Pergamon

Tetrahedron Letters 41 (2000) 3643–3646

TETRAHEDRON LETTERS

Synthesis of a 1′-α-phenylselenouridine derivative as a synthetic precursor for various 1′-modified nucleosides, via enolization at the 1′-position of 3′,5′-*O*-TIPDS-2′-ketouridine†

Tetsuya Kodama, Satoshi Shuto,* Makoto Nomura and Akira Matsuda *

Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

Received 17 February 2000; revised 6 March 2000; accepted 10 March 2000

Abstract

Synthesis of the 1′-α-phenylselenouridine derivative **1**α, a potentially useful precursor for the synthesis of a variety of 1′-modified nucleosides, was achieved via enolization of the 3′,5′-*O*-TIPDS-2′-ketouridine **2**. Successive treatment of **2** with LiHMDS and PhSeCl at ≤70°C in THF gave the corresponding 1′-phenylseleno product, which was reduced stereoselectively with $NaBH_4/CeCl_3$ in MeOH to give the target compound **1**α.

In recent years, we have been engaged in the synthetic study of medicinal chemically important branched-chain sugar nucleosides.[1] Although a number of procedures for preparing them have been developed, examples of newly synthesized 1′-branched-chain sugar nucleosides are limited.[2] Furthermore, their biological activities have not yet been investigated in a systematic manner presumably because efficient synthetic methods for their preparation have not been developed.

We previously demonstrated that 4′-phenylselenonucleosides **I** could be used successfully in preparing a variety of 4′-α-branched-chain sugar nucleosides **II** via the radical reaction with a temporary connecting vinylsilyl tether (Fig. 1).[3] Among these, 4′-α-ethenyl- and -ethynylthymidines showed potent antiviral effects.[3d] Considering the results of the synthetic study of 4′-branched-chain sugar nucleosides, 1′-phenylselenonucleosides should also be highly useful precursors for the synthesis of 1′-α-branched-chain sugar nucleosides having biological importance. In this communication, we describe the synthesis of a sugar-protected 1′-phenylselenouridine **1** via enolization of the 2′-ketouridine derivative followed by reaction with PhSeCl.

The 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) (TIPDS)-2′-ketouridine **2**, first prepared by our group,[4] has been widely used for the synthesis of 2′-modified nucleosides via nucleophilic addition reactions at the 2′-carbonyl.[5] We presumed that treatment of the 2′-ketouridine derivative **2** with a strong

* Corresponding author. Fax: +81-11-706-4980; e-mail: matuda@pharm.hokudai.ac.jp (A. Matsuda)

† This paper constitutes Part 199 of Nucleosides and Nucleotides. Part 198: Naka, T.; Minakawa, N.; Abe, H.; Kaga, D.; Matsuda, A., submitted for publication.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00432-9

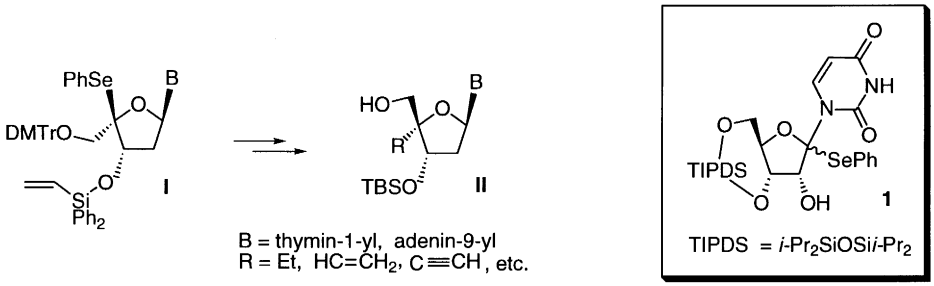
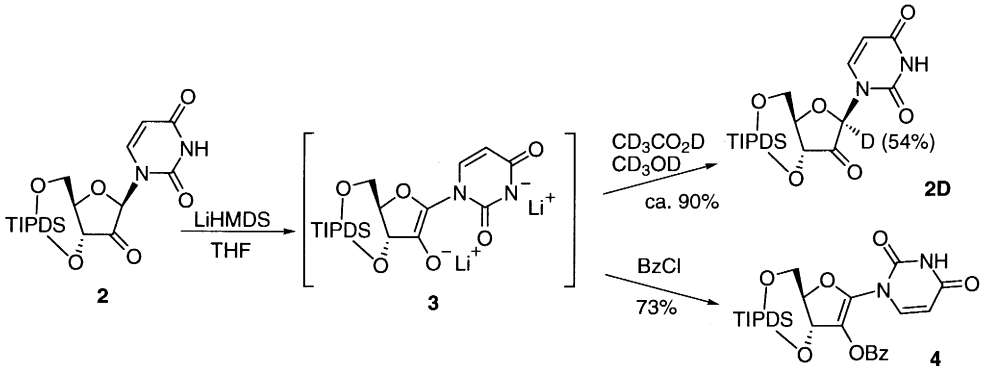


