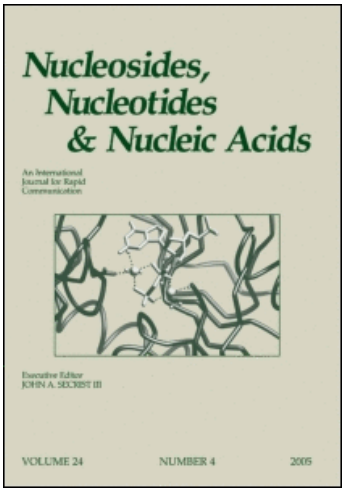

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Hirtz, Caroline and Leumann, Christian J.(2003) 'Synthetic Studies Towards a Novel, Chemical Stable, Abasic Site Analogue of DNA', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1203 — 1206
To link to this Article: DOI: 10.1081/NCN-120022836
URL: http://dx.doi.org/10.1081/NCN-120022836

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1203–1206, 2003

Synthetic Studies Towards a Novel, Chemical Stable, Abasic Site Analogue of DNA

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ABSTRACT

We synthesized the phosphinate **7** via photoaddition of methanol to the α, β unsaturated deoxyribono lactone as the key step, followed by an Arbusov reaction for the introduction of phosphorous. Precursor **7** serves for the synthesis and incorporation into DNA of a novel chemically stable abasic site analogue that might act as an inhibitor for DNA glycosylases.

Formation of an abasic site in DNA, leaving a deoxyribose residue behind, is a frequent lesion that occurs spontaneously or by enzymatic cleavage of the N-glycosidic bond in the DNA repair process. The abasic site exists as an equilibrium mixture of the α- and β-hemiacetal and the open chain aldehyde form of the ribose unit. Under basic conditions, β-elimination, and thus strand cleavage occurs.

We are interested in developing a new stable abasic site analogue, in which the usual 3′-phosphodiester linkage is replaced by a phosphonate linkage. Incorporated into an oligonucleotide, we expect increased chemical stability of the oligonucleotide

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DOI: 10.1081/NCN-120022836
1525-7770 (Print); 1532-2335 (Online)

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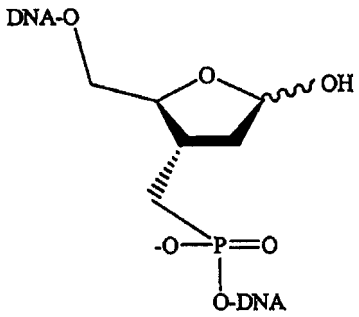
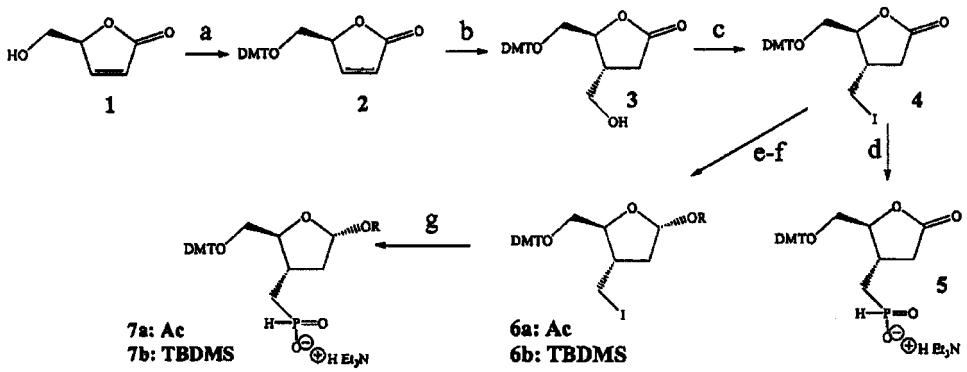


Figure 1.

at the abasic site, as well as inhibitory activity in the context of DNA glycosylases (Fig. 1).

In our synthetic strategy, we envisaged to introduce the 3′-*C*-methylene group stereoselectively into the ribose skeleton via a photochemical addition reaction developed by Mann and co-workers.[1,2] Starting from **2**, photochemical addition of methanol leads to **3** in acceptable yields of 48–53% (Sch. 1).

