Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 137–140
Tetrahedron Letters

A new protecting group '3′,5′-*O*-sulfinyl' for xylo-nucleosides. A simple and efficient synthesis of 3′-amino-3′-deoxyadenosine (a puromycin intermediate), 2,2′-anhydro-pyrimidine nucleosides and 2′,3′-anhydro-adenosine

Ken-ichi Takatsuki,[a,b,*] Makoto Yamamoto,[b] Sumito Ohgushi,[b] Shigeo Kohmoto,[b] Keiki Kishikawa[b] and Haruhiro Yamashita[a]

[a]*Ichikawa Research Institute, Kobayashi Perfumery Co., Ltd., 4-12-1 Ohwada, Ichikawa City 272-0025, Japan*
[b]*Department of Specialty Materials Science, Graduate School of Science and Technology, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263-8522, Japan*

Received 29 August 2003; revised 19 October 2003; accepted 20 October 2003

Abstract—We developed a new protecting group, the cyclic sulfite for the protection of the 3′,5′-dihydroxy group of nucleosides. Seven cyclic sulfites, **4a**–**c**, **5a**–**b**, and **6a**–**b** were prepared in high yields from the corresponding xylo-uridines **1** and **2**, and xylo-adenosines **3** with thionyl chloride, respectively. Synthesis of the puromycin intermediate **8** was carried out by deprotection of the sulfite moiety through an intramolecular cyclization of the 2′-α-carbamate **7**.

1. Introduction

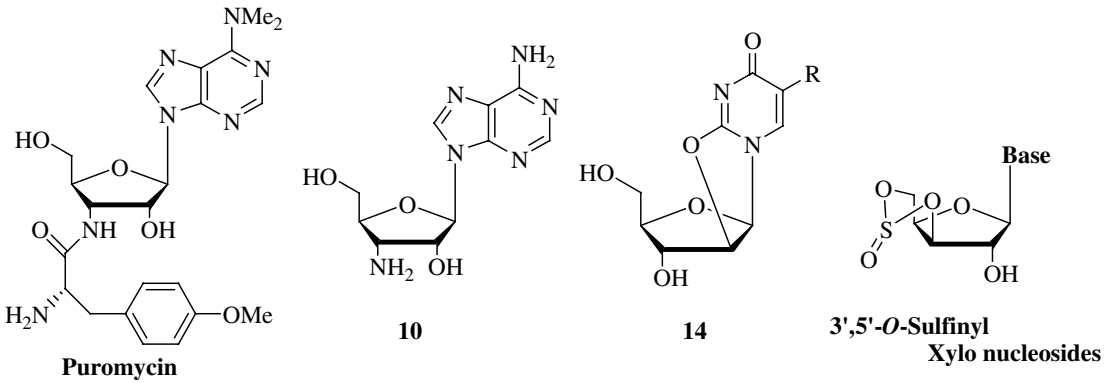
Although numerous methods for protection of hydroxyl groups have been developed in nucleoside chemistry, still new effective protective groups are desired in order to cope with rapid progress in this area.[1] We have exploited a new protective group, the cyclic sulfite, which is not only an efficient protective group for 3′,5′-hydroxy groups, but also a potent leaving group. This feature is demonstrated in the syntheses of 2,2′-anhydro-pyrimidines **14** and the puromycin intermediate **8**. The cyclic sulfite protecting group was eliminated either by an intramolecular nucleophilic attack with 2′-hydroxy group (synthesis of **14**) or with 2′-carbamoyl group (synthesis of **8**).

The antibiotic puromycin, a metabolite of *Streptomyces alboniger*, was first isolated by Porter et al. in 1952.[2] Puromycin has been used extensively for elucidation of the mechanism of protein biosynthesis.[3] It was recognized to have close structural similarity to the aminoacyl end of aminoacyl-tRNA.[4] Even though a number of synthetic routes to puromycin and its analogues have been reported, most of them have problems in numerous synthetic steps and low overall yields. Recently, Robins[5a] and Strazewski[5b] have reported synthesis of puromycin and its analogues via 3′-amino-3′-deoxyadenosine **10** starting from *ribo*-adenosine. However, their synthesis still has problems in a usage of pyrophoric bromodimethylborane,[5a] and 3′-regioselectivity.[5b] In this paper, we challenge these critical problems and establish the stereo and regioselective synthesis of nucleosides using 3′,5′-O-sulfinyl-xylo-adenosine with a reasonably safe procedure.

