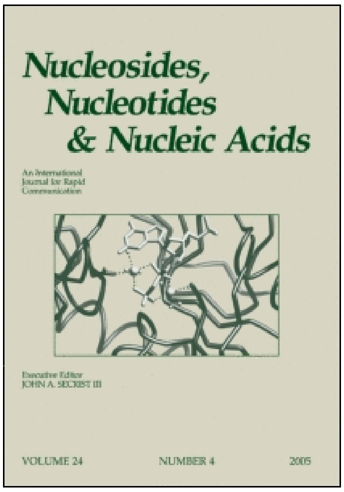

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Ribo-, *Xylo*-, and *Arabino*-Configured Adenine-Based Nucleoside Phosphonates: Synthesis of Monomers for Solid-Phase Oligonucleotide Assembly

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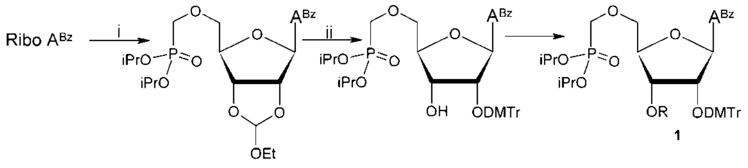
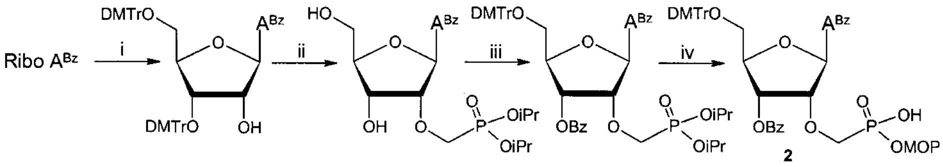
of internucleotide linkage-modified short oligonucleotides.[5–7] In the frame of our investigation of phosphonate-based nucleotide and oligonucleotide analogues we report here a novel class of monomers in the ß-D-series derived from appropriate *ribo*A, *xylo*A and *ara*A phosphonic acids.

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.



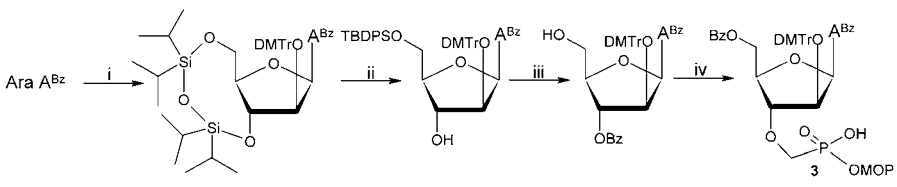
(i) a) $CH(OEt)_3$, 3M HCl/DMF, DMF, rt; b) $TsOCH_2PO(OiPr)_2$, NaH, DMF, rt (ii) c) 80% AcOH, rt; d) DMTrCl, DBU, CH_2Cl_2, rt; e) NH_3/MeOH; f) BzCl, Me_3SiCl, py, rt

Scheme 1.



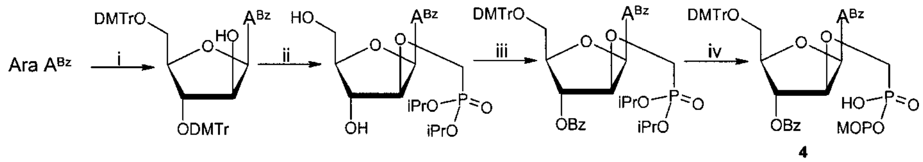
(i) a) DMTrCl, py, rt; b) DMTrCl, DBU, CH_2Cl_2, rt (ii) c) $TsOCH_2PO(OiPr)_2$, NaH, DMF, rt; d) 3% CCl_3COOH in CH_2Cl_2, rt
(iii) e) DMTrCl, py, rt; f) BzCN, Et_3N, CH_2Cl_2, rt (iv) g) Me_3SiBr, 2,6-lutidine, CH_3CN, rt; h) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 2.



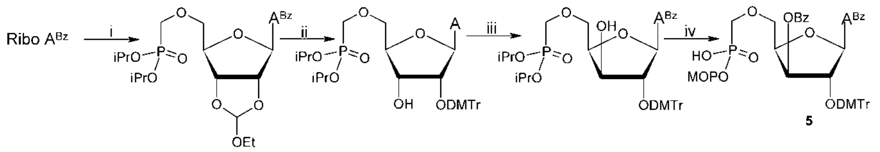
(i) a) 1,3-dichloro-1,1,3,3-tetraisopropydisiloxane, py, rt; b) DMTrCl, DBU, CH_2Cl_2, rt (ii) c) 1M Bu_4NF in THF, rt; d) TBDPSCl, py, rt
(iii) e) BzCN, Et_3N, CH_2Cl_2, rt; f) 1M Bu_4NF in THF, rt (iv) g) $TsOCH_2PO(OiPr)_2$, NaH, DMF, rt; h) Me_3SiBr, 2,6-lutidine, CH_3CN, rt;
i) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 3.



