NUCLEOSIDES AND NUCLEOTIDES. 110. [2,3]-SIGMATROPIC REARRANGEMENT OF THE ALLYLIC SELENIDES TO ALLYLIC AMINES IN SUGAR MOIETY OF PYRIMIDINE NUCLEOSIDES: SYNTHESIS OF 3'-AMINO-2',3'-DIDEOXY-2'-METHYLIDENECYTIDINE[1]

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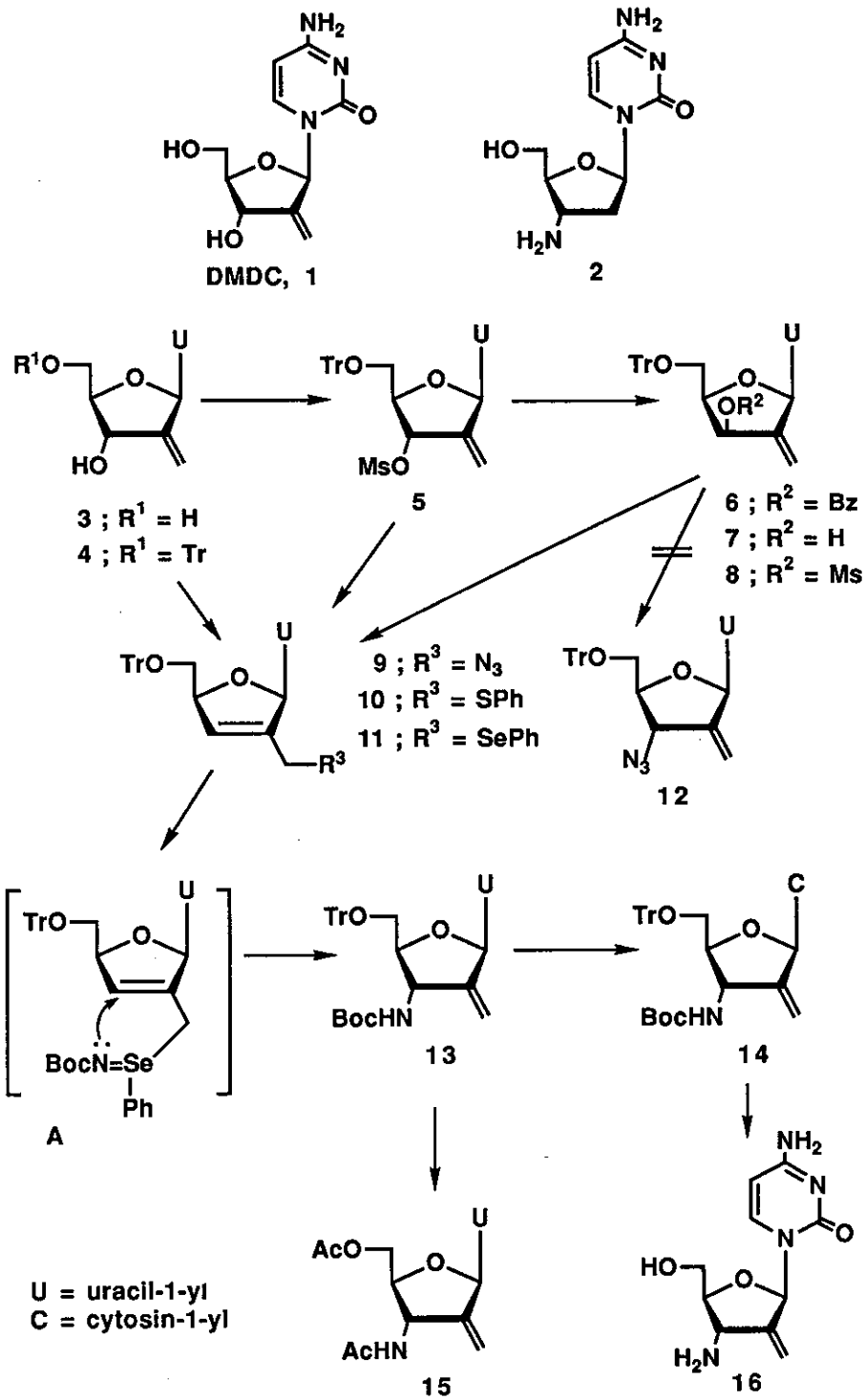
Abstract-----An allylic alcohol system in 2'-deoxy-2'-methylideneuridine derivative (**4**) was converted into the allylic selenide, 2',3'-didehydro-2',3'-dideoxy-2'-phenylselenomethyl derivative (**11**), which was treated with NCS and *tert*-butyl carbamate to afford a [2,3]-sigmatropic rearrangement product (**13**). Transformation of the uracil moiety of **13** into cytosine provided access to the title compound (**16**).