Our target nucleosides, 2,2′-anhydro-pyrimidine nucleosides **14** are key intermediates for the preparation of 2′-deoxy and 2′-functionalized pyrimidine nucleosides, such as β-thymidine and 2′-*O*-methyl-pyrimidinenucleosides.[6] The presence of 2′-*O*-methyl-pyrimidinenucleosides in oligonucleotides provides better stability and also binding capability to the complementary gene

Keywords: 3′-amino-3′-deoxyadenosine; 3′,5′-*O*-sulfinyl-xylo-nucleosides; puromycin.
* Corresponding author. Tel.: +81-473772033; fax: +81-473785951; e-mail: takatsuki@kobayashikoryo.co.jp; yamak@faculty.chiba-u.jp

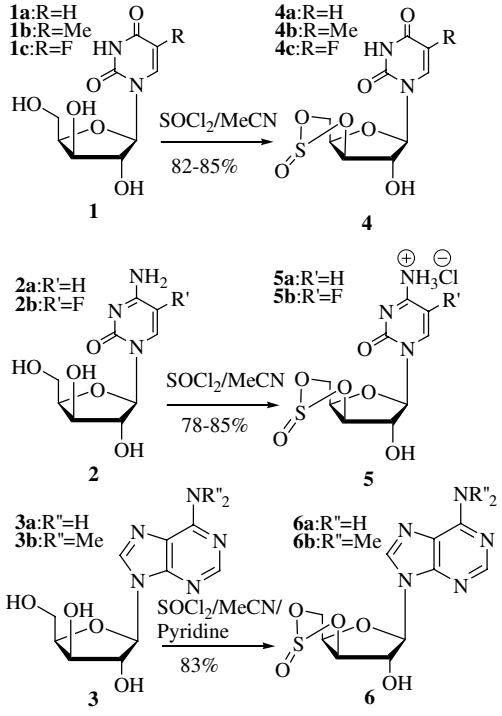
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.092



targets, for example, a second-generation antisense construction.[7] In general, 2′-deoxynucleosides[8] and 2′-functionalized pyrimidine nucleosides such as 2′-*O*-methyl-pyrimidinenucleosides and 2′-halogeno pyrimidinenucleosides, have been prepared from D-ribose.[5] However, the high cost of D-ribose poses a limitation to the method. An alternative method, 2-deoxy-D-ribose as a starting material, is fraught with poor anomer selectivity. It is desirable to use inexpensive sugars such as D-xylose as a starting material. So far, only one synthesis of β-thymidine has been known using D-xylose via a 2,2′-anhydro-thymidine **14b** in a moderate yield.[9]

Another target, 2′,3′-anhydro-adenosine **13a**, usually prepared from D-*ribo*-adenosine, is an important intermediate for the synthesis of antibiotics such as 3′-deoxyadenosine (Cordycepin).[10]

We report here an efficient and short-step synthesis of 3′-amino-3′-deoxyadenosine **10**, 2,2′-anhydro-pyrimidine nucleosides **14**, and 2′,3′-anhydro-adenosine **13**, through a novel and efficient *ribo*-stereoselective and 3′-regioselective rearrangement of 3′,5′-*O*-sulfinyl-xylo-nucleosides **4**, **5**, **6**, and **7** prepared from D-xylose. Also presented is a new type of stereospecific hydroxylation through 2,2′-anhydro-cytidines **15** resulting in a formation of *ribo*-cytidines **16**.

