Tetrahedron Letters,Vol.29,No.42,pp 5349-5352,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

AN EFFICIENT TOTAL SYNTHESIS OF 3'-AZIDO-3'-DEOXYTHYMIDINE (AZT) AND 3'-AZIDO-2',3'-DIDEOXYURIDINE (AZDDU, CS-87) FROM D-MANNITOL

Chung K. Chu*, J. Warren Beach, Giliyar V. Ullas and Yoshiyuki Kosugi

Department of Medicinal Chemistry and Pharmacognosy
College of Pharmacy, The University of Georgia
Athens, GA 30602

Summary: An efficient stereoselective total synthesis of 3'-azido-3'-deoxythymidine (AZT) and 3'-azido-2',3'-dideoxyuridine (AZDDU, CS-87) from readily available and inexpensive starting material, D-mannitol has been achieved.

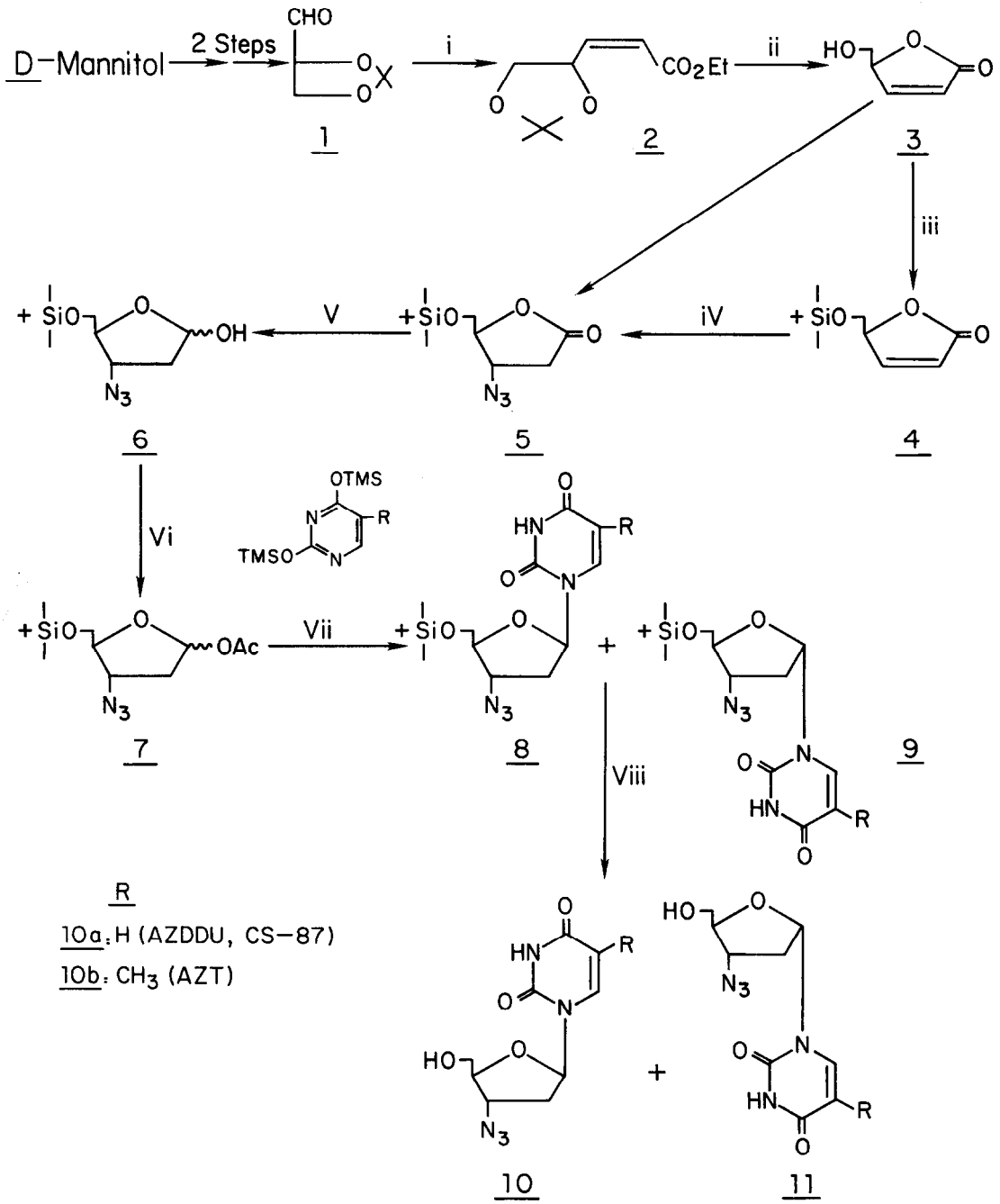
3'-Azido-3'-deoxythymidine (AZT) has been found to be a potent antiviral agent against human immunodeficiency virus type 1 (HIV-1) *in vitro*[1-5] and found to decrease the mortality and opportunistic infections in patients with acquired immunodeficiency syndrome (AIDS)[6]. Currently, AZT is the only chemotherapeutic agent available for AIDS patients. 3'-Azido-2',3'-dideoxyuridine (AZDDU, CS-87) has also been found to be a potent antiviral agent against HIV-1 *in vitro*[7,8] and is presently undergoing preclinical toxicology.