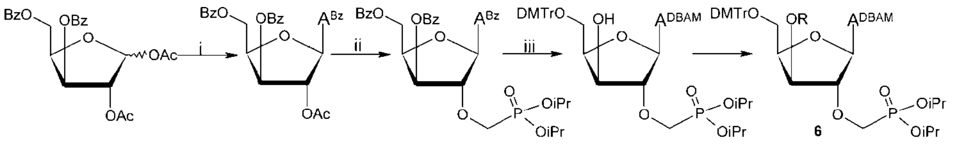
(i) a) DMTrCl, py, rt; b) DMTrCl, DBU, CH_2Cl_2, rt (ii) c) $TsOCH_2PO(OiPr)_2$, NaH, DMF, rt; d) 3% CCl_3COOH in CH_2Cl_2, rt
(iii) e) DMTrCl, py, rt; f) BzCN, Et_3N, CH_2Cl_2, rt (iv) g) Me_3SiBr, 2,6-lutidine, CH_3CN, rt; h) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 4.



(i) a) $CH(OEt)_3$, 3M HCl/DMF, DMF, rt; b) $TsOCH_2PO(OiPr)_2$, NaH, DMF, rt (ii) c) 80% AcOH, rt; d) DMTrCl, DBU, CH_2Cl_2, rt; e) NH_3/MeOH
(iii) f) BzCl, Me_3SiCl, py, rt; g) Ac_2O, DMSO, rt; h) $NaBH_4$, EtOH, 0°C (iv) i) BzCN, Et_3N, CH_2Cl_2, rt; j) Me_3SiBr, 2,6-lutidine, CH_3CN, rt;
k) 4-methoxy-1-oxido-2-pyridylmethanol, DCC, py, rt

Scheme 5.



(i) a) 6-N-benzoyl-9-N-trimethylsilyladenine, $SnCl_4$, CH_3CN, rt (ii) b) 1M HCl in MeOH, rt; c) $TsOCH_2PO(OiPr)_2$, NaH, DMF, rt (iii) d) NH_3 in MeOH, rt; e) $Bu_2NCH(OMe)_2$, 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.

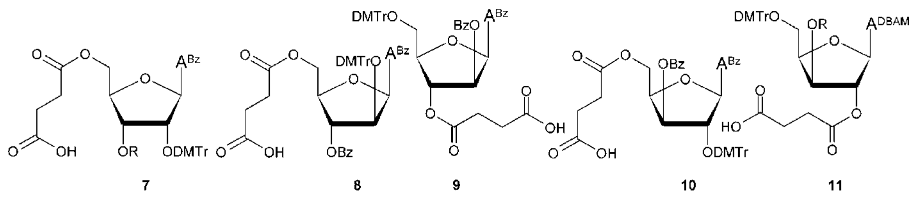


Figure 1.

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

ACKNOWLEDGMENTS

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REFERENCES

1. Endová, M.; Masojídková, M.; Buděšínský, M.; Rosenberg, I. 2′,3′-O-Phosphonoalkylidene derivatives of ribonucleosides: synthesis and reactivity. Tetrahedron **1998**, *54*, 11,151–11,186.
2. Endová, M.; Masojídková, M.; Buděšínský, M.; Rosenberg, I. 3′,5′-O-phosphonoalkylidene derivatives of 1-(2-deoxy-β-D-threo-pentofuranosyl)thymine: synthesis and reactivity. Tetrahedron **1998**, *54*, 11,187–11,208.
3. Králíková, Š.; Buděšínský, M.; Masojídková, M.; Rosenberg, I. Efficient synthesis of nucleoside 3′-*C*-phosphonates: reactivity of geminal hydroxyphosphonate moiety. Nucleosides, Nucleotides & Nucleic Acids **2000**, *19* (7), 1159–1183.
4. Králíková, Š.; Buděšínský, M.; Masojídková, M.; Rosenberg, I. Geminal hydroxy phosphonate derivatives of nucleosides: a novel class of nucleoside 5′-monophosphate analogs. Tetrahedron Lett. **2000**, *41*, 955–958.
5. Pressová, M.; Endová, M.; Točík, Z.; Liboska, R.; Rosenberg, I. UV spectroscopy of complexes of poly(U) with ApA analogs: prediction of oligonucleotide properties? Bioorg. Med. Chem. Lett. **1998**, *8*, 1225–1230.
6. Rejman, D.; Snášel, J.; Liboska, R.; Točík, Z.; Pačes, O.; Králíková, Š.; Rinnová, M.; Koiš, P.; Rosenberg, I. Oligonucleotides with isopolar phosphonate internucleotide linkage: a new perspective for antisense compounds? Nucleosides, Nucleotides & Nucleic Acids **2001**, *20*, 819–823.
7. Hanuš, J.; Barvík, I.; Ruszová-Chmelová, K.; Štěpánek, J.; Turpin, P.-Y.; Bok, J.; Rosenberg, I.; Petrová-Endová, M. -CH2-lengthening of the internucleotide linkage in the ApA dimer can improve its conformational compatibility with its natural polynucleotide counterpart. Nucl. Acids Res. **2001**, *29*, 5182–5194.
8. Pitsch, S.; Weiss, P.A.; Jenny, L.; Stutz, A.; Wu, X. Helv. Chim. Acta **2001**, *84*, 3773–3795.

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