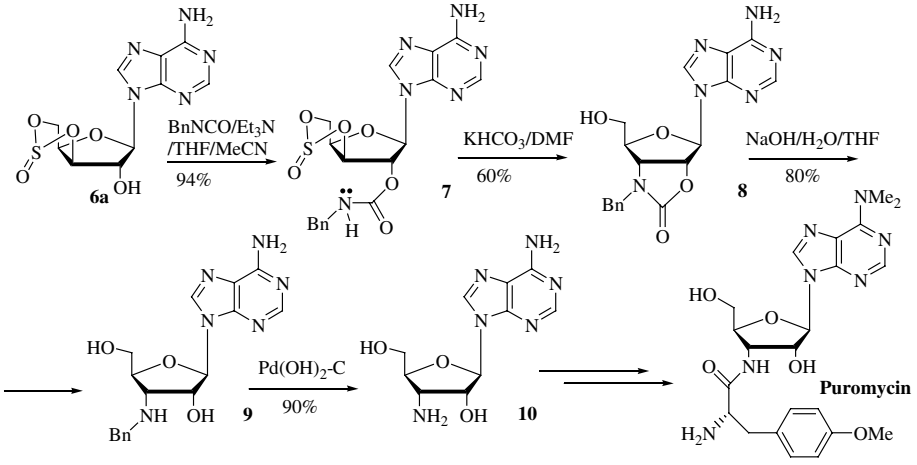


Scheme 1. Synthesis of 3′,5′-*O*-sulfinyl-xylo-nucleosides.

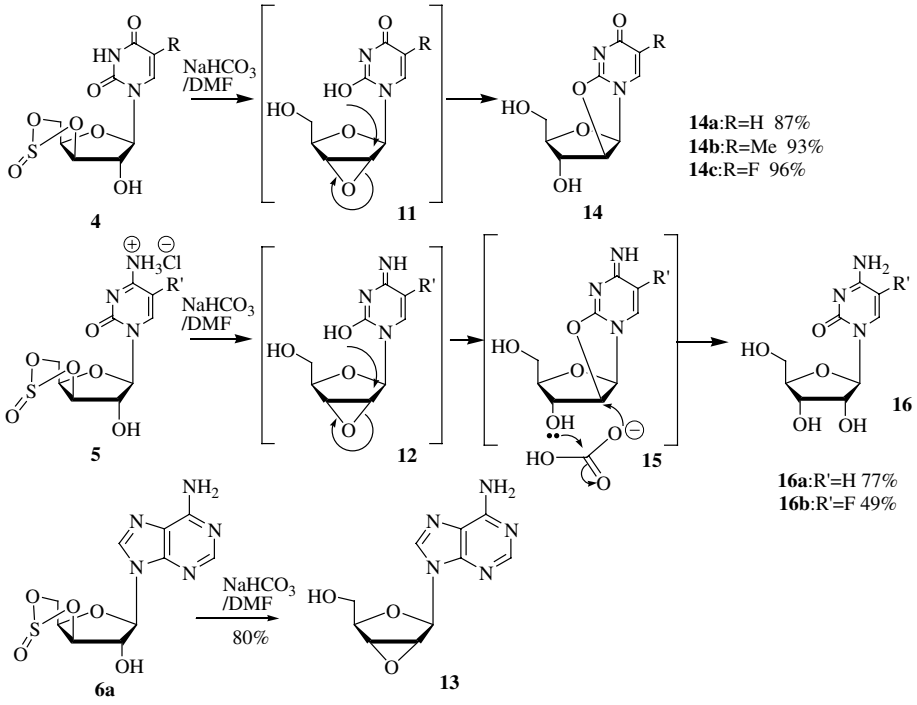
2. Results and discussion

β-D-Xylofuranosyl nucleosides **1**, **2**, and **3** were prepared from commercially available inexpensive D-xylose according to the literature.[9,11] *N,N*-Dimethyl-xylo-adenosine **3b** was obtained from *N,N*-dimethyl-adenine[12] and xylofuranoside. The synthesis of 3′,5′-*O*-sulfinyl-xylo-nucleosides **4**,[17] **5**, and **6** is shown in Scheme 1. Reactions of **1**, **2**, and **3** with thionyl chloride in dry acetonitrile afforded crystalline 3′,5′-*O*-cyclosulfinyl derivatives **4**, **5**, and **6**[17] in 77.9–85.3% yield[13] without chromatographic purification. Their infrared spectra showed sharp bands corresponding to the $\nu_{S=O}$ of the alkylated sulfinate ester at 1180–1257 cm^{-1}. Their structures were determined based on NMR and FAB-MS spectral analyses. The 3′,5′-sulfinyl group can be a good leaving group with an assistance of a nucleophilic attack by the 2′-hydroxyl or 2′-carbamoyl group from the α-side of 3′-position affording 3′-substituted *ribo*-nucleosides in an stereo- and regioselective way.

