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Synthesis of a phosphinic acid analogue of cyclic AMP

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Abstract

Synthesis of a cyclic phosphinate ester analogue of cyclic AMP was achieved by using a double Arbuzov-type cyclisation of bis-trimethylsilyl phosphonite onto a sugar dihalide derivative as the key step.

Cyclic AMP **1** (Fig. 1) is a well-known 'second messenger' in cell signalling.[1,2] It is formed in eukaryotic cells by membrane-bound adenyl cyclases, activated by a variety of hormones, and can have a wide range of effects in the cell, usually mediated by cyclic AMP-dependent protein kinases, or by cyclic nucleotide-gated ion channels. Cyclic AMP is broken down to AMP by cyclic nucleotide phosphodiesterases (PDEs), and this is an important mechanism for regulating its intracellular concentration. Replacement of both the oxygen atoms in the phosphate diester ring of cyclic AMP by methylene groups would give the corresponding phosphinic acid analogue **2**, which should be resistant to hydrolysis by PDEs. To our knowledge, this phosphinic acid analogue of cyclic AMP is novel, although the two *phosphonic* acid analogues **3** and **4**, where only one of the oxygen atoms is replaced by CH_2, have previously been reported.[3]

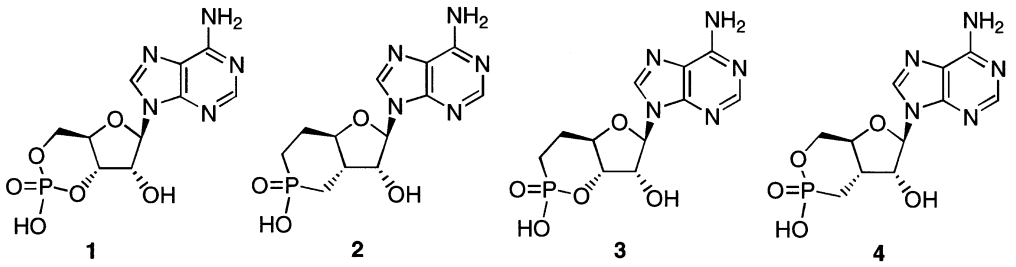

Figure 1.

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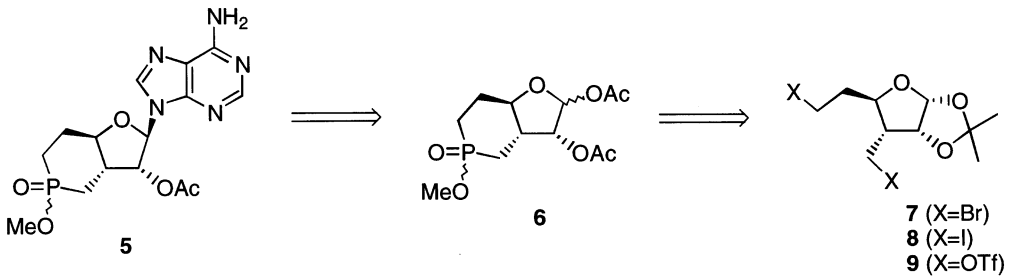
A variety of different PDEs are known, from different sources and with varying substrate specificities. Many of these PDEs cleave cyclic AMP specifically to give 5′-AMP, and consistent with this, a PDE from amoebae of *Dictyostelium discoideum* has been reported to hydrolyse phosphonate **3** as fast as cyclic AMP **1**, but phosphonate **4** was not cleaved.[4] A PDE from rabbit brain was found to cleave **3** slowly, but again did not cleave **4**.[5] However, a PDE from a plant source (Jerusalem artichoke) hydrolyses cyclic AMP to give a mixture of *both* 3′-AMP *and* 5′-AMP,[6] and so both phosphonates **3** and **4** might be susceptible to hydrolysis by PDEs of this type. The advantage of the phosphinate **2** is that *both* P–O bonds are replaced by P–CH_2, and so **2** should be resistant to cleavage in both the 3′- and the 5′-directions, as well as any non-specific hydrolysis.

