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Facile Synthesis of 2',3'-Unsaturated Nucleosides from 2-Deoxyribose

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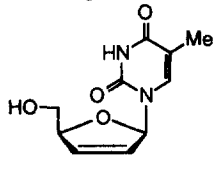
Abstract: A straightforward approach for the synthesis of 2',3'-unsaturated nucleosides starting from 2-deoxyribose is described. This novel route involves two new methods; (1) preparation of 2-deoxy-1-thioribofuranoside by direct condensation of 2-deoxyribose and thiophenol, (2) formation of the nucleoside skeleton by the direct coupling of 2,3-unsaturated 1-thiopentofuranoside with pyrimidine bases.

In recent years, there has been significant interest in 2',3'-unsaturated nucleosides as potential antiviral agents against human immunodeficiency virus (HIV).[1] The best known example of such a nucleoside is 3'-deoxy-2',3'-didehydrothymidine (d4T, **1**), which is currently used in the treatment of AIDS. A number of synthetic efforts have also been focused on this type of nucleoside analog.[2,3] They are largely classified into two approaches. One includes modification of the sugar part of intact nucleosides available from natural sources. Another consists of the coupling of a sugar moiety bearing an appropriate eliminating group with nucleoside bases, followed by formation of a double bond at the 2',3'-position by β-elimination. In the latter strategy, the introduction of the unsaturated bond is always carried out after the coupling reaction in every case. A direct coupling of a 2,3-unsaturated sugar moiety with nucleoside bases is thought to be one of the most straightforward approaches to 2',3'-unsaturated nucleoside derivatives. However, such a reaction has never been previously successful due to the lability of the 2,3-unsaturated sugar intermediate under the coupling conditions,[4] in which Lewis acids are often used as a promoter.

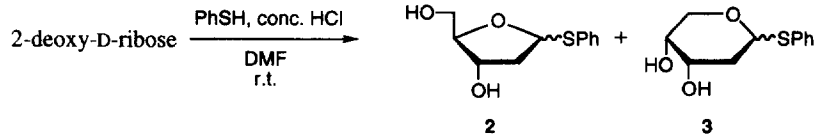


1 (d4T)

In our laboratory, convenient methods for the synthesis of nucleosides and their analogs have been developed by utilizing the NBS-promoted coupling reaction of 1-thioglycosides with nucleoside bases.[5] Herein, we successfully extended this methodology to the synthesis of 2',3'-unsaturated nucleosides by the use of the direct coupling of 2,3-unsaturated 1-thioglycosides with pyrimidine bases.

First, we planned to develop an efficient method for the preparation of 2-deoxy-1-thioribofuranoside as a precursor of a 2,3-unsaturated glycosyl donor. Generally, thioglycosides are synthesized from the

corresponding methyl glycosides,[6] glycosyl acetates,[7] or glycosyl halides.[8] For instance, we previously prepared phenyl 2-deoxy-1-thioribofuranoside (**2**) in four steps starting from 2-deoxyribose *via* the known methyl 2-deoxyribofuranoside.[9] If the thioriboside can be directly obtained from 2-deoxyribose and thiophenol, the overall process for producing the target molecule will be shortened and simplified. The difficulty to be overcome is selective formation of the desired thiofuranoside **2** over thiopyranoside **3** and dithioacetal. We therefore examined the reaction conditions regarding the solvent, the acid catalyst, and equivalents of the thiol used. Some representative results are shown in Table 1. The best yields of **2** were obtained using hydrochloric acid as a catalyst in the presence of an excess amount (10 to 40 equiv.) of the thiol in DMF. The solvent is essential for obtaining **2** predominantly, because the condensation without solvent led to loss of the selectivity (run 4). Other acids such as $BF_3{\cdot}OEt_2$, TMSOTf, and an ion exchange resin (H^+-form) or solvent (MeCN) were much less satisfactory than the above conditions.



(1)

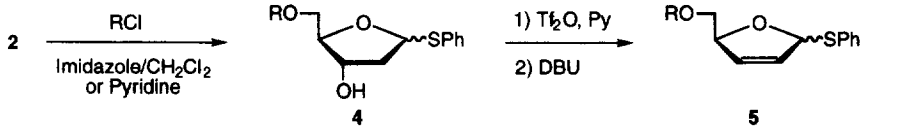
2 **3**

Table 1. Synthesis of Phenyl 2-Deoxy-1-thioribofuranoside.

Run	PhSH (ml) : conc. HCl (ml) : DMF (ml) / Sugar (10 mmol)	Combined Yield of **2** and **3**	Ratio (**2**:**3**)[a]
1	1 (1 equiv.) : 0.2 (0.24 equiv.) : 2.5	66%	89:11
2	10 : 0.5 : 2.5	93%	91:9
3	40 : 0.2 : 10	94%	95:5
4	40 : 0.2 : 0	83%[b]	58:42

a) The ratio was determined by ^{1}H NMR. Products **2** and **3** are separable by silica gel chromatography.
b) The corresponding diphenyldithioacetal was also obtained in 16% yield.

After protection of the C-5 hydroxyl group of **2**, the 2,3-unsaturated bond was formed by a two-step procedure (triflic anhydride-pyridine, then DBU). According to this scheme, some 5-*O*-silyl and 5-*O*-trityl derivatives, **5**, were obtained in moderate to good yields. Benzyl- and pivaloyl-protected derivatives were obtained by transformation of the 5-*O*-*t*-$BuMe_2Si$ derivative of **5** *via* the usual deprotection/protection procedure.



