Pergamon

Tetrahedron Letters 41 (2000) 407–411

TETRAHEDRON LETTERS

Stereoselective synthesis of nucleosides from 1-thio and 1-seleno glycosides through consecutive 1,2-migration and glycosylation under Mitsunobu conditions

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Received 22 September 1999; accepted 2 November 1999

Abstract

2-Deoxy-2-sulfenyl-*arabino*-α-nucleosides and 2-deoxy-2-sulfenyl-*ribo*-β-nucleosides were obtained with excellent stereoselectivity from 1-thio-*ribo*- and 1-thio-*arabino*-glycosides under Mitsunobu conditions. © 2000 Elsevier Science Ltd. All rights reserved.

A general problem in the synthesis of 2′-deoxy- and 2′,3′-dideoxy-nucleosides is controlling the stereoselectivity in the formation of the glycosidic bond. To overcome this lack of stereoselectivity, we used sugars with easily removable electron donor groups at position 2 of the sugar ring as glycosyl donors (e.g. phenylsulfenyl[1] and phenylselenenyl[2] to give the corresponding 2-phenylsulfenyl and 2-phenylselenenyl nucleosides). Phenylsulfenyl and phenylselenenyl groups were introduced into the sugar ring by reacting PhSCl or PhSeCl with the corresponding lactone enolate followed by reduction of the lactone (Scheme 1, via 1). An alternative procedure starts from glycals, and successive NIS, I_2, PhSCl or PhSeCl addition and glycosylation (Scheme 1, via 2, X=I, SPh, SePh, respectively) leads to the corresponding 2′,3′-dideoxy-2′-iodo-,[3] 2′,3′-dideoxy-2′-phenylsulfenyl-,[4] and 2′,3′-dideoxy-2′-phenylselenenyl nucleosides[5] with good to excellent stereoselectivities. Recently, we obtained 2,3′-dideoxy-3′-fluoro-β-nucleosides by converting phenyl 3-deoxy-3-fluoro-1-seleno-α-*arabino*-furanosides to 2′,3′-dideoxy-3′-fluoro-2′-phenylselenenyl-β-*ribo* nucleosides through consecutive 2-OH activation, 1,2-migration and glycosylation in Mitsunobu conditions (Scheme 1, via 3) and subsequent deselenization.[6] An *epi*-ion (B) (Scheme 1) has been proposed in these cases although some reports doubt this proposal, suggesting that oxonium cation A is the real intermediate.[7]

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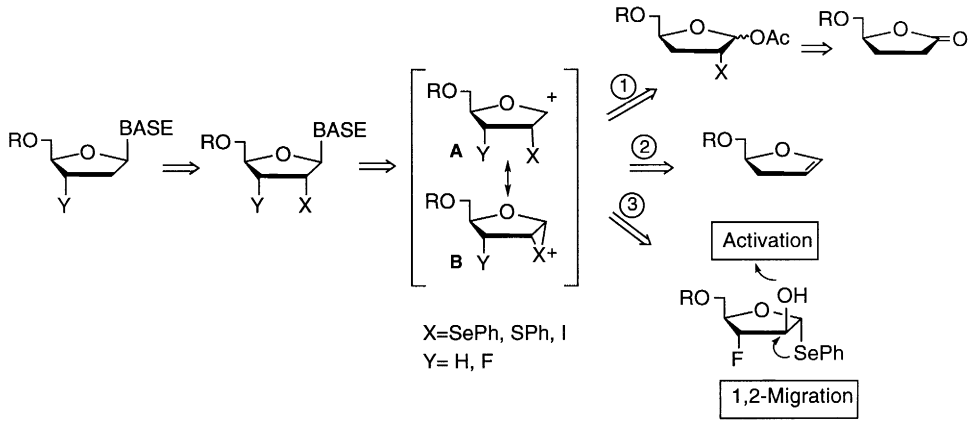
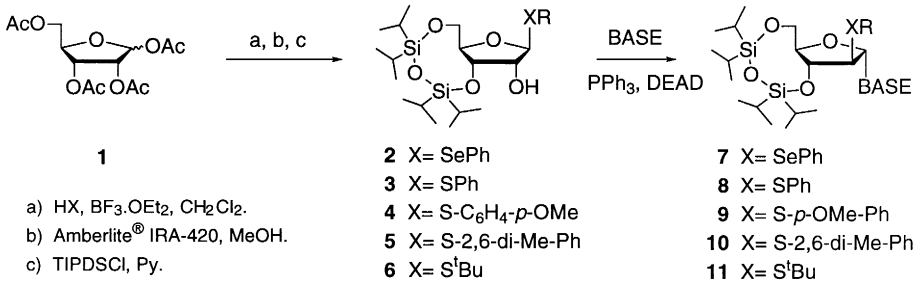
PII: S0040-4039(99)02071-7