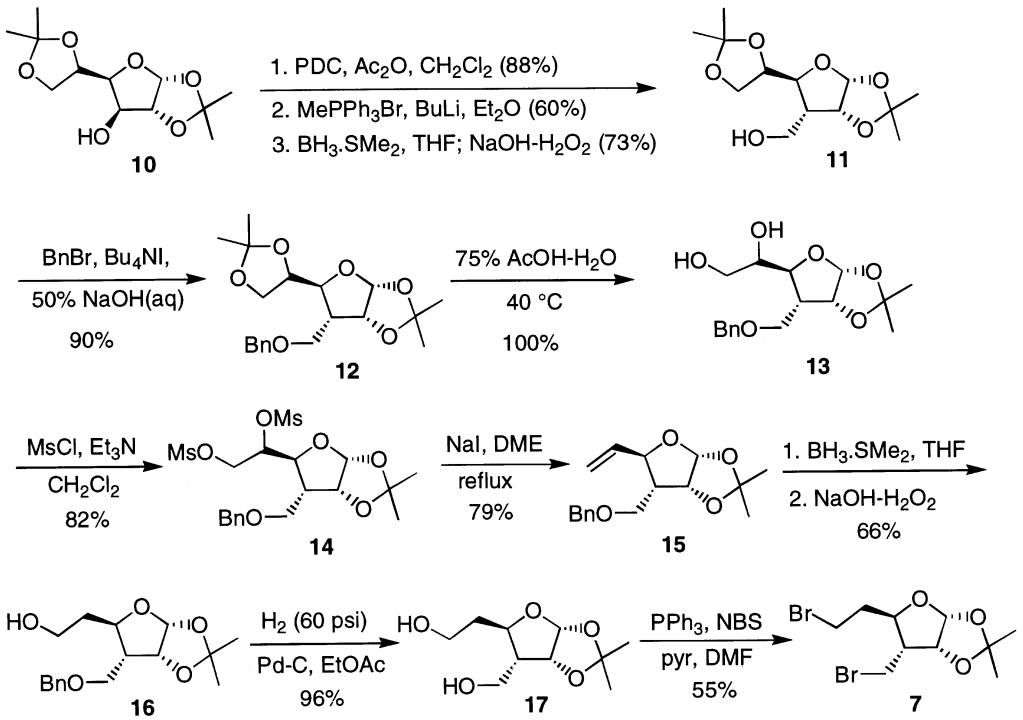
In this Letter, we report a synthesis of a methyl phosphinate ester analogue **5**, and its subsequent hydrolysis to the phosphinic acid analogue of cyclic AMP **2**. The retrosynthetic analysis is shown in Scheme 1, and involves a double Arbuzov-type reaction to generate a cyclic phosphinic acid from a dihalo-sugar derivative e.g. **7** or **8**, or ditriflate **9**.



Scheme 1.

The starting material for the synthesis is diacetone glucose **10**, which was converted into the C3-homologated compound **11** using literature procedures,[7–9] as shown in Scheme 2. The C3α-hydroxyl group in **11** was protected as the benzyl ether using phase-transfer conditions, and selective hydrolysis of the side-chain acetonide in **12** using warm aqueous acetic acid afforded the diol **13**.

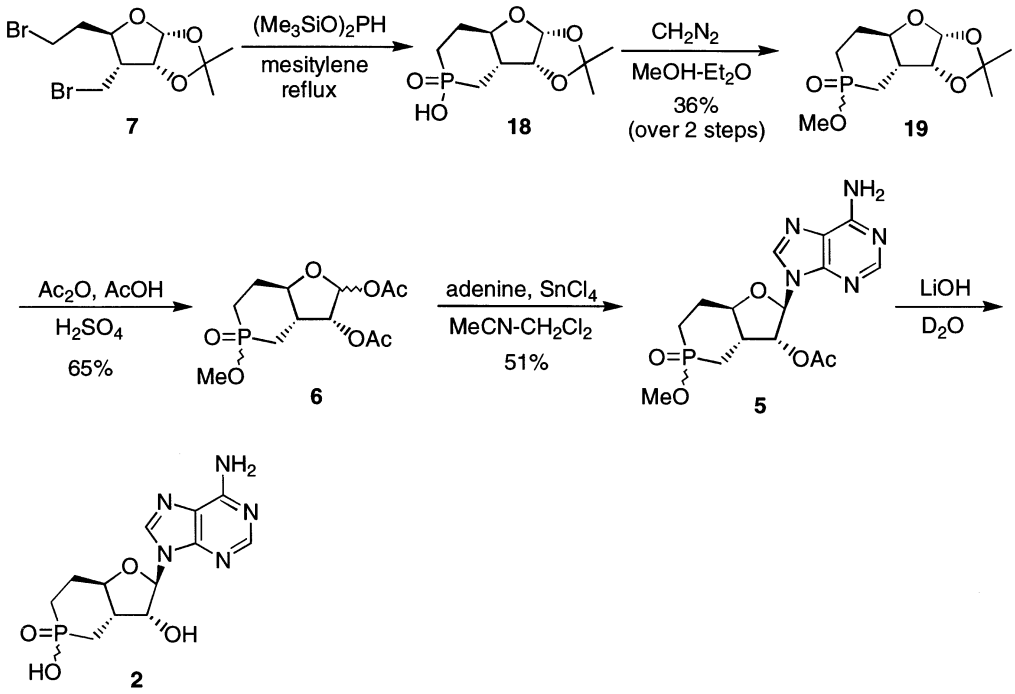
Selective deoxygenation of the 5-hydroxyl group in **13** was investigated using several procedures, and the most efficient involved formation of the dimesylate **14**, elimination of both mesylate groups using sodium iodide[10,11] to give the alkene **15**, followed by hydroboration–oxidation to reintroduce the 6-hydroxyl group in **16**. Removal of the C3α-benzyl group then gave the diol **17**, which was converted into the dibromide **7** using triphenyl phosphine and NBS, with the addition of pyridine.[9] The corresponding diiodide **8** and ditriflate **9** were also prepared from the diol **17**, and the stereochemistry of diiodide **9** was confirmed by an X-ray structure determination.