Fig. 1.

base would produce the corresponding 1′-enolate **3** (Scheme 1) and that the subsequent reaction with PhSeCl as an electrophile would give the 1′-phenylseleno-2′-ketouridine derivative. The stereoselective hydride reduction of the 2′-carbonyl from the β-face would provide the desired 1′-α-phenylselenouridine derivative **1**α.

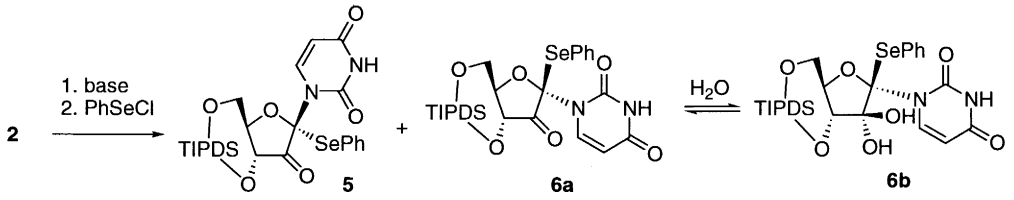


Scheme 1.

We first examined whether enolization at the 1′-positon occurred by deuterium-labeling experiments. A mixture of **2** and LiHMDS (2.1 equiv.) in THF was stirred at ≤70°C for 1 h and quenched with CD_3CO_2D/CD_3OD. The 2′-ketouridine **2D** was obtained in about 90% yield,[6] of which 54% of the 1′-proton was replaced by a deuterium atom. A similar experiment with LDA as the base also gave the 1′-deuterium-labeled product **2D** (yield 72%, deuterium-incorporation 50%). Furthermore, when the reaction mixture of **2** and LiHMDS (2.1 equiv.) in THF was treated with BzCl at ≤70°C, the enol-*O*-benzoate **4** was obtained in 73% yield. These experiments clearly show that the 1′-enolate **3** was produced under these conditions, as predicted. As far as we know, this is the first example demonstrating enolization at the 1′-position of a 2′-ketonucleoside.[7]

Introduction of a phenylseleno group at the 1′-position was next investigated (Scheme 2), and the results are summarized in Table 1. The reactions were carried out as follows. A mixture of **2** and a base in a solvent was stirred at ≤70°C for 1 h. Two equivalents of PhSeCl were added and the resulting mixture was further stirred at the same temperature for 1 h. The reaction products were purified by neutral silica gel column chromatography. The reaction was first performed with 1.5 equivalents of LiHMDS to give the desired 1′-phenylseleno product in 47% yield as an anomeric mixture of **5** and **6** (**5**:**6**=2.9:1, entry 1), respectively. It is noteworthy that the 1′-β-phenylseleno product **6** was in equilibrium between the 2′-keto-form **6a** and its 2′-hydrate **6b**. The stereochemistries were confirmed by NOE experiments of **6b**, as shown in Fig. 2. When 2.1 or 3.0 equivalents of LiHMDS were used, the yield increased significantly (entry 2, yield 85%; entry 3, yield 73%).[8] However, using 4.0 equivalents of the base resulted in poorer yield (entry 4).[9] In all these reactions, the 1′-α-phenylseleno product **5** was selectively obtained as the