Scheme 1.

In this report we show that 1-thio-β-*ribo*- and 1-thio-α-*arabino*-glycosides are appropriate starting materials for preparing 2′-deoxy-2′-sulfenyl-*arabino*-α-nucleosides and 2′-deoxy-2′-sulfenyl-*ribo*-β-nucleosides, respectively, which are precursors of 2′-deoxy nucleosides, with excellent stereoselectivity.

The selenoglycoside **2** and thio-glycosides **3**–**6** were prepared by reacting tetra-*O*-acetyl-D-ribose (**1**) with phenyl selenol or the corresponding thiols in the presence of $BF_3 \cdot OEt_2$ and subsequent deprotection and protection with TIPDSCl (Scheme 2).



1

a) HX, $BF_3.OEt_2$, CH_2Cl_2.
b) Amberlite® IRA-420, MeOH.
c) TIPDSCl, Py.

2 X= SePh
3 X= SPh
4 X= S-C_6H_4-*p*-OMe
5 X= S-2,6-di-Me-Ph
6 X= S^{t}Bu

7 X= SePh
8 X= SPh
9 X= S-*p*-OMe-Ph
10 X= S-2,6-di-Me-Ph
11 X= S^{t}Bu

Scheme 2.

Initially we tested the reaction of the 1-seleno-*ribo*-glycoside **2** with 3-benzoylthymine (N^3-BzThy) under Mitsunobu conditions (PPh_3/DEAD) in DMF as the solvent, and we obtained the *arabino*-nucleoside **7** in a 60% yield and an α:β ratio of 3:1 (Table 1, entry 1). This means that after the OH has been activated there is a 1,2-transposition and then the base enters at position 1 (see Scheme 1, via 3).[8] When the 1-thio-glycoside **3**, a more useful starting material, reacted in similar conditions, the reaction was very slow; after 72 h it still had not finished. However, when the reaction was carried out at 50°C, nucleoside **8** was obtained in a 65% yield and with low stereoselectivity in 30 min (entry 2). The reaction was then tried in other solvents such as THF at low (entry 3) and high temperatures (entry 4). The resulting conversions and selectivities were always poor. When dichloroethane was used as the solvent the yield increased but the stereoselectvity was nil (entry 5). In all cases we obtained α/β mixtures of nucleosides with an *arabino* configuration. This suggests that the reaction intermediate is not a thiiranium cation but an oxonium cation.