A new type of antineoplastic nucleosides, 2'-deoxy-2'-methylidenecytidine (DMDC, **1**) has been synthesized[2,3] and its activity has been evaluated.[4] DMDC showed, unlike the activity of 1-β-D-arabinofuranosylcytosine (*ara*-C), highly potent antineoplastic activity against not only mouse and human leukemia cell lines but also human adenocarcinoma and carcinoma cells *in vitro*. DMDC also had therapeutic activity against some human tumor xenografts.[4] DMDC is not a substrate of cytidine deaminase from mouse kidney, which deaminates *ara*-C to chemotherapeutically inactive 1-β-D-arabinofuranosyluracil.[2] The mechanism of its action has been extensively studied: 5'-triphosphate of DMDC strongly inhibits DNA polymerases from calf thymus[5] and 5'-diphosphate of DMDC time-dependently inhibits ribonucleoside diphosphate reductase[6] from *E. coli*. Thus, DMDC is an interesting and promising antitumor agent having a dual mechanism to inhibit tumor cell proliferation.


DMDC, 1
2
3 ; R1 = H
4 ; R1 = Tr
5
6 ; R2 = Bz
7 ; R2 = H
8 ; R2 = Ms
9 ; R3 = N3
10 ; R3 = SPh
11 ; R3 = SePh
12
A
13
14
15
16
U = uracil-1-yl
C = cytosin-1-yl

On the other hand, 3'-amino-2',3'-dideoxycytidine (**2**)[7,8] and -thymidine[9,10] are also known to have antiproliferative activity toward tumor cells as well as antiviral activity. Whether a combination of both structural features of DMDC and 3'-amino-2',3'-dideoxy nucleosides into one molecule would have additive antineoplastic activity or not is of interest. In this communication, we describe the synthesis of 3'-amino-2',3'-dideoxy-2'-methylidene pyrimidine nucleosides *via* a [2,3]-sigmatropic rearrangement of allylic selenides to allyl amines in the sugar moiety of pyrimidine nucleosides.

A straightforward method for the synthesis of the target nucleoside is thought to be conversion of either a preformed methanesulfonyl ester of allyl alcohol (**8**) with an azide anion (NaN_3 or $Bu_4N^+N_3^-$) or direct treatment of **7** with diphenylphosphoryl azide or hydrogen azide under Mitsunobu reaction conditions through the SN2 manner, followed by reduction of the azide group. Starting materials (**7**) and (**8**) were readily available from **3**[3,11] from uridine. The reaction of **4** with benzoic acid under the Mitsunobu reaction conditions or the reaction of the methanesulfonyl ester (**5**) with sodium benzoate gave **6** in 98% and 55% yields, respectively. Base-catalyzed hydrolysis of **6** furnished **7**, and methanesulfonylation of **7** gave **8**. However, on the reaction of **7** or **8** under the conditions described above, we always obtained an SN2' product, 2',3'-didehydro-2',3'-dideoxy-2'-azidomethyl derivative (**9**)[12] but not the desired **12**. Similar reactions of **4** and **5** again gave exclusively **9**. When we attempted the reaction of **5** or **8** with other nucleophiles such as phenylthiolate or phenylselenium anions, the reaction pattern was predominantly SN2' type to give the 2',3'-didehydro-2',3'-dideoxy-2'-phenylthiomethyl derivative (**10**) or 2'-phenylselenomethyl derivative (**11**) in excellent yields. Therefore, we started synthesizing the target nucleoside (**16**) from the allylic phenylselenide (**11**) *via* an oxidative [2,3]-sigmatropic rearrangement.[13]

When **11** was treated with *N*-chlorosuccinimide (NCS) in the presence of *tert*-butyl carbamate and triethylamine in THF/MeOH, the desired nucleoside (**13**) was obtained in 71% yield. The structure was assigned from its ^{1}H-nmr spectrum: ($CDCl_3$) δ ppm; 1.45 (9H, s, *t*-Bu), 3.73 (1H, m, H-4'), 5.13 (1H, m, H-3'), 5.44 (1H, br s, H-2"a), 5.51 (1H, br s, H-2"b), 6.62 (1H, d, J = 1.5 Hz, H-1'), 8.16 (1H, br s, 3'-NH), 8.49 (1H, br s, 3-NH). The configuration at the 3'-position could not be identified at this stage because of low resolution of the protons at the 3' and 4' positions. Therefore, **13** was deblocked by 80% aqueous trifluoroacetic acid in CH_2Cl_2, followed by acetylation with Ac_2O in pyridine to afford diacetate (**15**). A proton signal at 5.04 ppm (H-3') was coupled

with the 4'-protons (3.95 ppm) with 8.3 Hz in its ^{1}H-nmr spectrum.[14] This value is consistent with the "down" configuration at the 3' position so that the sigmatropic rearrangement proceeded in stereospecific mode from the structure A.

