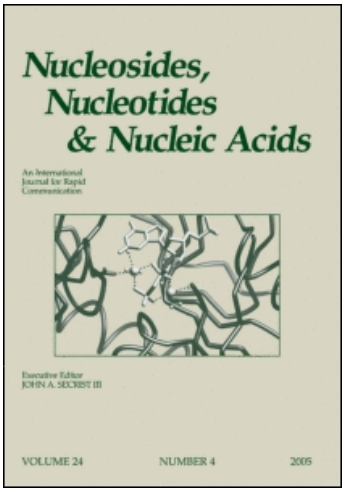

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2'-DEOXYISOINOSINE: SYNTHESIS OF A HIGHLY FLUORESCENT NUCLEOSIDE AND ITS INCORPORATION INTO OLIGONUCLEOTIDES

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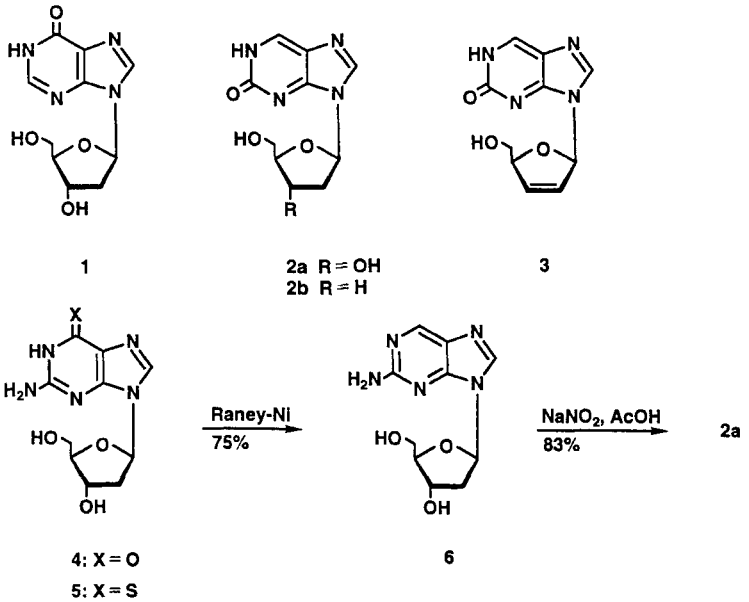
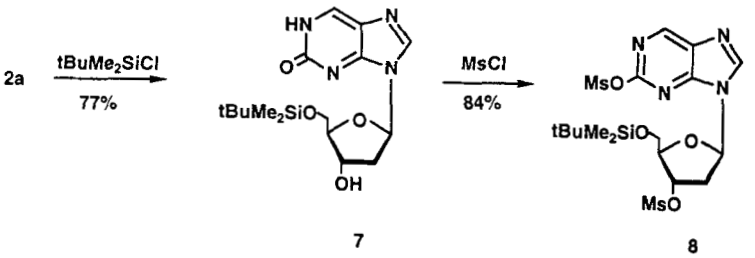
ABSTRACT: The synthesis of 2'-deoxyisoinosine (**2a**) and the related 2',3'-dideoxynucleosides **2b** and **3** is reported. The 3'-phosphonate **4b** as well as the phosphoramidite **4c** were prepared and employed in solid-phase oligonucleotide synthesis.

The 2'-deoxyinosine (**1**) is used as ambiguous nucleoside in oligonucleotide chemistry. We have synthesized the isomeric 2'-deoxyisoinosine (**2a**)[1] as well as the sugar derivatives **2b** and **3**. As an intermediate the aminonucleoside **6** was prepared. It was obtained from 2'-deoxyguanosine (**4**) via the 6-thioxo compound **5** by desulfurization[2]. Treatment of **6** with $NaNO_2$/AcOH yielded **2a**.

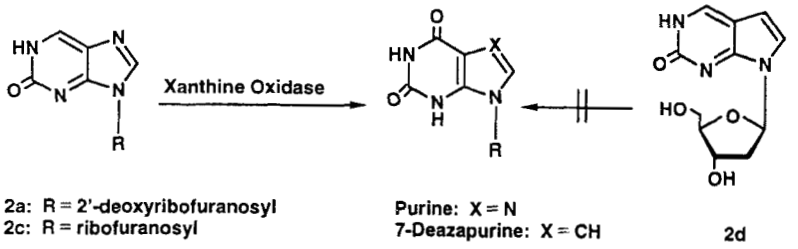


The synthesis of 2',3'-didehydro-2',3'-dideoxyisoinosine (**3**) was performed starting from 2'-deoxyisoinosine (**2a**). This was silylated to give compound **7**.

Mesylation afforded **8** containing two mesyl groups, one at the OH-3' group and the other at the oxygen-2. This was proved by ^{13}C-NMR spectra of **2a** and **8** which exhibit a completely altered pattern of ^{13}C-NMR resonances of the base. Moreover, compound **8** is no longer fluorescent. Compound **8** was then treated with Bu_4NF to give **3**. Subsequently, it was hydrogenated to 2',3'-dideoxyisoinosine (**2b**).



The 2-oxo nucleosides **2a, b** and **3** show strong fluorescence (excitation: 315 nm, emission: 380 nm, in H_2O and MeOH). Treatment of the compounds **2a,c**[3] with xanthine oxidase furnished the corresponding xanthine derivatives. The related 7-deaza-2'-deoxyisoinosine (**2d**) was found to be resistant towards the enzyme.