To promote the formation of the thiiranium cation we prepared the 1-thioglycoside **4** with higher electron density in the sulfur. However, when it was used as the starting material in the glycosylation neither the yield nor the selectivity improved (entry 6). Then we synthesized the 1-thio-glycosides **5** and **6** with a bulkier substituent at the anomeric position. Compound **5** did not react even after 5 h at 50°C

Table 1
Synthesis of 2-phenylselenenyl- and 2-phenylsulfenyl-*arabino*-nucleosides from 1-seleno- and 1-thio-*ribo*-glycosides[a]

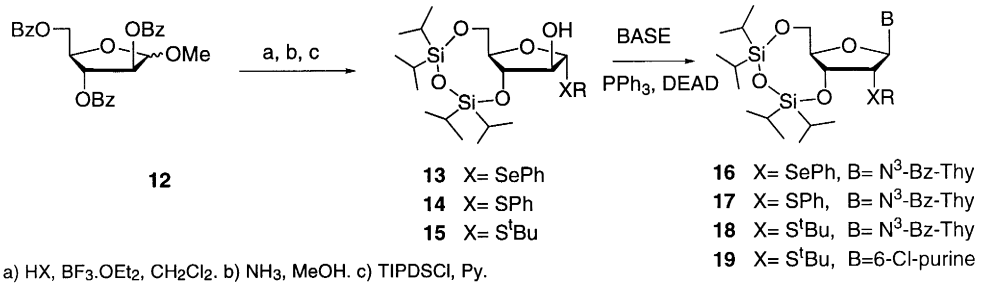
Entry	Starting material	Base	Solvent	T (°C)	t(h)	Product	Yield (%)	α/β
1	**2**	N^3-BzThy	DMF	rt	0.5	**7**	60	3:1
2	**3**	N^3-BzThy	DMF	50	0.5	**8**	65	2:1
3	**3**	N^3-BzThy	THF	rt	3	**8**	11	7:1
4	**3**	N^3-BzThy	THF	reflux	3	**8**	40	3:1
5	**3**	N^3-BzThy	$Cl_2C_2H_4$	reflux	0.5	**8**	60	1.1
6	**4**	N^3-BzThy	DMF	50	1	**9**	54	2.5:1
7	**5**	N^3-BzThy	DMF	50	5	**10**	--	--
8	**6**	N^3-BzThy	DMF	rt	12	**11**	64	10:1
9	**6**	N^3-BzThy	DMF	50	1	**11**	54	5:1
10	**6**	N^3-BzThy	THF	rt	24	**11**	10	1.5:1

[a]For a typical experimental procedure see ref 10.

(entry 7). *tert*-Butyl 1-thio-glycoside **6**, however, gave nucleoside **11** in a 64% yield and a ratio α:β=10:1 (entry 8). In this case results were best in DMF at room temperature. Thus, when the temperature was increased (entry 9) or the solvent changed (entry 10), the yield and the stereoselectivities were worse.

In the previous reactions no *O*-glycosylation product was obtained, as has been observed in other Mitsunobu reactions involving pyrimidinic bases.[9]

Taking into account the results obtained with the 1-seleno and 1-thio-*ribo*-glycosides, we prepared the 1-seleno-*arabino*-glycoside **13** and the 1-thio-*arabino*-glycosides **14** and **15**, which have the anomeric substituents identical to the ones that the best results in the *ribo* series (e.g. compounds **2**–**6**) (Scheme 3). In these cases the 1,2-transposition of the anomeric substituents should take place on the more hindered α face to provide nucleosides with a *ribo* configuration.



12

13 X= SePh
14 X= SPh
15 X= S^{t}Bu

16 X= SePh, B= N^3-Bz-Thy
17 X= SPh, B= N^3-Bz-Thy
18 X= S^{t}Bu, B= N^3-Bz-Thy
19 X= S^{t}Bu, B=6-Cl-purine

a) HX, $BF_3.OEt_2$, CH_2Cl_2. b) NH_3, MeOH. c) TIPDSCl, Py.

Scheme 3.