Finally, **13** was converted into the cytosine derivative (**16**): triisopropylbenzenesulfonylation of the O^4 position of **13** in the presence of DMAP in MeCN, and then treatment with concentrated NH_4OH, followed by deblocking with 80% aqueous TFA afforded 3'-amino-2',3'-dideoxy-2'-methylidenecytidine (**16**)[15] in quantitative yield. None of these nucleosides showed any significant cytotoxicity against L1210 cells *in vitro* and their evaluation as inhibitors of HIV is underway.

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REFERENCES

1. Part 109: H. Nishio, A. Ono, A. Matsuda, and T. Ueda, *Nucleic Acids Res.*, in press.
2. K. Takenuki, A. Matsuda, T. Ueda, T. Sasaki, A. Fujii, and K. Yamagami, *J. Med. Chem.*, **1988**, *31*, 1063.
3. A. Matsuda, K. Takenuki, M. Tanaka, T. Sasaki, and T. Ueda, *J. Med. Chem.*, **1991**, *34*, 812.
4. K. Yamagami, A. Fujii, M. Arita, T. Okumoto, S. Sakata, A. Matsuda, T. Ueda, and T. Sasaki, *Cancer Res.*, **1991**, *51*, 2319.
5. K. Takenuki and A. Matsuda, unpublished results.
6. C. H. Baker, J. Banzon, J. M. Bollinger, J. Stubbe, V. Samano, M. J. Robins, B. Lippert, E. Jarvi, and R. Resvick, *J. Med. Chem.*, **1991**, *34*, 1879.
7. T. S. Lin and W. R. Mancini, *J. Med. Chem.*, **1983**, *26*, 544.
8. W. R. Mancini, M. S. Williams, and T. S. Lin, *Biochemistry*, **1988**, *27*, 8832.
9. T. S. Lin and W. H. Prusoff, *J. Med. Chem.*, **1978**, *21*, 109.
10. T. S. Lin, M. S. Chen, C. Mclarren, Y-S. Gao, I. Ghazzouli, and W. H. Prusoff, *J. Med. Chem.*, **1987**, *30*, 440.

11. T. Sano, S. Shuto, H. Inoue, and T. Ueda, *Chem. Pharm. Bull.*, **1985**, *33*, 3617.

12. Physical data for **9**: EI-ms *m/z* 508 (M^+); ir ($CHCl_3$) ν_{N3} 2100 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 8.43 (1H, br s, NH), 7.88 (1H, d, $J_{6,5}$ = 8.1 Hz, H-6), 7.32 (15H, m, Ph), 6.95 (1H, br s, H-1'), 6.22 (1H, m, H-3'), 5.02 (1H, dd, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz, H-5), 4.96 (1H, m, H-4'), 3.97 (1H, d, $J_{a,b}$ = 15.0 Hz, 2'-CH_a), 3.83 (1H, d, $J_{a,b}$ = 15.0 Hz, 2'-CH_b), 3.54 (1H, dd, $J_{5'a,4'}$ = 2.9, $J_{a,b}$ = 15.0 Hz, H-5'a), 3.47 (1H, dd, $J_{5'b,4'}$ = 2.6, $J_{a,b}$ = 15.0 Hz, H-5'b).

13. J. N. Fitzner, R. G. Shea, J. E. Fankhauser, and P. B. Hopkins, *J. Org. Chem.*, **1985**, *50*, 417.

14. The coupling constants for $J_{3',4'}$ of **4** and **7** are 7.3 and 4.0 Hz, respectively.

15. Physical data for **16**: mp 120 °C (dec, crystallized from EtOH); ^{1}H-nmr (D_2O) δ 7.75 (1H, d, $J_{6,5}$ = 7.8 Hz, H-6), 6.68 (1H, br s, H-1'), 6.22 (1H, br d, $J_{5,6}$ = 7.8 Hz, H-5), 5.85 (1H, d, J = 2.0 Hz, H-2"a), 5.64 (1H, d, J = 1.5 Hz, H-2"b), 4.57 (1H, m, H-3'), 4.31 (1H, m, H-4'), 3.93 (1H, dd, $J_{5'a,4'}$ = 4.4, $J_{a,b}$ = 12.7 Hz, H-5'a), 3.85 (1H, dd, $J_{5'b,4'}$ = 3.4, $J_{a,b}$ = 12.7 Hz, H-5'b).

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