As it is unknown which of the common nucleosides show base pairing with **2a,c**, oligonucleotides were synthesized. For this purpose, the nucleoside **2a** was protected at OH-5' with a DMT-residue (**9**) and subsequently converted into its 3'-phosphonate **10a** (a: PCl_3 / 1,2,4-triazole; ^{31}P-NMR: 0.52 J(P, H) = 587 Hz) as well as into the phosphoramidite **10b** (b: Cl-P((i-Pr)$_2$N)O(CH$_2$)$_2$CN; ^{31}P-NMR: 149.0, 148.3).

The polymer-linked 2'-deoxyisoinosine **10d** was also prepared from **9** by succinylation (**10c**) followed by condensation with amino-functionalized CPG. The ligand concentration was 90 μmol/g. ^{13}C-NMR data are shown in the Table.

Table. ^{13}C-NMR Data of 2'-deoxyisoinosine and derivatives in d_6-DMSO.

Compd.	C-2	C-6	C-5	C-8	C-4	CH_3O/CH_3	
2a	156.1	139.4	123.6	145.5	158.8		
3	157.5	142.7[t]	123.2	142.5[t]	159.5		
7	155.9	139.1	123.5	145.3	158.7	25.9/18.1	
9	155.9	139.5	123.6	145.7	159.0	55.1	
10a	156.0	139.5	123.6	145.4	158.9	55.1	
10c	155.8	139.3	123.6	145.5	159.0	55.1	

Compd.	C-1'	C-2'	C-3'	C-4'	C-5'	COOH	CO
2a	82.9	-	70.9	87.9	61.7		
3	87.9	125.6	134.4	87.1	62.9		
7	82.5	-	70.2	87.1	63.2		
9	82.4	-	70.5	85.8	64.2		
10a	82.7	-	72.5	80.5	63.9		
10c	82.8	-	74.8	83.6	65.0	173.5	171.5

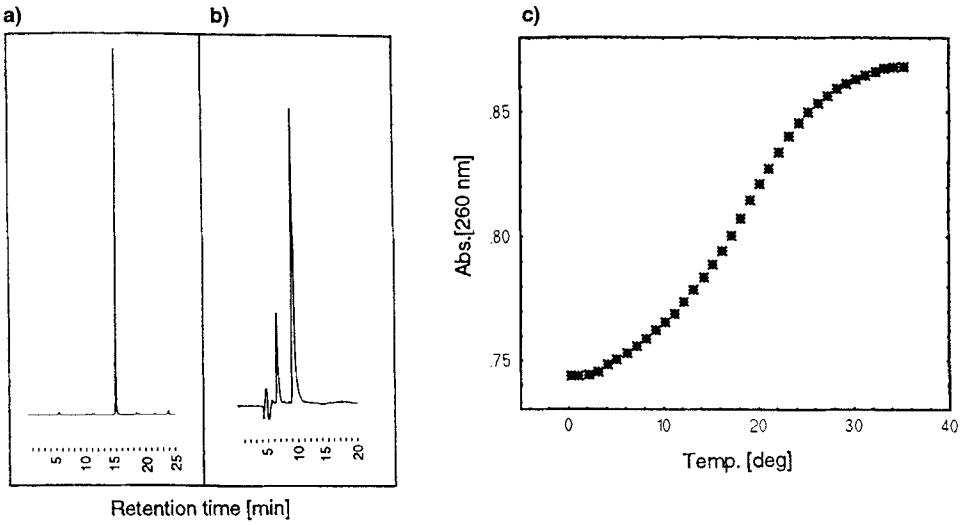
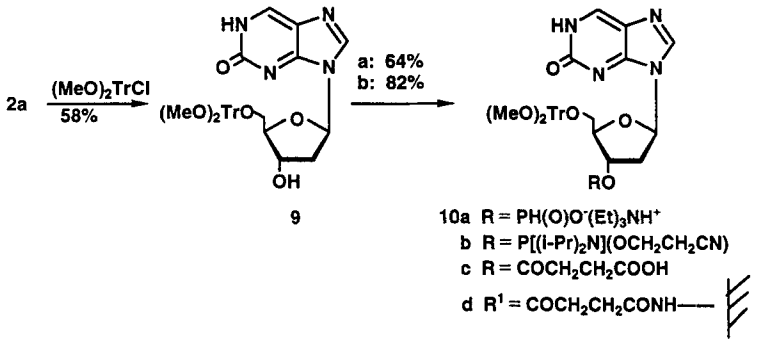


FIG. a) HPLC profile of **11**, gradient 0-20% MeCN in 0.1 M $(Et_3NH)OAc$ (pH 7.0) / MeCN, 95:5, at 260 nm; b) HPLC profile of the enzymatic digest of **11**, at 290 nm; c) Melting curve of **11·12**, at 260 nm.



The phosphonate **10a** was employed in solid-phase synthesis of the oligomers **11-13** using the phosphonate chemistry. HPLC profiles are shown in the Figure.

```
5'-d(TTTTTiIiITTTTT)  (11)        5'-d(TTTTTiIiITTTTT)  (11)
     •••••   •••••                     •••••   •••••
5'-d(AAAAA-T-TAAAAA)  (12)        5'-d(AAAAA-G-GAAAAA)  (13)
```

Next, the duplex formation of the oligonucleotide **11** with compounds **12** and **13** was studied. In both cases cooperative melting profiles were observed (Figure). A T_m value of 19°C was found for **11**·**12** and 20°C for **11**·**13**. The related $d(A)_{12}$·$d(T)_{12}$ showed a much higher T_m (44°C). This indicates that 2'-deoxyisoinosine does not base pair, neither with 2'-deoxythymidine nor with 2'-deoxyguanosine.

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