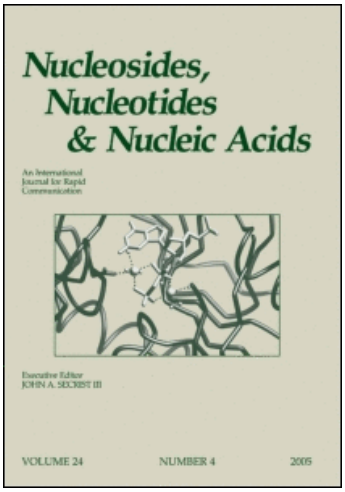

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Elzagheid, Mohamed I. , Tedeschi, Anna Lisa and Damha, Masad J.(2003) 'Synthesis of 2',3'-Dideoxy-2'-fluoro-3'-thioarabinothymidine and Its 3'-Phosphoramidite Derivative', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1343 — 1346
To link to this Article: DOI: 10.1081/NCN-120022961
URL: http://dx.doi.org/10.1081/NCN-120022961

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1343–1346, 2003

Synthesis of 2′,3′-Dideoxy-2′-fluoro-3′-thioarabinothymidine and Its 3′-Phosphoramidite Derivative

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ABSTRACT

An efficient method for the synthesis of 5′-O-monomethoxytrityl-2′,3′-dideoxy-2′-fluoro-3′-thioarabinothymidine [$^{5'\text{-MMT}}$araF-$T_{3'\text{SH}}$, (**5**)] and its 3′-phosphoramidite derivative (**6**) suitable for automated incorporation into oligonucleotides, is demonstrated. A key step in the synthesis involves reaction of 5′-O-MMT-2,3′-O-anhydrothymidine (**4**) (Eleuteri, A.; Reese, C.B.; Song, Q., J. Chem. Soc. Perkin Trans. 1 **1996**, 2237 pp.) with sodium thioacetate to give $^{5'\text{-MMT}}$araF-$T_{3'\text{SAc}}$ (**5**) (Elzagheid, M.I.; Mattila, K.; Oivanen, M.; Jones, B.C.N.M.; Cosstick, Lönnberg, H. Eur. J. Org. Chem. **2000**, 1987–1991). This nucleoside was then converted to its corresponding phosphoramidite derivative, **6**, as described previously ((a) Sun, S.; Yoshida, A.; Piccirilli, J.A. RNA, **1997**, *3*, 1352–1363; (b) Matulic-Adamic, J.; Beigelman, L. Helvetica Chemica Acta **1999**, *82*, 2141–2150; (c) Fettes, K.J.; O'Neil, I.; Roberts, S.M.; Cosstick, R. Nucleosides, Nucleotides and Nucl. Acids **2001**, *20*, 1351–1354).

Key Words: Thionucleosides; Arabinonucleic acids; Antisense.

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DOI: 10.1081/NCN-120022961
1525-7770 (Print); 1532-2335 (Online)

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Synthetic oligonucleotides are of considerable importance because of their ability to inhibit gene expression through antisense effects.[4] The most efficacious antisense oligonucleotides (AON) are those that possess stabilities against nucleases, and adequate lipophilicity to ensure efficient cell permeation. Ideally, they should also suppress gene activity with the assistance of intracellular ribonuclease H (RNase H), an enzyme that degrades the RNA strand of the AON/RNA hybrid (see Ref.[5], and references therein). However, most AONs lack the appropriate structural attributes for RNase H elicitation and typically display less than optimal cellular potencies. Our laboratory has recently demonstrated that arabinonucleic acids

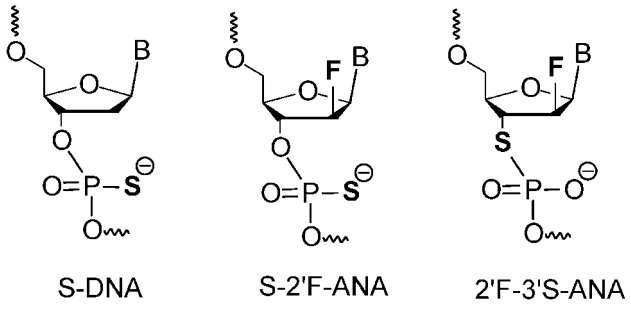
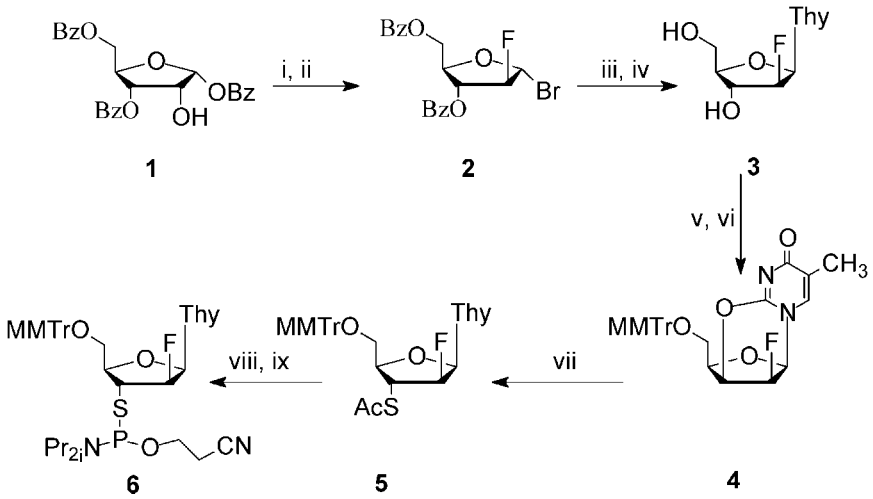


