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

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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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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/3h/92%; b) hv 350 nm/1 eq Benzophenone/MeOH/8h/48-53%; c) 1,2 eq. MeP⁺(OPh)₃ I⁻/2 eq. Lutidine/DMF/4h/58% or 1 eq. I₂/1 eq. PPh₃/2 eq. Im/THF/2h/86%; d) ^{1.} 12 eq. BTSP/CH₃CN/Hunig's base/ -42° C; ^{2.} Triethyl-ammonium hydrogen carbonate (aq.)/8h/32%; e) 1.2 eq. Dibal/CH₂Cl₂/ -78° C/2h/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/CH₃CN/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. $Tf_2O/CH_2Cl_2/-78^{\circ}C/3 h/78\%$; 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/CH₂Cl₂/-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. $Tf_2O/CH_2Cl_2/-78^{\circ}C/3 h/52\%$; g) ^{1.} 150 eq. BTSP/CH₃CN/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 (EtNiPr₂, or 2,6-di-ter-butylpyridine) to avoid loss of the DMT group. At r.t. and in CH₂Cl₂, 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 CH₃CN 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 CH₃CN 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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