The reaction of the 1-seleno-*arabino*-glycoside **13** with N^3-BzThy in DMF at room temperature gave nucleoside **16** in a 48% yield and an α:β ratio of 1:7 (Table 2, entry 1). As expected, only nucleosides with *ribo* configuration were obtained, the major one being the β anomer. When the phenyl 1-thio-glycoside **14** was used as starting material the yield of nucleoside **17** improved to 71% and the α:β ratio increased to 1:10 (entry 2). Interestingly, starting from the *tert*-butyl 1-thio-glycoside **15**, anomer β was obtained as the only product in a 52% yield, although in this case the reaction was slower (entry 3). Solvents other than DMF (such as THF) required more drastic conditions and provided very low yields, although the stereoselectivity was also excellent (entry 4). Starting from **15** and using 6-chloro-purine as base, nucleoside **19** was obtained with excellent stereoselectivity. DMF probably plays two different roles in

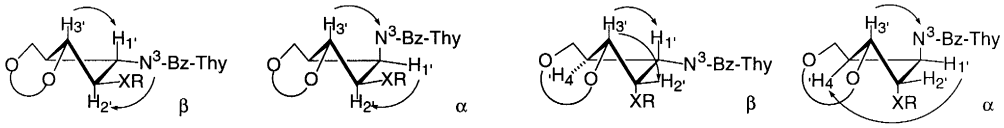
this process; it solubilizes the pyrimidinic base and stabilizes the oxonium intermediate, thus increasing the reaction rate.

Table 2
Synthesis of 2-phenylselenenyl- and 2-phenylsulphenyl-*ribo*-nucleosides from 1-seleno- and 1-thio-*arabino*-glycosides[a]

Entry	Starting material	Base	Solvent	T (°C)	t(h)	Product	Yield (%)	α/β
1	**13**	N^3-BzThy[b]	DMF	rt	4	**16**	48	1:7
2	**14**	N^3-BzThy[b]	DMF	rt	5	**17**	71	1:10
3	**15**	N^3-BzThy[b]	DMF	rt	24	**18**	52	0:1
4	**15**	N^3-BzThy[b]	THF	reflux	24	**18**	5	0:1
5	**15**	6-Cl-purine[c]	DMF	50°C	24	**19**	50	1:12[d]

[a]For a typical experimental procedure see ref 10. [b]Ratio sugar/PPh_3/DEAD/base 1:1.9:2:4.
[c]Ratio sugar/PPh_3/DEAD/base 1:1.5:1.5:2.1. [d]For the N9 derivative. Ratio N9/N7= 5:1.

The structure of nucleosides was determined by NMR spectroscopy. Characteristic signals at 49–60 ppm in ^{13}C NMR are indicative of the presence of RSe and RS groups at C-2. The configuration of the nucleosides obtained could not be determined by the coupling constants values. NOE experiments shown below confirm the proposed stereochemistry.



In conclusion, 2-deoxy-2-sulfenyl-*arabino*-α-nucleosides and 2-deoxy-2-sulfenyl-*ribo*-β-nucleosides were obtained with excellent stereoselectivity from 1-thio-*ribo*- and 1-thio-*arabino*-glycosides in a one pot reaction under Mitsunobu conditions. The stereoselectivity depends on the substituent bonded to the sulfur and on the reaction conditions, particularly the solvent. From the results obtained it is apparent that the reaction intermediate is an oxonium cation and not the thiiranium cation.

Acknowledgements

Financial support by DGICYT PB95-521-A (Ministerio de Educacion y Cultura, Spain) is acknowledged. Technical assistance by the Servei de Recursos Cientifics (URV) is acknowledged.

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10. Typical experimental procedure: The base (0.38 mmol), Ph_3P (0.3 mmol), DEAD (0.3 mmol) in DMF (2.5 ml) were added under vigorous stirring to a mixture of the thio- or seleno-glycoside (0.2 mmol) which had been pre-dried by heating at 40°C under vacuum. After the reaction was complete, the reaction mixture was diluted with EtOAc (25 ml) and washed with H_2O (3×10 ml). The combined H_2O extracts were washed with EtOAc (10 ml) and the organic extracts were combined, dried, and evaporated to dryness. The residue was chromatographed using MPLC with a linear EtOAc gradient in hexane (0–75% v/v).