraldehyde-2-phosphoglycoaldehyde 3

Diels-Alder reaction of this furan with singlet oxygen followed by sodium borohydride reduction of the resultant ozonide furnished (Z)-1-*tert*-butyldimethylsilyl-3-pentene-1,4,5-triol **10**. Phosphorylation with phosphoryl chloride and triethylamine gave two diastereomeric chlorophosphates **11** which could be purified but not separated by chromatography on alumina. Simultaneous hydrolysis and desilyation of **11** to give **15** could not be effected because of neighbouring group participation between the hydroxymethyl group and the phosphoryl group which led to a mixture of regioisomeric cyclic phosphodiesters. Accordingly, the chlorophosphate **11** was hydrolysed in the presence of triethylamine to give the partially deprotected derivative

13. Desilylation was then brought about by exposure of **13** to acid giving **12**. Ozonolysis of **12** as its sodium salt in methanol then afforded glyceraldehyde-2-phosphoglycoaldehyde **3** contaminated with a molar equivalent of sodium chloride. Difficulties in purifying large quantities of the chlorophosphate **11** and the inelegance of the multi-stage hydrolysis led us to explore an alternative route. Phosphitylation with *tert*-butyloxyphosphodichloridite followed by oxidation with *meta*-chloroperbenzoic acid gave low yields of the cyclic phosphotriester **14** and was accompanied by the formation of 3-*tert*-butyldimethylsilyloxymethyl-2,5-dihydrofuran. To circumvent these problems we synthesised the new phosphorodiamidite, $Bu^tOP(NMe_2)_2$ by treatment of bis-(dimethylamino)-phosphochloridite[8] with *tert*-butanol in the presence of triethylamine according to the general procedure of Hargis and Alley[9]. Reaction of **10** with this phosphorodiamidite and tetrazole followed by oxidation with *tert*-butyl hydroperoxide gave the cyclic phosphotriester **14** in 57% yield as a separable, 4:1 mixture of diastereoisomers. Acid hydrolysis of either diastereoisomer gave the cyclic phosphodiester **15** in quantitative yield. Conversion of **15** to its sodium salt followed by ozonolysis with reductive work-up then afforded glyceraldehyde-2-phosphoglycoaldehyde **3** again in quantitative yield.
Studies on the solution structures adopted by compounds **1**, **2** and **3** in aqueous solution and the enolisation chemistry of **2** are described in the following paper.

Acknowledgements
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References and footnotes

1 Altman, S. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 749; Cech, T. R. *ibid.* **1990**, *29*, 749.
2 See for example: Beaudry, A. A.; Joyce, G. F. *Science*, **1992**, *257*, 635, Green, R.; Szostak, J. W. *ibid.* **1992**, *258*, 1910.
3 Reviews: Orgel, L. E. *Cold Spring Harbor Symp. Quant. Biol.* **1987**, *7*, 9, Joyce, G. F. *ibid.* **1987**, *7*, 41, Joyce, G. F. *Nature (London)* **1989**, *338*, 217.
4 All new compounds gave satisfactory analytical and/or spectral data.
5 The ETH group of Eschenmoser has previously reported the synthesis of **1** by ozonolysis of diallyl hydrogenphosphate (Wagner, E.; Xiang, Y.-B.; Baumann, K.; Glück, J.; Eschenmoser, A. *Helv. Chim. Acta* **1990**, *73*, 1391.). The method described herein has the advantage that there are no involatile by-products produced obviating the requirement for purification.
6 We thank Dr. R. C. Whitehead and Dr. L. M. Harwood of this department for useful suggestions concerning this procedure.
7 Ozonolysis of the triethylammonium salt of **9** also proceeds satisfactorily but is accompanied by the formation of substantial amounts of triethylamine-N-oxide. Ozonolysis of the free acid form of **9** followed by reductive work-up gave a mixture of glycoaldehyde phosphate, dihydroxyacetone phosphate, glycoaldehyde and dihydroxyacetone, the apparent hydrolysis products of **2**. This apparent hydrolysis occurs in the ozonolysis step presumably by attack of a carbonyl oxide or α-methoxyhydroperoxide on the phosphodiester group.
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