The synthesis of 3′-amino-3′-deoxyadenosine **10** is shown in Scheme 2. Treatment of the cylosulfinyladenosine **6a** with benzylisocyanate at room temperature gave the carbamate **7**[17] keeping the sulfinyl group and the amino group intact. Subsequent treatment of the carbamate with potassium hydrogencarbonate in dry DMF at room temperature for 11 days gave 3′-cyclization product **8**[5a] in 60% yield after silica gel column chromatography with **13** as a minor product. Following hydrolytic decarbonylation ($NaOH/H_2O/THF$) of **8** gave the 3′-benzylamine derivative **9** (80%). Hydrogenolysis of **9**[5a] with $Pd(OH)_2$–C as a catalyst afforded **10** (90%), which was a key intermediate in the synthesis of puromycin and its analogues.[5]



Scheme 2. Synthesis of 3′-amino-3′-deoxyadenosine **10**, and a practical route to puromycin.



Scheme 3. Synthesis of 2,2′-anhydro-pyrimidine nucleosides, cytidines, and 2′,3′-anhydro-adenosine **13**.

The synthesis of to 2,2′-anhydro-pyrimidine nucleosides **14** is carried out as shown in Scheme 3. Treatment of the cyclosulfinyluridines **4a**, **4c**, and cyclosulfinylthymidine **4b** with sodium hydrogencarbonate in dry DMF at 90 °C for 5 h gave 2,2′-anhydro-nucleosides **14a**,[16] **14c**, and **14b**[14] in 87.3–95.9% yields. The reaction proceeded in a high yield irrespective of the electronic nature of substituents at the 5-position.

Cyclosulfinylcytidines **5a** and **5b** obtained by the same procedure as for **4**, were stable at room temperature. Surprisingly, they were transformed into *ribo*-cytosines **16a**[16] and **16b** in 76.5% and 49.2% yields, respectively. In contrast to the synthesis of **14**, neither the formation of 2,2′-anhydro-cytidines nor arabino-cytosines was observed. In order to confirm the reaction mechanisms, we carried out the reaction using an independently prepared **15a** (R′ = H). The reaction of **15a** under the same reaction conditions as for the preparation of **16a** from **5**, afforded **16a** in 80.9% yield. Consequently, the results verify the assumption that the reaction proceeds via 2,2′-anhydro-cytidines **15** with an assistance of carbonate anion in dry DMF as shown in Scheme 3. It is well known that the hydrolysis of 2,2′-anhydro-cytidine gives arabino-cytosine (ara-C).[13a,15]

In order to elucidate the reaction intermediate, we examined the rearrangement of 3′,5′-sulfinyl-xylo-adenosine

6a under the similar conditions as for **4** and **5**. In contrast to the reaction of **4** and **5**, the intermediate 2′,3′-oxirane, 2′,3′-anhydro-adenosine **13**, was isolated in 83.0% yield (Scheme 3). It is obvious that the cyclosulfinyl group at 3′-position is substituted with the 2′-hydroxy group from the α-side. The results indicate the involvement of the 2′3′-oxirane intermediates, **11** and **12**, in the rearrangement of **4** and **5**, respectively.

We have established an efficient synthesis of 3′-amino-3′-deoxyadenosine **10**, 2,2′-anhydro-pyrimidine nucleosides **14**, and 2′,3′-anhydro-adenosine **13**, which furnishes puromycine,[5] 2′-deoxy, 2′-functional pyrimidine nucleosides,[6,9,11,15] and 3′-deoxyadenosines.[10] Further synthetic study of puromycin via **6b** is now in progress.

