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Ribo-, Xylo-, and Arabino-Configured Adenine-Based Nucleoside Phosphonates: Synthesis of Monomers for Solid-Phase Oligonucleotide Assembly

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Ribo-, Xylo-, and *Arabino-*Configured Adenine-Based Nucleoside Phosphonates: Synthesis of Monomers for Solid-Phase Oligonucleotide Assembly

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ABSTRACT

Adenine-based, regioisomeric nucleoside phosphonates with *ribo*, *xylo* and *arabino* configuration were synthesized in the protected form suitable for the phosphotriester-like, solid-phase synthesis of oligonucleotides. Phosphonate moiety was protected by 4-methoxy-1-oxido-2-picolyl group and the furanose hydroxyl by the dimethoxytrityl group.

Key Words: Nucleoside phosphonic acids; Adenosine; 9-(Arabinofuranosyl)adenine; 9-(Xylofuranosyl)adenine; Protection; Phosphonylation; Nonisosteric phosphoester-like moiety.

RESULTS AND DISCUSSION

Nucleoside phosphonic acids have been systematically studied in our laboratory for a long time.^[1-4] These compounds with absolute stability against phosphomonoesterases and nucleotidases represent a pool of compounds for the construction

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of internucleotide linkage-modified short oligonucleotides.^[5–7] In the frame of our investigation of phosphonate-based nucleotide and oligonucleotide analogues we report here a novel class of monomers in the β-D-series derived from appropriate *riboA*, *xyloA* and *araA* phosphonic acids.

Starting from adenine β -D-nucleosides with *ribo*, *xylo* and *arabino* configuration, we have elaborated the synthesis of two series of protected nucleoside derivatives with free 2' and 5' hydroxy group, resp. (Sch. 1–6). These compounds were phosphonomethylated with diisopropyl tosyloxymethylphosphonate to afford fully protected nucleoside phosphonates in both 2' and 5' series. Further transformation of these compounds gives the monomeric building blocks in the 5' (1, 3, 5) and 2' (2, 4, 6) series. Phosphonylation reaction in the step (iv) g) in Sch. 3 has led, surprisingly, to the 3'-O-methylphosphonate **3** instead of the expected 5'-derivative. In the presence of NaH, the 3'-O-benzoyl group migrates completely to the 5'-hydroxyl so that phosphonylation takes place at the 3'-hydroxy function.



(i) a) CH(OEt)₃, 3M HCI/DMF, DMF, rt; b) TsOCH₂PO(OiPr)₂, NaH, DMF, rt (ii) c) 80% AcOH, rt; d) DMTrCl, DBU, CH₂Cl₂, rt; e) NH₃/MeOH; f) BzCl, Me₃SiCl, py, rt





(i) a) DMTrCl, py, rt; b) DMTrCl, DBU, CH₂Cl₂, rt (ii) c) TsOCH₂PO(OiPr)₂, NaH, DMF, rt; d) 3% CCl₃COOH in CH₂Cl₂, rt (iii) e) DMTrCl, py, rt; f) BzCN, Et₃N, CH₂Cl₂, rt (iv) g) Me₃SiBr, 2,6-lutidine, CH₃CN, rt; h) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 2.



(i) a) 1,3-dichloro-1,1,3,3-tetraisopropydisiloxane, py, rt; b) DMTrCl, DBU, CH₂Cl₂, rt (ii) c) 1M Bu₄NF in THF, rt; d) TBDPSCl, py, rt (iii) e) BzCN, Et₃N, CH₂Cl₂, rt; f) 1M Bu₄NF in THF, rt (iv) g) TSOCH₂PO(OiPr)₂, NaH, DMF, rt; h) Me₃SiBr, 2,6-lutidine, CH₃CN, rt; i) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 3.

Adenine-Based Nucleoside Phosphonates

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(i) a) DMTrCl, py, rt; b) DMTrCl, DBU, CH₂Cl₂, rt (ii) c) TsOCH₂PO(OiPr)₂, NaH, DMF, rt; d) 3% CCl₃COOH in CH₂Cl₂, rt (iii) e) DMTrCl, py, rt; f) BzCN, Et₃N, CH₂Cl₂, rt (iv) g) Me₃SiBr, 2,6-lutidine, CH₃CN, rt; h) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 4.



⁽i) a) CH(OEt)₃, 3M HCl/DMF, DMF, rt; b) TsOCH₂PO(OiPr)₂, NaH, DMF, rt (ii) c) 80% AcOH, rt; d) DMTrCl, DBU, CH₂Cl₂, rt; e) NH₃/MeOH (iii) f) BzCl, Me₃SiCl, py, rt; g) Ac₂O, DMSO, rt; h) NaBH₄, EtOH, 0°C (iv) i) BzCN, Et₃N, CH₂Cl₂, rt; j) Me₃SiBr, 2,6-lutidine, CH₃CN, rt; k) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 5.



(i) a) 6-N-benzoyl-9-N-trimethylsilyladenine, SnCl_a, CH₃CN, rt (ii) b) 1M HCl in MeOH, rt; c) TsOCH₂PO(OiPr)₂, NaH, DMF, rt (iii) d) NH₃ in MeOH rt; e) Bu₂NCH(OMe)₂, MeOH, rt; f) DMTrCl, py, rt

Scheme 6.

A key importance for the synthesis of the oligonucleotides has the protection of the 3'-hydroxyl of monomers 1 and 5. In case of *trans* configuration of the free 3'-hydroxyl and the DMTr group-protected hydroxyl (2–5) we can use benzoyl protecting group, although, for *cis* configured compounds (1, 6) the use of benzoyl or silyl protecting groups is excluded because of their hydroxyl-to-hydroxyl migration under conditions of phosphotriester condensation method. We have checked, therefore, the use of several types protecting groups to find among them the group stable both under detritylation conditions and towards migration. This study is underway.



Figure 1.

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For the solid-phase synthesis of oligomers were also prepared "first letters" (Fig. 1), which were anchored to LCAA-CPG via hemisuccinate, resulting in starting units for the synthesis of modified 2'-5' linked oligoadenylates with the regioisomeric 2'-O- CH_2 -P-O-5'' and 2'-O-P- CH_2 -O-5'' linkage, resp.

ABBREVIATIONS

Bz	Benzoyl
DBAM	Dibutylaminomethylen
DMTr	Dimethoxytrityl
MOP	4-Methoxy-1-oxido-2-picolyl
TOM	Triisopropylsilyloxymethyl

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