AZT was originally synthesized from thymidine by Horwitz and his coworkers[9]. AZDDU (CS-87) has also been synthesized from 2'-deoxyuridine by a similar approach[10,11]. Short supplies of AZT, due to the high demand for the drug as well as the expensive starting material (thymidine and 2'-deoxyuridine) required for the synthesis of both AZT and AZDDU prompts us to develop an efficient general method for these compounds.

Recently, total synthesis of AZT by the condensation of thymine with a preformed 3-azido-2-deoxyribofuranose derivative has been reported[12,13]. However, in these methods, the intermediate azido sugar has been prepared from D-xylose via the intermediate 1,2:3,5-di-O-isopropylidene-D-xylofuranose or methyl 3,5-O-isopropylidene-D-xylofuranoside through multistep processes[13-16]. In anticipation of the requirement of large quantities of AZDDU for clinical studies, we wished to develop an efficient synthetic method utilizing a readily available and inexpensive starting material. In this paper we describe a new synthetic method for both AZT and AZDDU from azido sugar 7, which can also be readily utilized for the synthesis of other 3'-azido-2',3'-dideoxy-pyrimidine and -purine nucleosides.

The D-glyceraldehyde derivative 1, which can be readily prepared from D-mannitol in two steps[17,18], was treated with (carbethoxymethylene)triphenylphosphorane in methanol at 0°C to obtain predominately the Z-isomer 2 (8:1)[19,20] (Scheme 1). The E- and Z-isomers were readily separated by a flash silica gel column using hexanes-ethyl acetate (8:1) as the eluent. The Z-isomer 2 was treated with dil-HCl to obtain the key intermediate, the α,β-unsaturated lactone 3[21,22] in good yield (90%). The procedure is a modification of the method of Hafele and Jager[18] and amenable to a large scale synthesis (>100 g). Our initial approach for introducing the azide group at the 3-position of 3[23] with lithium azide produced a

Scheme 1



i. $Ph_3P{=}CH{\cdot}CO_2Et$, MeOH, 0°C; ii. dil. HCl; iii. t-Bu$(Me)_2$SiCl, imidazole, DMF; iV. LiN_3, THF, AcOH, H_2O; V. DIBAL, CH_2Cl_2; −78°C; Vi. Ac_2O, Pyridine; Vii. TMS-Triflate, $ClCH_2CH_2Cl$; Viii. n-$Bu_4N^+F^-$, THF.