References and Notes

1. (a) Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*; John Wiley & Sons, 2001; (b) Ichikawa, E.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 385–423.
2. Porter, J. N.; Hewitt, R. I.; Hesseltine, C. W.; Krupka, G.; Lowery, J. A.; Wallace, W. S.; Bohonos, N.; Williams, J. H. *Antibiot. Chemother.* **1952**, *2*, 409–410.
3. (a) Suhadolnik, R. J. *Nucleoside Antibiotics*; Wiley: New York, 1970; pp 1–50; (b) Suhadolnik, R. J. *Nucleosides as Biological Probes*; Wiley: New York, 1979; pp 96–102.
4. Yarmolinsky, M. B.; De la Haba, G. L. *Proc. Natl. Acad. Sci. U.S.A.* **1959**, *45*, 1721–1729.
5. (a) Robins, M. J.; Miles, R. W.; Samano, M. C.; Kaspar, R. L. *J. Org. Chem.* **2001**, *66*, 8204–8210; (b) Nguyen-Trung, N. Q.; Botta, O.; Terenzi, S.; Strazewski, P. *J. Org. Chem.* **2003**, *68*, 2038–2041, and references cited therein.
6. (a) McGee, D. P. C.; Zhai, Y. *Nucleosides Nucleotides* **1996**, *15*, 1797–1803; (b) Ross, B. S.; Springer, R. H.; Tortorici, Z.; Dimock, S. *Nucleosides Nucleotides* **1997**, *16*, 1641–1643; (c) Saroj, R.; Tang, J.-Y. U.S. Patent 5,739,314; (d) Saroj, R.; Tang, J.-Y. *Org. Process Res. Develop.* **2000**, *4*, 170–171; (e) Parmentier, G.; Schmitt, G.; Dolle, F.; Luu, B. *Tetrahedron* **1994**, *50*, 361–5368; (f) Cordington, J. F.; Doerr, I. L.; Fox, J. J. *J. Org. Chem.* **1964**, *29*, 558.
7. (a) Lubini, P.; Zürcher, W.; Egli, M. *Chem. Biol.* **1994**, *1*, 39–45; (b) Adamiak, D. A.; Milecki, J.; Popenda, M.; Adamiak, R. W.; Dauter, Z.; Rypniewski, W. R. *Nucleic Acids Res.* **1997**, *25*, 4599–4607.
8. (a) Hoffer, M.; Duschinsky, R.; Fox, J. J.; Yung, N. *J. Am. Chem. Soc.* **1959**, *81*, 4112–4113; (b) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654; (c) Skulnick, H. *J. Org. Chem.* **1978**, *43*, 3188–3194; (d) Hubbard, A. J.; Jones, A. S.; Walker, R. T. *Nucleic Acids Res.* **1984**, *12*, 6827–6837; (e) Freskos, J. N. *Nucleosides Nucleotides* **1989**, *8*, 549–555; (f) Aoyama, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2073–2077.
9. Rama Rao, A. V.; Gurjar, M. K.; Lalitha, S. V. S. *J. Chem. Soc., Chem. Commun.* **1994**, 1255–1256.
10. Aman, S.; Anderson, D. J.; Connolly, T. J.; Crittall, A. J.; Ji, G. *Org. Process Res. Develop.* **2000**, *4*, 601–605, and references cited therein.
11. (a) Nakayama, C.; Saneyoshi, M. *Nucleosides Nucleotides* **1982**, *1*, 139–146; (b) Gosselin, G.; Bergogne, M.-C.; Rudder, J.; De Clercq, E.; Imbach, J.-L. *J. Med. Chem.* **1986**, *29*, 203–213; (c) Koshkin, A. A.; Fensholdt, J.; Pfundheller, H. M.; Lomholt, C. *J. Org. Chem.* **2001**, *66*, 8504–8512.