Scheme 2.

The key step in the synthesis is the formation of the cyclic phosphinic acid **18**, by a double Arbuzov-type reaction[12,13] between bistrimethylsilyl phosphonite (BTSP) and the dibromide **7** (Scheme 3). Since pure BTSP is highly pyrophoric, it was formed in situ from ammonium phosphinate and hexamethyldisilazane, as in our previous work.[14] This reaction was initially attempted using simple model dihalides 1,5-dibromopentane and 1,5-diiodopentane, and also pentane-1,5-ditriflate. Various reaction conditions were explored, with the best results being obtained in refluxing mesitylene, using the conditions of Frost.[12] When the same reaction was performed on the halides **7** and **8**, and also on the triflate **9**, only the dibromide **7** gave satisfactory results. The resulting phosphinic acid **18** was not isolated, but was immediately converted into the methyl ester **19**[15] using diazomethane, which allowed easier purification by flash chromatography. The methyl ester **19** was formed as a mixture of two diastereoisomers, resulting from the new stereogenic centre at the phosphorus atom.

The acetonide protecting group in **19** was removed using conditions which also converted the resulting diol into the diacetate **6** in situ. Reaction of **6** with adenine in the presence of several equivalents of tin(IV) chloride, using the methodology of Saneyoshi and Satoh,[16] afforded the protected nucleotide analogue **5**.[17] The 1-acetate group in **6** served as a leaving group for the introduction of the adenine base, with neighbouring group participation from the 2-acetyl being used to control the stereochemistry, ensuring formation of the β-substitution product. Hydrolysis of both the methyl ester and acetate protecting groups in **5** in one step, using lithium hydroxide, was followed in the NMR tube by recording a time series of NMR spectra, with the methyl ester being removed much more slowly than the 2′-acetate group.



Scheme 3.

In conclusion we have demonstrated a viable synthetic route to a phosphinic acid analogue of cyclic AMP, involving a double Arbuzov-type reaction on the dibromide intermediate **7** as the key step.

Acknowledgements

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15. ^{1}H NMR data for **19**: δ_{H} (300 MHz, $CDCl_3$) 1.27 (3H, s), 1.46 (3H, s), 1.46–2.35 (7H, m), 3.58 (1H, m), 3.68 (3 H, d, $^{3}J_{POCH}$ 11.0), 4.43 (1H, dd, *J* 4.0, 4.0), 5.77 (1H, d, *J* 4.0). Evidence for a second diastereroisomer from presence of extra set of peaks at δ 4.52 and 5.77.
16. Saneyoshi, M.; Satoh, E. *Chem. Pharm. Bull*. **1979**, *27*, 2518–2521. For an example of the use of this methodology, see: Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem*. **1990**, *55*, 948-955.
17. NMR data for **5**: δ_{H} (300 MHz, CD_3OD) 1.75–2.30 (7H, m), 2.02 (3H, s), 3.79 (3H, d, $^{3}J_{POCH}$ 11.0), 4.04 (1 H, m), 4.49 (1H, m), 6.03 (1 H , d, *J* 3.0), 7.98 (1H, s), 8.10 (1H, s). Evidence for a second diastereroisomer from extra peaks superimposed on those at δ 4.04, 4.49, and 6.03. δ_{P} (122 MHz, CD_3OD) 56.94 and 58.50 (two diastereoisomers).