3-azido-α,β- mixture (6:1). However, the formation of the undesirable isomer (β-azide) was circumvented by introducing a bulky group such as t-butyldimethylsilyl or t-butyldiphenylsilyl group at 5-position of 3. The bulky group in 4 probably prevents the azide ion from approaching from the top side of the double bond, which results in only the desired α-isomer 5[24,25]. The reduction of lactone 5 was accomplished with DIBAL in methylene chloride at -78°C to give lactol 6[26] in good yield (77%), which was acetylated to the key sugar intermediate 7[27]. Condensation of 7 with silylated thymine in 1,2-dichloroethane in the presence of trimethylsilyl triflate[28] gave a α,β-mixture of 8b and 9b (66%), which was inseparable to individual isomers by column chromatography. However, ^{1}H NMR spectrum showed a α,β-mixture in a ratio of 1:1. The mixture was desilylated with n-tetrabutylammonium fluoride and then separated by a silica gel column using a mixture of ethyl acetate-hexanes (10:1) as the eluent to give 10b and 11b[29a,29b] (overall yield of 10b from 7 was 25%). In the case of AZDDU (CS-87), the condensation of 7 with silylated uracil in 1,2-dichloroethane with trimethylsilyl triflate followed by silica gel chromatography (chloroform:methanol, 19:1) gave a 55% yield of α,β- mixture (33:67). After treatment of the inseparable α,β-mixture (33:67) with n-tetrabutylammonium fluoride and passage through a short silica gel flash column, AZDDU (CS-87)[29a] was crystallized from isopropanol in the presence of its α-isomer 11a[30] (overall yield of 10a from 7 was 20%).

Acknowledgement

This research was supported by Public Health Service Research Grant (AI 26055 and AI 25899) from the National Institute of Allergy and Infectious Diseases.

References

1. H. Mitsuya, S. Broder, Nature, 325, 773, (1987).
2. R. Yarchoan, S. Broder, New Engl. J. Med., 316, 557, (1987).
3. H. Mitsuya, M. Matsukura, S. Broder, in AIDS. Modern Concepts and Therapeutic Challenges; S. Broder, Ed.; Marcel Dekker, New York, 1987; p. 303.
4. H. Mitsuya, K.J. Weinhold, P.A. Furman, M.H. St. Clair, S.N. Lehrman, R.L. Gallo, D. Bolognesi, D.W. Barry. S. Broder, Proc. Nat'l Acad. Sci., USA, 82, 7096 (1985).
5. P.A. Furman, J.A. Fyfe, M.H. St. Clair, K. Weinhold, J.L. Rideout, G.A. Freeman, S.N. Lehrman, D.P. Bolognesi, S. Broder, H. Mitsuya, D.W. Barry, ibid, 83, 8333, (1986).
6. M.A. Fischl, D.D. Richman, M.H. Grieco, M.S. Gottlieb, P.A. Valberding, O.L. Laskin, J.L. Leedom, J.E. Groopman, D. Mildvan, R.T. Scholey, G.G. Jackson, D.T. Durack, and K. King, New Engl. J. Med., 317, 185, (1987).
7. R.F. Schinazi, C.K. Chu, M.K. Ahn, J.P. Sommadossi, H. McClure, J. Cell Biochem. Suppl. 11D, 74, (1987). An Abbott-UCLA Symposium, Keystone, Colorado, April 1-5, 1987. Paper No. P-405.
8. R.F. Schinazi, B.F.H. Eriksson, C.K. Chu, 2nd International Conference on Antiviral Research, Williamsburg, VA, April 10-14, 1988; Antiviral Research, 9, 84, (1988).
9. J.P. Horwitz, J. Chua, and M. Noel, J. Org. Chem., 29, 2076, (1964).
10. T.S. Lin and W.R. Mancini, J. Med. Chem., 26, 544 (1983).

