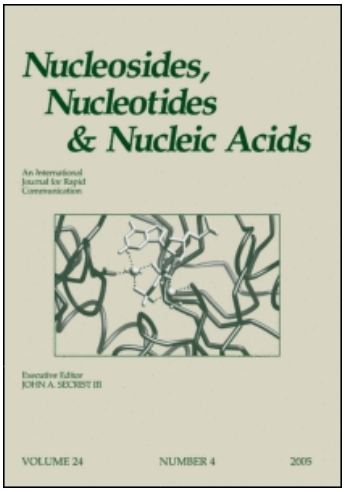

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Synthesis of Oligoarabinonucleotides Using H-Phosphonates

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SYNTHESIS OF OLIGOARABINONUCLEOTIDES USING H-PHOSPHONATES

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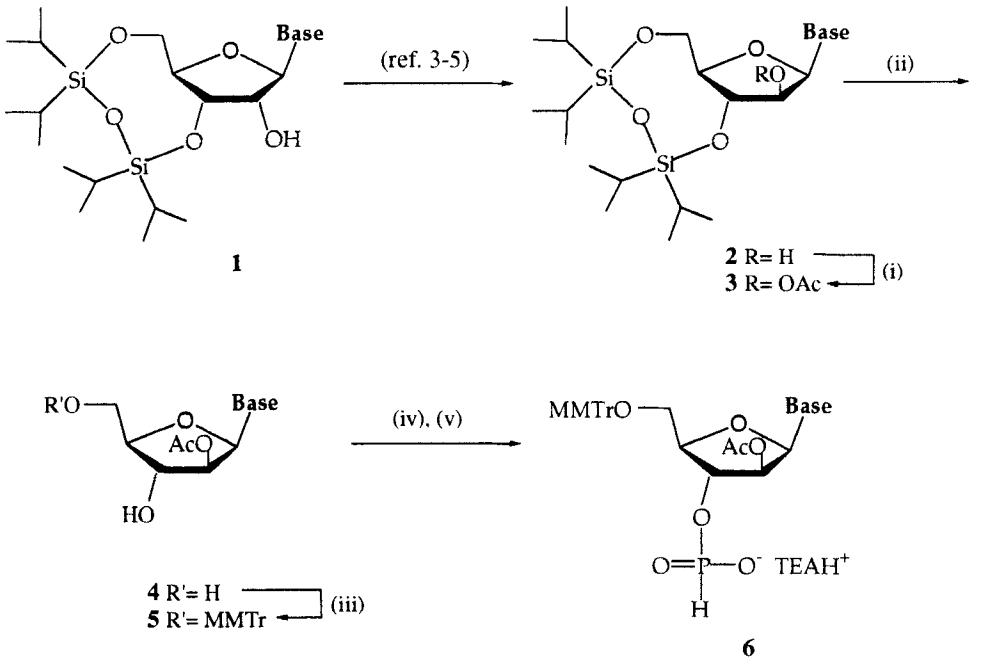
Abstract: Protected arabinonucleoside H-phosphonates have been prepared starting from ribonucleosides and used in solid phase synthesis of oligoarabinonucleotides.

Oligonucleotides containing sugar modified nucleoside residues are of general interest for biological and biophysical studies. Out of these oligoarabinonucleotides could also have interesting properties for medical applications.

Following successful use of 2'-O-(2-chlorobenzoyl) group in synthesis of oligoribonucleotides[1] we were further interested to evaluate 2'-O-acyl protections in the synthesis of oligoarabinonucleotides. The efficiency of such approach can be envisaged because it would not suffer from the disadvantages of 2'-3' isomerization and degradation of oligonucleotide under basic conditions when removing acyl protections.