4

R=*t*-$BuMe_2Si$ 83%
R=*t*-$BuPh_2Si$ 75%
R=Tr 91%

5

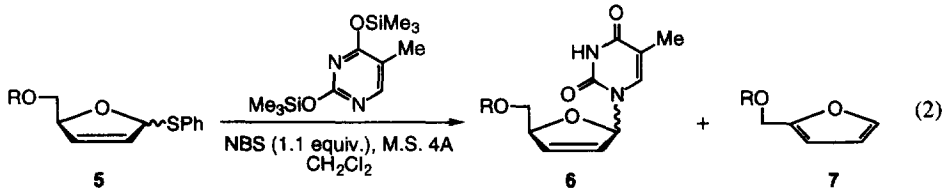
R=*t*-$BuMe_2Si$ 82%
R=*t*-$BuPh_2Si$ 71%
R=Tr 77%

Scheme 1. Preparation of 2,3-unsaturated 1-thiopentofuranoside

With appropriately protected 2,3-unsaturated 1-thiopentofurnosides **5** in hand, we next explored the coupling reaction with silylated thymine. As mentioned previously, 2,3-unsaturated pentofuranosides are sensitive to both acidic and basic conditions, easily affording furan derivatives.[4,10,11] Therefore, we first chose NBS as a promoter, which can activate thioglycosides under almost neutral conditions. As shown in Table 2, all the thioglycosides employed gave the protected d4T, **6**, in moderate yields along with small amounts of furan **7**.

Concerning the anomeric ratio, thioglycosides bearing sterically more bulky protective groups afforded nucleoside **6** in favor of the β-anomer. The reaction of the trityl derivative, which showed the highest β-anomer selectivity, was further investigated in detail (runs 6–10). When the α-anomer of the thioglycoside was used in the coupling reaction, the ratio of the β-nucleoside was improved though the yield of furan **7** also increased. On the other hand, starting from the β-anomer, nucleoside **6** was obtained in quantitative yield with somewhat lower β-anomer selectivity. The reactions which were carried out at –30 and 0 °C resulted in low yields and low anomeric ratios. These observations imply that furan **7** is formed at least at –78 °C through only a reaction intermediate generated from the α-anomer of **5**[12] and that the thioglycosides are unstable under the reaction conditions at higher temperature to be easily decomposed into furan **7**, but the 2',3'-unsaturated nucleoside once formed is stable even at –30 °C.

The use of other promoters such as NIS, $Me_2S(SMe)BF_4$, or $I(collidine)_2ClO_4$ caused loss of the anomeric selectivity and/or a significant decrease in the chemical yield.



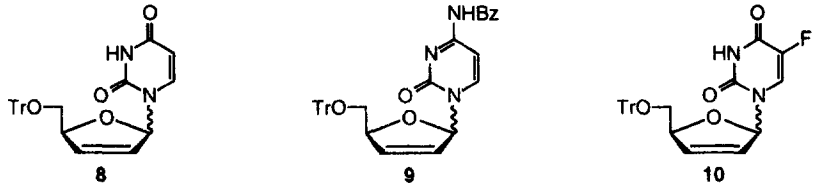
5 **6** **7**

Table 2. Coupling Reaction of **5** with Silylated Thymine.

Run	R	Temperature (°C)	Yield (%) of **6**	β/α	Yield (%) of **7**
1	Piv	–78	60	1.8/1	—a)
2	Bzl	–78	73	1.9/1	—a)
3	*t*-$BuMe_2Si$	–78	71	1.6/1	—a)
4	*t*-$BuPh_2Si$	–78	75	3.0/1	—a)
5	Tr (α/β=2.5/1)	–78	83	3.7/1	17
6	Tr (α)	–78	72	3.9/1	27
7	Tr (β)	–78	98	2.6/1	trace
8	Tr (α/β=2.5/1)	–30	37	2.8/1	30
9	Tr (α/β=2.5/1)	0	8	1.7/1	61
10	Tr (α/β=2.5/1)	–78 to –30	81	3.4/1	18

a) Yield was not determined.

The generality of this method was explored by reacting trityl-protected thioglycoside **5** (R=Tr, α/β=2.5/1) with different pyrimidine bases. In each case, the desired 2',3'-unsaturated nucleosides **8**, **9**, and **10** were produced in satisfactory yields and ratios, accompanied by furan **7** (22–32% yields).



8 59% (β/α=5.0/1)

9 67% (β/α=3.2/1)

10 52% (β/α=4.8/1)

Finally, deprotection of 5'-*O*-tritylated d4T, **6** (R=Tr), by acidic hydrolysis (Dowex® 50W, H^+-form in MeOH, 76%), followed by chromatographic separation of the α- and β-anomers led to d4T. The novel methodology outlined herein provides a rapid and efficient access to 2',3'-unsaturated nucleosides.

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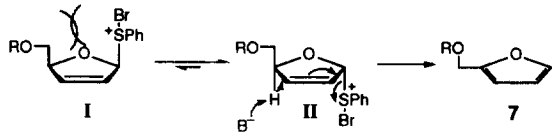
12. At the present time, we assume that the intermediates of the coupling reaction are bromosulfonium ions I and II, which would be in equilibrium. An S_N2-type attack of pyrimidine bases on these intermediates would provide the nucleoside skeleton. The elimination may easily proceed when the relationship between the abstracted proton and the bromosulfonium moiety is *cis*, giving furan **7**.



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