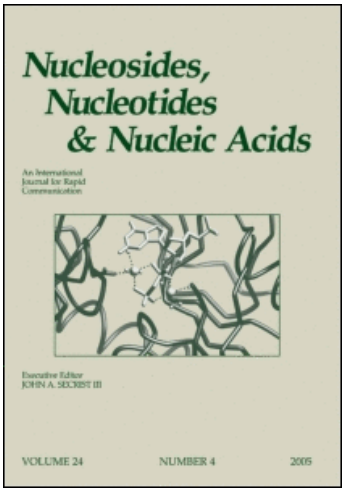

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2'-Deoxy-2'(*S*)-ethynyl Oligonucleotides: Synthesis and Pairing Properties

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2'-DEOXY-2'(*S*)-ETHYNYL OLIGONUCLEOTIDES: SYNTHESIS AND PAIRING PROPERTIES

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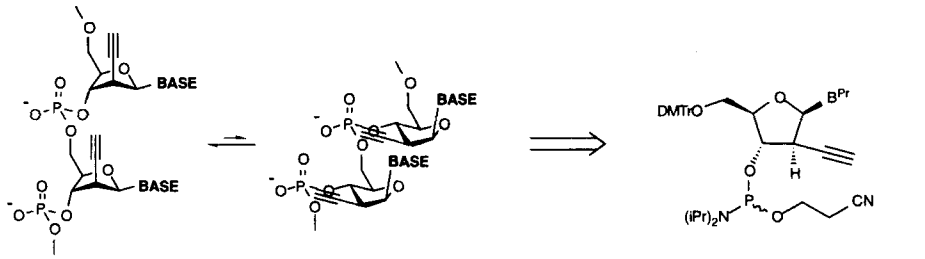
ABSTRACT: Oligonucleotides from 2'-deoxy-2'(*S*)-ethinyl-adenosine, -cytidine, -guanosine, -thymidine and -uridine have been prepared. Whereas the modified pyrimidine oligonucleotides uniformly lead to weaker binding affinity with DNA and RNA complements, the corresponding adenine oligonucleotides show enhanced thermal stability in duplexes with complementary DNA and decreased stability with RNA.

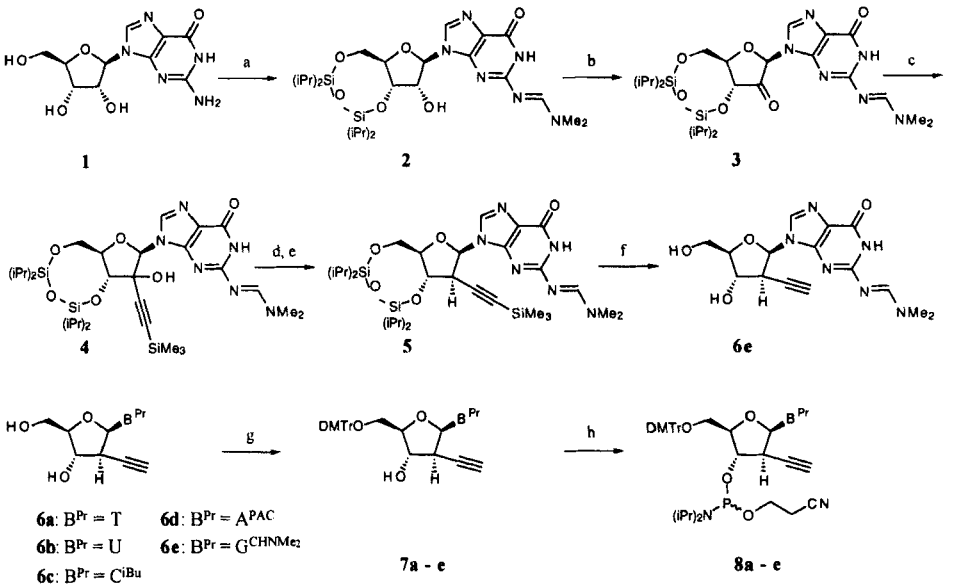
DNA double helices are capable of adopting a multitude of conformations whereas double-stranded RNA is confined to A-form duplexes. Selectivity for a DNA complement should thus be possible if an A-form conformation of the resulting double helix is not accessible. To this end, we sought to introduce an (*S*)-configured ethynyl substituent at the C(2')-position of deoxynucleosides. We assumed that the individual nucleosides in such an oligodeoxynucleotide adopt a C(2')-*endo* conformation, typical of B-form DNA double helices, because the alternative C(3')-*endo* (RNA) conformation would lead to sterically unfavorable interactions with the 3'-neighbouring nucleotide.



C(2')-endo conformation
(preferred, as in DNA)

B^{Pr} = U, T, C^{iBu}, A^{PAC}, G^{CHNMe_2}

The synthesis of 2'-deoxy-2'(S)-ethynyl-uridine, -thymidine, -cytosine, and -adenosine have previously been reported.[1,2] The synthesis of the corresponding guanosine analog — which illustrates the strategy common to all these syntheses — is shown below.



*a) Ref. 3; b) Dess-Martin periodinane, CH_2Cl_2, r.t., 2h; c) BuLi, TMSC≡CH, THF, -78°C, 2h, 61% (2 steps); d) $H_3COCOCOCl$, DMAP, CH_2Cl_2, 0°C→r.t., 2h; e) Bu_3SnH, AIBN, toluene, 95°C, 1h, 65% (2 steps); f) TBAF, AcOH, THF, r.t., 4h, 87%. g) DMTrCl, pyridine, r.t., 3h, **6a**: 81%, **6b**: 79%, **6c**: 83%, **6d**: 61%, **6e**: 67%; h) (OCH_2CH_2CN)-$(iPr_2N)PCl$, iPr_2NEt, THF, r.t., 1h, **6a**: 92%, **6b**: 87%, **6c**: 96%, **6d**: 80%, **6e**: 95%*

From the phosphoramidites **8** oligonucleotides could be prepared by standard automated synthesis. Whereas the 2'(*S*)-ethynyl-modified pyrimidine oligonucleotides uniformly lead to weaker binding affinity with DNA and RNA complements, the corresponding adenine oligonucleotides show enhanced thermal stability in duplexes with complementary DNA and decreased stability in RNA heteroduplexes.

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