Our initial attempts to introduce the 2-chlorobenzoyl group selectively at the 2'-position of the 5'-protected arabinonucleoside failed. Mixtures of 2' and 3'-acyl derivatives were obtained. It is most likely that the 2'-OH is more sterically hindered in 5'-O-MMTr arabinonucleosides than in the corresponding ribo analogues. Therefore we developed alternative route to arabinonucleoside H-phosphonates[2] (Scheme). Suitably protected ribonucleosides **1** were converted into corresponding arabinonucleosides **2** in 25-50 % yields using the published oxidation-reduction methods[3-5]. Reaction conditions have been studied and optimised for particular compounds bearing labile N-protecting groups[2]. Acylation with acetic anhydride followed by removal of TIPDS group and introduction of 5'-O-methoxytrityl protection yielded selectively protected arabinonucleosides **5**. These were further converted into H-phosphonates **6** using known methods[6]. The use of inexpensive starting materials (ribonucleosides) and



Base = Ura, N^6-isovalerylAde, N^4-isobutyrylCyt, N^2-phenoxyacetylGua. Reagents: (i) Acetic anhydride, DMAP (ii) Triethylammonium hydrofluoride in acetonitrile (iii) 4-Methoxytrityl chloride (iv) PCl_3, imidazole, triethylamine (v) 1M Triethylammonium bicarbonate aq.

Scheme

straightforward chemical procedures lowers the overall cost and makes the method particularly suitable for large scale synthesis.

The building blocks prepared were successfully used in solid phase synthesis (LCAA-CPG, loaded with 5'-O-MMTr-2'- or 3'-O-(2-chlorobenzoyl)ribonucleoside 3'- or 2'-succinates) of short oligoarabinonucleotides. The syntheses were performed in syringe and modified Gene Assembler (Pharmacia) using a standard protocol[7]. The use of 2'-O-acetyl protection in combination with easily removable N-protecting groups allowed simple and mild deprotection of the final oligomer. All protecting groups were removed in 32 % ammonia (aq)-ethanol (3:1) at room temperature, overnight.

The results from the synthesis of ara(UpUpUpCpCpUpCpCpUpCp)U are shown in the Figure. The target oligonucleotide was isolated in 35 % yield after consecutive purification using anion exchange and reverse phase HPLC (Fig.).

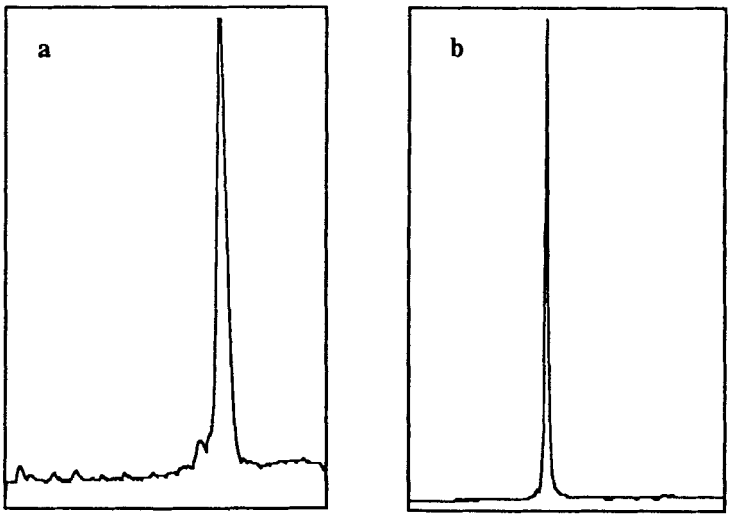


Figure. HPLC profiles of ara(UpUpUpCpCpUpCpCpUpCp)U; a) anion exchange separation of crude oligonucleotide, b) reverse phase purification of the fraction separated by anion exchange.

In summary, the approach allows quite simple and relatively cheap preparation of protected arabinonucleoside 3'-hydrogenphosphonates. These can be efficiently used in solid phase synthesis of oligoarabinonucleotides. The approach can be combined with regular oligonucleotide synthesis allowing incorporation of arabinonucleosides at selected sites in DNA and RNA fragments.

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