In order to introduce the phosphonate function, the hydroxymethyl derivative **3** was converted into a precursor suitable for subsequent Arbusov reaction with BTSP (bis-(trimethylsilyl) -hypophosphite) as the nucleophile.[3] As leaving groups, we decided to explore the iodide (as in **4**, **6a**, and **6b**) as well as sulfonates such as the trifluoromethylsulfonate (triflate) (as in **8a** and **11**) and the 4-methylbenzenesulfonate (tosylate) (as in **8b**).[4] These compounds were treated with BTSP in order to



Scheme 1. a) 1.2 eq. DMT-Cl/Pyridine/3 h/92%; b) *hv* 350 nm/1 eq Benzophenone/MeOH/8 h/48–53%; c) 1,2 eq. $MeP^{+}(OPh)_3\ I^{-}$/2 eq. Lutidine/DMF/4 h/58% or 1 eq. I_2/1 eq. PPh_3/2 eq. Im/THF/2 h/86%; d) [1.] 12 eq. BTSP/CH_3CN/Hunig's base/−42°C; [2.] Triethylammonium hydrogen carbonate (aq.)/8 h/32%; e) 1.2 eq. Dibal/CH_2Cl_2/−78°C/2 h/quant; f) for **6a**, 1.2 eq. Anhydride acetic/0.2 eq. DMAP/Pyridine/overnight/91%; for **6b**, 2q. TBDMS-Cl/2 eq. Im./0.2 eq. DMAP/DMF/overnight/78%; g) [1.] 10 eq. BTSP/CH_3CN/Hunig's base; [2.] Triethylammonium hydrogen carbonate (aq.)/22–31% for **7a**; 20% for **7b**.

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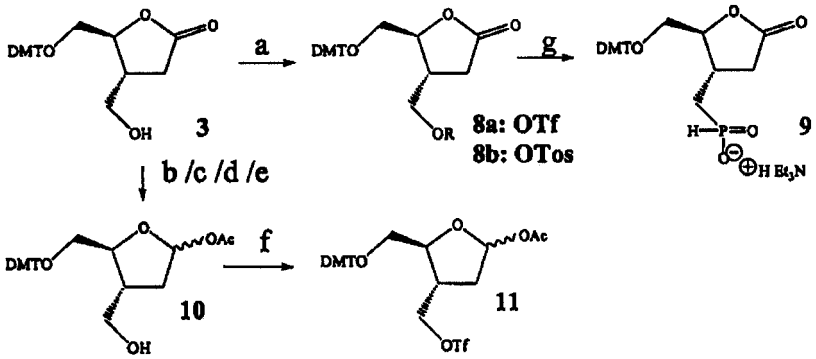

Scheme 2. a) for **8a**, 2,5 eq. 2,6-di-ter-butylpyridine/1,2 eq. $Tf_2O/CH_2Cl_2/-78°C/3$ h/78%; for **8b**, 1.2 eq. TosCl/Pyridine/ overnight/rt/76%; b) 1.6 eq. TBDMS-Cl/2 eq Im./DMF/ overnight/77%; c) 1.6 eq Dibal/$CH_2Cl_2/-78°C/2$ h/quant; d) 2 eq. Anhydride acetic/0.2 eq. DMAP/Pyridine/overnight/86%; e) 1.5 eq. Acetic acid/1.5 eq. TBAF/THF/0°C to rt/ overnight/74%; f) 2,5 eq. 2,6-di-ter-butylpyridine/1,2 eq. $Tf_2O/CH_2Cl_2/-78°C/3$ h/52%; g) [1.] 150 eq. BTSP/CH_3CN/Hunig's base/ 0°C/ 8 h; [2.] Triethylammonium hydrogen carbonate (aq.)/22%.

introduce the C-P bond in form of a 3′-*C*-methylphosphonate linkage in the presence of base ($EtNiPr_2$, or 2,6-di-ter-butylpyridine) to avoid loss of the DMT group. At r.t. and in CH_2Cl_2, we observed in all cases that carry the iodide as leaving group (**4**, **6a** and **6b**) mostly products of reduction and incomplete consumption of the halides with less than 5% of the desired phosphonate salts. The reduction as a competition reaction by BTSP has been reported previously.[5] For **6a** and **6b**, the best results were obtained by using CH_3CN at r.t. with 10 eq. of BTSP for 48 hours. Thus, we observed the formation of the desired phosphinate derivatives **7a** (22–31%) and **7b** (20%), together with the corresponding reduced compounds (ca. 55%). Decreasing the temperature to −42°C, did not lead to improved product formation.

In order to favor substitution over reduction, the triflates **8a** and **11** and tosylate **8b** were tested, too.[4] However, only the triflate **8a** was stable enough. The phosphinate derivative **9** was obtained in 22% yield, by treatment of 150 eq. BTSP in CH_3CN at 0°C during 8 h. The other compounds **11** and **8b** were not stable at r.t. and under neutral conditions, and rapidly decomposed.

With phosphinate **7a** in hands we now approach the synthesis of the corresponding building block for oligonucleotide synthesis.

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