Figure 1. Structure of modified oligonucleotides.



Scheme 1. i) [Bis(2-methoxyethyl)amino]sulfur trifluoride, CH_2Cl_2, 50 °C, 83%; ii) HBr, CH_2Cl_2, rt, 24h, 90%; iii) silylated thymine, CCl_4, 3d, 77 °C, 75%; iv) NH_4OH, MeOH, rt, 24h, 90%; v) MMTr-Cl, pyridine, 87%; vi) MsCl, pyridine/ Et_3N, EtOH, reflux, 16h, 92%; vii) NaSAc, dioxane, reflux, 12h, 84%; viii) 1M NaOMe, MeOH, 1h; ix) 2-cyanoethyl-*N,N*-diisopropylchlorophosphoramidite,1-methylimidazole, diisopropyl- ethylamine, CH_2Cl_2, 80%.

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(e.g., 2′F-ANA), like DNA phosphorothioates (S-DNA), possess the ability to elicit RNase H-mediated hydrolysis of target RNA.[6]

The antisense activity of phosphorothioate linked 2′-deoxy-2′-fluoro-arabinonucleic acids (S-2′F-ANA, Fig. 1) has been evaluated,[5] however, nothing is known about the isomeric analogue in which a sulfur atom replaces one of the two bridging oxygen atoms, i.e., 2′,3′-dideoxy-2′-fluoro-3′-thioarabinonucleic acids (2′F-3′S-ANA; Fig. 1). Here we report preparation of one of the four nucleoside monomers required for the solid-phase synthesis of 2′F-3′S-ANA.

The synthesis is depicted in Sch. 1. Sugar precursor **1** (from Pfanstiehl) was converted into the α-1-bromoarabinose **2** with retention of sugar C-1 configuration.[7] Compound **2** was then used, without isolation, for S_N2-type glycosylation reaction with silylated thymine base according to literature procedure[7] which resulted, after removal of 5′- and 3′-*O*-benzoyl groups, in the formation of nucleoside **3**. The latter nucleoside then 5′-monomethoxytritylated and 3′-mesylated before being converted to 2,3′-anhydronucleoside **4**.[2] Direct ring opening of the 2,3′-anhydro linkage, in nucleoside **4**, with thioacetate gave nucleoside **5**[a] that was then converted to the phosphoroamidothioite derivative **6**[b] following literature protocols.[3] The synthesis of 2′F-3′S-ANA oligonucleotides is in progress.

ACKNOWLEDGMENT

We wish to thank CIHR (Canada) for financial support.

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[a]Nucleoside **5**: TLC (20:1 [v/v] chloroform/methanol)0.49;^{1}H-NMR (400 MHz acetone-d_6, tetramethylsilane as internal reference): 10.15 (1H, s, N-H), 7.60–6.90 (16H, m, trityl and H-6), 6.33 (1H, dd, $J_{1',F} = 15.6$Hz $J_{1',2'} = 4.4$Hz H-1′), 5.3 (1H, dt, $J_{2',F} = 54.8$Hz, $J_{2',3'} = 5.2$Hz 5.2Hz H-2′) 4.3 (1H, dm or ddd, $J_{3',F} = 16.8$Hz $J_{3',F} = 3.6$Hz H-3′), 4.1 (1H, m, H-4′), 3.79 (3H, s, CH_3O), 3.36 (2H, dd, H-5′,5″), 2.37 (3H, s, CH_3CO-S), 1.64 (3H, CH_3-C5); ^{19}F-NMR (283MHz, acetone-d_6, 99% trifluoroacetic acid as external reference): –106,63 (ddd); ESI-MS: 589.1 (M-1), 590.1 (M^+), 613.1 ($M + Na^+$).

[b]Phosphoroamidothioite. **6**: ^{31}P-NMR (200 MHz, DMSO-d_6, 85%H_3PO_4 as external reference): 162.2, 158.7.

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