Pergamon

Tetrahedron Letters, Vol. 35, No. 23, pp. 3987-3990, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0639-F

A Novel Type of Unsaturated Seconucleoside Analogues

Valerije Vrček and Vesna Čaplar*

Laboratory of Stereochemistry and Natural Compounds, Department of Organic Chemistry and Biochemistry, "Ruđer Bošković" Institute, P.O. Box 1016, 41001 Zagreb, Croatia

Abstract: 1',2'-Unsaturated secoadenosine **3-6** and secouridine **15, 16** analogues were synthesized by the base promoted regioselective elimination of corresponding 2',3'-ditosylates. Efficient and selective O-detritylation of these acid sensitive compounds was achieved by $ZnBr_2$ in dichloromethane.

Nucleoside analogues are widely studied as potential antiviral chemotherapeutic agents. Among them, especially after the discovery of acyclovir, important are "acyclic" analogues,[1-4] formally derived from the parent nucleoside by a cleavage of one or more bonds of the furanose ring. Furthermore, some unsaturated nucleoside analogues, possessing a double bond in the sugar part, like 2',3'-dideoxy-2',3'-didehydro-cytidine and 3'-deoxy-2',3'-didehydro-thymidine, are known as inhibitors of HIV-1 reverse transcriptase [5,6] and are more active then their respective saturated analogues.[7]

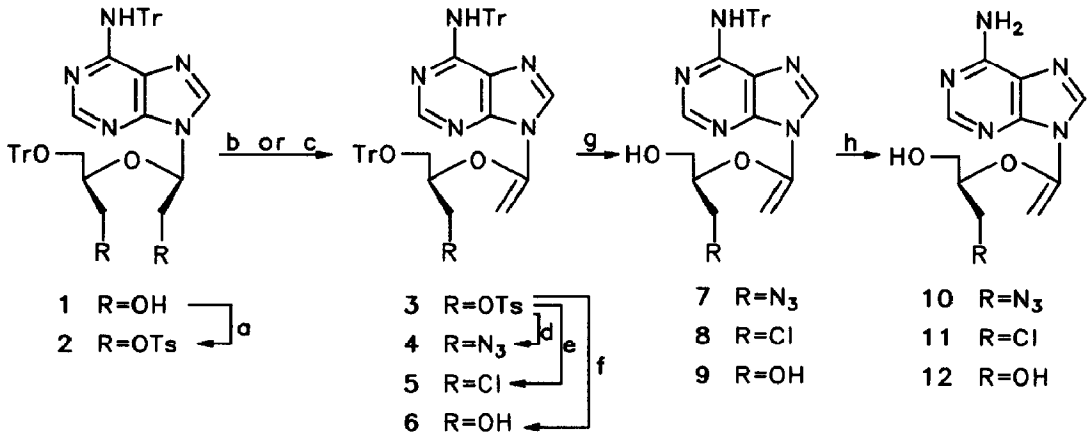
Continuing our work on the synthesis of acyclic nucleosidic structures with potential antiviral and antiretroviral activities,[8,9] we have prepared a series of 1',2'-unsaturated 2',3'-seconucleoside analogues incorporating two mentioned structural nucleosidic features (*i.e.* an acyclic sugar moiety with a double bond).

Very few 1',2'-unsaturated nucleoside analogues have been described so far[10]. In nucleoside chemistry these *N,O*-ketene acetal structures were first reported by Robins and coworkers.[11,12] The present work provides the new seconucleoside 1'-ene system both in purine and pyrimidine series.

1',2'-Unsaturated secoadenosines **3-6** were obtained starting from corresponding protected secoadenosine **1**,[13] activated by tosylation to give ditosylate **2** in 80% yield (Scheme 1.). Ditosylate **2** was treated with potassium tert-butoxide in THF at 40 °C for 75 h, giving in regioselective elimination, the mono-unsaturated product **3**[14] (63% yield). The observed regioselectivity may be explained by the higher acidity and hence preferential elimination of the anomeric C(1')-hydrogen in comparison to C(4')-hydrogen, due to the presence of electron-withdrawing nitrogen and oxygen substituents at anomeric C(1')--atom.

In order to reduce the influence of the possible steric effects of the base on the elimination selectivity, we used sodium hydride in THF. After the treatment of ditosylate **2** for 18 hours with the base of smaller steric requirements, the only product isolated was again 1',2'-unsaturated secoadenosine **3**, but in this case in lower yield (48%). The prolongation of the reaction time led to 1',3'-diene analogue already described by Prisbe.[13] Temperature raising or adding more equivalents of NaH gave rise to the same diene. Thus, we obtained a small selectivity decrease but this could be also influenced by the higher basicity of sodium hydride. The elimination reaction with NaH was faster than the reaction with potassium tert-butoxide resulting in a lesser extent of regioselectivity.