major product. The effect of the solvent on the reaction was next examined. Although DME was suitable for this reaction (entry 5) and gave results similar to the reaction in THF, the yield decreased when Et_2O was used (entry 6). Although the anomeric ratio did not change in the reactions in DME or Et_2O, the facial selectivity was almost lost in the reaction in THF/HMPA as the solvent (entry 7, yield 75%, **5**:**6**=1.4:1). Reactions were further carried out with other strong bases. Although the yield decreased in the reaction with LDA as the base, the 1′-phenylseleno products were obtained in excellent yields similar to those with LiHMDS, when NaHMDS or KHMDS was used as the base (entries 9 and 10). It is interesting to note that the α-selectivity is lost when the counterion of HMDS is changed to sodium. Furthermore, the stereoselectivity was reversed to give 1′-β-phenylseleno derivative **6** as the major product (**5**:**6**=1:3.0) when potassium was used as the counterion. These results with different counterions, together with the result in the presence of HMPA (entry 7), suggest that the 1′-α-phenylseleno product **5** is probably produced via a chelation-controlled reaction pathway.[10]



Scheme 2.

Table 1
The introduction of a phenylseleno group at the 1′-position of **2**

entry	base (equiv)	solvent	yield (**5** + **6**, %)	ratio (**5**:**6**)[a]	**2** (recovered, %)
1	LiHMDS (1.5)	THF	47	2.9:1	47
2	LiHMDS (2.1)	THF	85	2.5:1	6
3	LiHMDS (3.0)	THF	73	2.7:1	16
4	LiHMDS (4.0)	THF	5	only **6**	57
5	LiHMDS (2.1)	DME	85	2.7:1	9
6	LiHMDS (2.1)	Et_2O	53	2.4:1	36
7	LiHMDS (2.1)	THF/HMPA (9:1)	75	1.4:1	3
8	LDA (2.1)	THF	62	2.6:1	12
9	NaHMDS (2.1)	THF	76	1.2:1	10
10	KHMDS (2.1)	THF	79	1:3.0	6

[a] The ratio was obtained from their isolated yield.

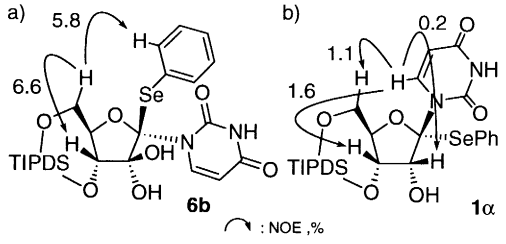


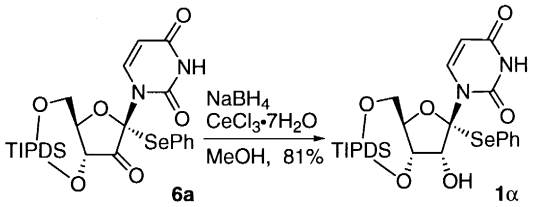
Fig. 2.

The 1′-α-phenyseleno product **5**, which was obtained in a pure form after neutral silica gel column chromatography, was subjected to reduction at the 2′-keto moiety. After investigation of various reaction

conditions, we found that the 2′-carbonyl group of **5** was functionally- and stereoselectively reduced from the β-face when it was treated with $NaBH_4/CeCl_3$ in MeOH[11] at ≤70°C to give the desired sugar-protected 1′-phenylselenouridine **1**α in 81% yield as the sole product.[12]

As far as we know, this is the first example of functionalization at the anomeric 1′-position of a nucleoside, starting from a natural nucleoside, to produce a *ribo*-type 1′-modified nucleoside.[13]

In summary, we have successfully introduced a phenylseleno group at the 1′-position via enolization of the 2′-ketouridine derivative **2**. Subsequent functional- and stereoselective reduction of the 2′-keto moiety gave the desired sugar-protected 1′-phenylselenouridine **1**α (Scheme 3), which should be a highly useful precursor in the preparation of various 1′-α-modified nucleosides of biological interest.[14]



Scheme 3.