12. Girgis, N. S.; Pedersen, E. B. *Synthesis* **1982**, 480–482.
13. (a) Sowa, T.; Tsunoda, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 505–507; (b) Sowa, T.; Tsunoda, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3243–3245, They synthesized 2′,3′-*O*-sulfinate of *ribo*-nucleosides using thionyl chloride in acetonitrile.
14. Murtiashaw, C. W. Eur. Pat. Appl. EP 351,126.
15. (a) Doerr, I. L.; Fox, J. J. *J. Org. Chem.* **1967**, *32*, 1462–1471; (b) Kikugawa, K.; Ichino, M. *J. Org. Chem.* **1972**, *37*, 284–288; (c) Wang, M. C.; Sharma, R. A.; Bloch, A. *Cancer Res.* **1973**, *33*, 1265.
16. ^{1}H, ^{13}C NMR, and mp data were identical with those of the authentic sample (Sigma–Aldrich).
17. Spectral data of selected compounds: **4a**: Mp (4-methyl-2-pentanone) 185 °C. IR (KBr): $\nu = 3271, 3169, 3043, 1671, 1471, 1415, 1273, 1210$ (RO–SO–OR), 1191, 1113, 1089, 1010, 833, 768, 715 cm^{-1}. ^{1}H NMR (DMSO-d^6): δ 11.41 (s, 1H, NH), 7.61 (d, $J = 8.2$ Hz, 1H, H-6), 6.27 (d, $J = 4.3$ Hz, 1H, H-1′), 5.73 (s, 1H, 2′-OH), 5.71 (dd, $J = 8.2$ and 1.5 Hz, 1H, H-5), 4.91 (dd, $J = 13.4$ and 1.8 Hz, 1H, H-4′), 4.71 (d, $J = 2.4$ Hz, 1H, H-3′), 4.39 (br s, 1H, H-5′), 4.34 (d, $J = 13.4$ Hz, 1H, H-5′), 4.21 (d, $J = 4.3$ Hz, 1H, H-2′). ^{13}C NMR (DMSO-d^6): δ 163.1, 150.4, 139.4, 101.5, 91.0, 78.7, 73.1, 70.5, 55.8. FAB-MS m/z: 291.0295 ($[M+H]^+$, $C_9H_{11}N_2O_7S$ requires m/z: 291.0287). **6a**: Mp (4-methyl-2-pentanone) 229 °C. ^{1}H NMR (DMSO-d^6): δ 8.22 (s, 1H, 2-H), 8.15 (s, 1H, 8-H), 7.37 (br s, 2H, NH_2), 6.48 (d, 1H, $J = 4.0$ Hz, OH), 6.09 (br s, 1H, H-1′), 4.98 (dd, 1H, $J = 13.3$ and 1.9 Hz, H-4′), 4.87 (d, 1H, $J = 2.4$ Hz, H-3′), 4.63 (d, 1H, $J = 2.8$ Hz, H-2′), 4.51 (d, 1H, $J = 1.8$ Hz, H-5′), 4.36 (d, 1H, 13.1 Hz, H-5′). MS (m/z, %): 314 ($[M+H]^+$) (100), 165 (15), 120 (35) 89 (56), 77 (50). **7** Mp (4-methyl-2-pentanone) 174 °C. ^{1}H NMR (DMSO-d^6): δ 8.23 (t, $J = 6.2$ Hz, 1H, NH), 8.20 (pseudo-s, 2H, H-2, and H-8), 7.38 (br s, 2H, NH_2), 7.29 (m, 5H, Ph-H), 6.25 (d, 1H, $J = 1.8$ Hz, H-1′), 5.48 (s, 1H, H-2′), 5.12 (d, 1H, $J = 2.4$ Hz, H-3′), 4.97 (dd, 1H, $J = 13.3$ and 2.0 Hz, 1H, H-4′), 4.45 (pseudo-s, 1H, H-5′), 4.35 (d, $J = 13.4$ Hz, 1H, H-5′), 4.23 (d, $J = 6.1$ Hz, 2H, Ph-CH_2). ^{13}C NMR (DMSO-d^6): δ 156.0, 154.4, 153.0, 149.1, 138.9, 137.7, 128.2, 127.1, 126.9, 118.5, 86.7, 80.4, 72.9, 69.3, 55.4, 44.0. MS (m/z, %): 447 ($[M+H]^+$) (93), 312 (54), 307 (33), 91 (100), 89 (65).