SCHEME 1.



a) TsCl/py, RT; b) KOt-Bu/THF, 40°C, 75h; c) NaH/THF, 40°C, 18h;
d) LiN_3/DMF, 80°C; e) LiCl/DMF, 80°C; f) H_2O/DMF, $NaHCO_3$, 100°C;
g) $ZnBr_2/CH_2Cl_2$, 1h; h) $ZnBr_2/CH_2Cl_2$, 18h.

After the introduction of double bond at the 1',2'-position of acyclic sugar moiety, it was possible to achieve substitution at the 3'-position of 2',3'-seconucleosides. Various analogues were obtained by nucleophilic substitution of tosyl group in **3** by azide or halide ions, carried out in DMF at 80 °C, giving the products **4** and **5** in good yields (70-80%). To convert primary tosylate **3** to alcohol **6**, a solution of **3** in 20% (v/v) aqueous DMF was heated at 100 °C for 18 hours, with $NaHCO_3$ added to neutralize generated acid.

Due to the extreme acid lability of 1',2'-unsaturated compounds (**3-6**), trityl deprotection could not be achieved using strong or even mild acids.[11,13] However, we have found that the Lewis acid $ZnBr_2$ in dry dichloromethane could be used for a successful removal (85%) of trityl protective group without any cleavage of the *N,O*-ketene acetal function. We also observed that in secoadenosine series O-trityl bond could be cleaved much faster then corresponding N-trityl bond thus allowing us to isolate separately N-protected 5'-hydroxy derivatives (**7-9**) and fully deprotected secoadenosine analogues **10-12** (80%) as well (Scheme 1).

In uridine series it was necessary to protect N(3)-imide function to avoid an intramolecular

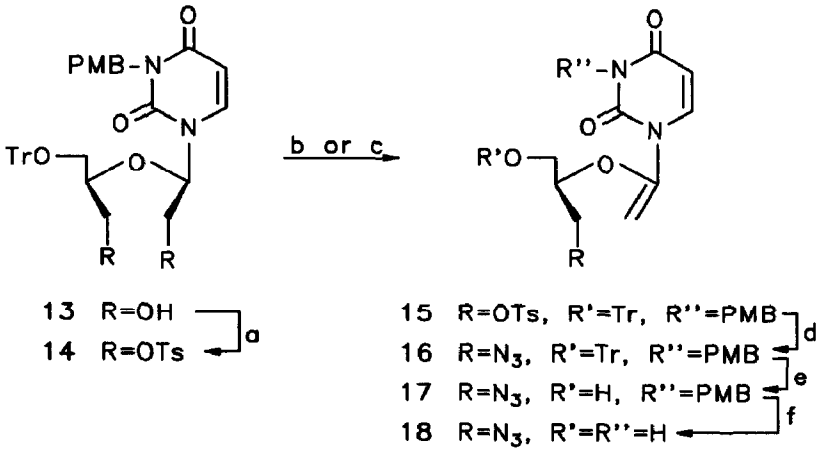
cyclization in basic conditions. The selective protection of uridine was afforded by p-methoxybenzylation (90% yield) at N(3)-position,[15] and tritylation at C(5')-oxygen.[16] This p-methoxybenzylic group was stable under all applied conditions (periodate oxidation of starting uridine and sodium borohydride reduction, base catalyzed elimination, nucleophilic displacement and detritylation).

We have found that the presence of different nucleic base moiety in seconucleosides **2** and **14** had a significant effect on overall reactivity. 2',3'-Ditosylate **14** treated in an identical manner as **2** (either with potassium tert-butoxide or sodium hydride in THF) (Scheme 2), afforded the mono-unsaturated secouridine **15**[17], but in lower yields (33%). The remaining was starting material. Thus, adenosine analogue **2** had a greater tendency to lose its anomeric C(1')-hydrogen than uridine analogue **14** did, probably due to its higher acidity.

Both adenosine and uridine ditosylates **2** and **14** were resistant to the treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and no unsaturated seconucleosides were formed under the same conditions as in above eliminations. This is consistent with the weaker basicity of DBU in comparison to potassium tert-butoxide or sodium hydride.

Nucleophilic displacement of the tosyl group in **15** by azide ion gave compound **16** (80% yield), which was deprotected by $ZnBr_2$ in dichloromethane to **17** and then by $AlCl_3$ in anisole to give the fully deprotected secouridine **18** (Scheme 2.).

SCHEME 2.



a) TsCl/py, RT; b) KOt-Bu/THF, 40°C, 75h; c) NaH/THF, 40°C, 18h; d) LiN_3/DMF, 80°C; e) $ZnBr_2/CH_2Cl_2$, 1h; f) $AlCl_3$/anisole.

It is interesting to note that introduction of 1',2'-unsaturation into prepared seconucleosides is accompanied by a batochromic shift of 7-8 nm in ultraviolet spectrum, relative to starting seconucleosides.[18] The observed shift results from the extended conjugation of the nucleobase ring with the 1',2'-double bond.