References

1. Ichikawa, S.; Shuto, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem*. **1997**, *62*, 1368–1375, and references cited therein.
2. For examples, see: (a) Elliott, R. D.; Niwas, S.; Riordan, J. M.; Montgomery, J. A.; Secrist III, J. A. *Nucleosides Nucleotides* **1992**, *11*, 97–119. (b) Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem*. **1995**, *60*, 656–662. (c) Goodman, B. K.; Greenberg, M. M. *J. Org. Chem*. **1996**, *61*, 2–3.
3. (a) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 5676–5677. (b) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 746–754. (c) Ueno, Y.; Nagasawa, Y.; Sugimoto, I.; Kojima, N.; Kanazaki, M.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 1660–1667. (d) Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 385–388. (e) Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem*. **1999**, *64*, 7153–7157. (f) Kanazaki, M.; Ueno, Y.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc*. **2000**, *122*, 2422–2432.
4. Ueda, T.; Shuto, S.; Inoue, H. *Nucleosides Nucleotides* **1984**, *3*, 173–182.
5. For examples, see: Azuma, A.; Nakajima, Y.; Nishizono, N.; Minakawa, N.; Suzuki, M.; Hanaoka, K.; Kobayashi, T.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem*. **1993**, *36*, 4183–4189, and references cited therein.
6. It included a trace of an inseparable unknown compound, which might be the corresponding α-anomer.
7. The 3′-lithium enolate of 3′-deoxy-2′-ketouridine derivative has been reported: Haraguchi, K.; Tanaka, H.; Itoh, Y.; Miyasaka, T. *Tetrahedron Lett.* **1991**, *32*, 777–780.
8. When 3′,5′-bis-*O*-TBS-2′-ketouridine was treated under the conditions identical to those in entry 3, it gave a mixture of 1′-α- and 1′-β-phenylseleno products in a ratio of ca. 1:1 in 56% yield. Although we also tried to use 3′,5′-*O*-di-*tert*-butylsilylene-2′-ketouridine as the substrate, it was too unstable not to be obtained in a pure form.
9. The 1′-phenylseleno group is likely to be replaced by lithium in the presence of an excess of LiHMDS, since the substrate **2** was obtained in 90% yield when **6a** was treated again with LiHMDS (4 equiv.) at ≤70°C in THF.
10. While the structure of the chelation intermediate is unclear, a chelation of Li^+ between the 2′-enol-oxygen and 2-carbonyl-oxygen of the uracil moiety may be possible.
11. Luche, J.-L. *J. Am. Chem. Soc*. **1978**, *100*, 2226–2227.
12. The reduction of a 1′-α-methoxycarbonylethyl-2-ketouridine derivative, synthesized from D-fructose, with $NaBH_4$ has been reported, in which the corresponding *arabino*- and *ribo*-type products were obtained in a ratio of 1:5 in 87% yield: Yoshimura, Y.; Ueda, T.; Matsuda, A. *Tetrahedron Lett*. **1991**, *32*, 4549–4552.
13. 2′-Deoxy-1′-modified uridines have been synthesized from uridine via electrophilic addition reactions on a 1′,2′-unsaturated uridine derivative: Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem*. **1995**, *60*, 656–662.
14. After introduction of a vinylsilyl tether at the 2′-hydroxy of **1**α, its radical reactions successfully gave the corresponding 1′-α-branched-chain sugar nucleosides. These results will be reported elsewhere.