Further investigations on mono-unsaturated seconucleoside analogues with other nucleobases, as well as biological testing of products, will be reported in due course.

Acknowledgement. We are thankful to dr. D. Katalenić for helpful suggestions. This work was supported by Ministry of Science and Technology, Republic of Croatia, project no. 1-07-188.

REFERENCES AND NOTES

1. Chu, C.K.; Cutler, S.J.; *J. Heterocycl. Chem.* **1986**, *23*, 289-319.
2. Phadtare, S.; Zemlicka, J.; *J. Amer. Chem. Soc.* **1989**, *111*, 5925-5931.
3. Nasr, M.; Litterst, C.; McGowan, J.; *Antiviral. Res.* **1990**, *14*, 125-148.
4. deClercq,E. in *Recent Advances in Search for Antiviral Agents*; Testa, B. Ed.; Academic Press, Ltd.: London, 1988: p. 1.
5. de Clercq, E.; van Aerschot, A.; Herdewijn, P.A.M.; Baba, M.; Pauwels, R.; Balzarini, J.; *Nucleosides Nucleotides* **1989**, *8*, 659-671.
6. Chu, C.K.; Bhadtí, V.S.; Doboszewski, B.; Gu, Z.P.; Kosugi. Y.; Pullaiah, K.C.; van Roey, P.; *J. Org. Chem.* **1989**, *54*, 2217-2225.
7. van Roey, P.; Taylor, E.W.; Chu, C.K.; Schinazi, R.F.; *J. Amer. Chem. Soc.* **1993**, *115*, 5365-5371.
8. Škarić, V.; Čaplar, V.; Škarić, Đ.;Žinić, M.; *Helv. Chim. Acta* **1992**, *75*, 493-506.
9. Čaplar, V.; Škarić, V.; *Helv. Chim. Acta* **1993**, *76*, 2553-2562.
10. For recent examples: a) Haraguchi, K.; Itoh, Y.; Tanaka, H.; Yamaguchi, K.; Miyasaka, T.; *Tetrahedron Lett.* **1993**, *34*, 6913-6916. b) Haraguchi, K.; Tanaka H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T.; *J. Org. Chem.* **1991**, *56*, 5401-5408.
11. Robins, M.J.; Trip, E.M.; *Tetrahedron Lett.* **1974**, 3369-3372.
12. a) Robins, M.J.; Jones, R.A.; *J. Org. Chem.* **1974**, *39*, 113-115. b) McCarthy, J.R.; Robins, M.J.; Townsend, L.B.; Robins, R.K.; *J. Amer. Chem. Soc.* **1966**, *88*, 1549-1553.
13. Prisbe, E.J.; *J. Med. Chem.* **1986**, *29*, 2445-2450.
14. Two protons of a newly formed terminal methylene group appeared as two doublets with the coupling constant of 4 Hz. A signal at 4.31 ppm was assigned to the C(2') proton in *trans* position relative to the purine, while the doublet of *cis* C(2') proton was markedly shifted to 5.40 ppm. The stereochemistry was determined by a NOESY experiment which confirmed the expected through-space interaction with other protons on the acyclic moiety only for *trans* C(2') proton. A signal of C(1')-proton dissapeared. Other acyclic signals were only slightly changed: 4.71 ppm (m, C(4')); 4.53 (m, 2H-C(3')); 3.48 ppm (dd,2H-C(5')). In ^{13}C-nmr spectrum anomeric carbon was shifted from 81.28 ppm (in **2**) to 147.55 ppm and appeared as singlet, while C(2') signal shifted from 68.9 ppm (in **2**) to 78.13 ppm. Other acyclic carbon signals were at 75.93 ppm (for C(4')), 68.48 ppm (C(3')), 61.45 ppm (C(5')). All other structures were determined by UV, IR and NMR spectra, as well.
15. Akiyama, T.; Nishimoto, H.; Ozaki, S.; *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3356-3357.
16. R.S. Tipson, in *Synthetic Procedures in Nucleic Acid Chemistry*, Eds. W.W. Zorbach and R.S. Tipson, Interscience Publishers (J. Wiley & Sons), New York-London-Sydney-Toronto, 1968, p.441.
17. In ^{1}H-nmr spectrum C(2')-protons occured as two doublets at 4.3-4.5 ppm (J=3.5 Hz). In ^{13}C-nmr spectrum C(1') signal was markedly shifted from 82.96 ppm (in **14**) to 145.62 ppm. Other chemical shifts in ^{1}H-nmr and in ^{13}C-nmr spectra exhibited similar effects as those observed for **3**[14].
18. Thus, for N,O-ditrityl-2',3'-secoadenosine **1** λ_{max}(EtOH)=265.6 nm while for N,O-dititryl-2',3'-secoadenosin-1'-ene **6** λ_{max}(EtOH)=272.5 nm.

(*Received in UK* 1 *March* 1994; *accepted* 29 *March* 1994)