11. C.K. Chu, R.F. Schinazi, M.K. Ahn, G.V. Ullas, and Z.P. Gu, submitted for publication.
12. N.B. Dyatkina, A.A. Kraevskii and A.B. Azhaev, Soviet J. Biorg. Chem., 12, 563 (1986).
13. G.W.J. Fleet, J.C. Son and A.E. Derome, Tetrahedron, 44, 625 (1988).
14. N.B. Dyatkina and A.V. Azhayev, Synthesis, 11, 961 (1984).
15. B.R. Baker, R.E. Schaub and J.H. Williams, J. Am. Chem. Soc., 77, 7 (1955).
16. B.R. Baker and R.E. Schaub, ibid, 77 5900 (1955).
17. E. Baer in Biochemical Preparations, Vol. 2, Ed. E.G. Ball, John Wiley, New York, 1952; p. 31.
18. B. Hafele and V. Jager, Liebigs Ann. Chem., 85 (1987).
19. H. Matsunaga, T. Sakamaki, H. Nagaoka, and Y. Yamada, Tetrahedron Lett., 24, 3009 (1983).
20. S. Valverde, M. Martin-Lomas, B. Herradon, and S. Garcia-Ochoa, Tetrahedron, 43, 1895 (1987).
21. P. Camps, J. Cardellach, J. Font, R.M. Ortuno, and O. Ponsati, Tetrahedron, 38, 2395 (1982).
22. J.A.J.M. Vekemans, G.A.M. Franken, C.W.M. Dapperens, E.F. Godefroi, and G.J.F. Chittenden, J. Org. Chem., 53, 627 (1988).
23. Compounds 3, 4 and 5 are numbered as sugar derivatives.
24. All new compounds have been fully characterized by IR and ^{1}H NMR.
25. 5: m.p. 35-36°C; IR(Neat): 2110(N_3), 1790 cm^{-1}(C = 0); ^{1}H NMR ($CDCl_3$): δ0.08(6H, s, CH_3), 0.89(9H, s, t-butyl), 2.50(1H, dd, J = 18, 3.25 Hz, H-2), 2.97(1H, dd, J = 18, 7.25 Hz, H-2), 3.84(2H, m, H-5), 4.40(2H, m, H-3 and H-4). Anal. Calcd. for $C_{11}H_{21}N_3O_3Si$: C, 48.68; H, 7.80; N, 15.49. Found: C, 48.58; H, 7.82; N, 15:45.
26. 6: (α,β-mixture, 1:2): IR(Neat): 3600-3100 (OH), 2110 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$): δ0.07 and 0.13 (6H, 2s, CH_3), 0.89 and 0.93 (9H, 2s, t-butyl), 2.0 - 2.5 (2H, m, H-2), 2.99(1H, d, J = 6.37 Hz, OH exchangeable), 3.5 - 3.8 (2H, m, H-5), 4.0 - 4.3 (2H, m, H-3 and H-4), 5.4 - 5.6 (1H, m, H-1). Anal. Calcd. for $C_{11}H_{23}N_3O_3Si$: C, 48.32; H, 8.48; N, 15.37. Found: C, 48.39; H, 8.52; N, 15.28.
27. 7: (α,β-mixture, 1:2): IR(Neat): 2110(N_3) and 1755 cm^{-1} ($COCH_3$); ^{1}H NMR(250 MHz, $CDCl_3$):δ 0.086 (β) and 0.091 (α) (5H, 2s, CH_3), 0.89 (β) and 0.92 (α) (9H, 2s, t-butyl), 2.04 (β) and 2.09 (α) (3H, 2s, $COCH_3$), 2.10-2.24 (1H, m, H-2), 2.34-2.49 (1H, m, H-2), 3.62-3.8(3H, complex multiplet, H-4 and 5), 3.95-4.27 (1H, complex multiplet, H-3), 6.29[0.66H, dd, J=1.6 and 5.27 Hz, H-1(β)] 6.34[0.33H, dd, J = 0.83 and 5.35 Hz, H-1 (α)] Anal. Calcd. for $C_{13}H_{25}N_3O_4Si$: C, 49.52; H, 7.93; N, 13.33. Found: C, 49.60; H, 8.03; N, 13.30.
28. H. Vorbruggen, K. Krolikiewicz, and B. Bennua, Chem. Ber., 114, 1234 (1981).
29. (a) Compounds 10a, 10b were identical in physical and spectroscopic properties with authentic samples. (b) Physical and spectroscopic properties for 11b were identical to those previously reported in Ref. 13.
30. 11a: Hygroscopic foam: $[\alpha]_D$ - 4.6° (c, 0.49, CH_3OH); IR(KBr): 2120 cm^{-1} (N_3); ^{1}H NMR (DMSO-d_6):δ 2.1(1H, dt, J = 14, 4 Hz, H-2'b), 2.73(1H, dt, J = 14, 7 Hz, H-2'a), 3.47(2H, m, H-5'), 4.1-4.45 (2H, complex multiplet, H-3' and 4'), 5.02(1H, t, OH-5', exchangeable), 5.63(1H, d, J = 8 Hz, H-5), 6.07(1H, dd, $J_{1',2'a}$ = 7 Hz, $J_{1',2'b}$ = 4 Hz, H-1'), 7.67(1H, d, J = 8Hz, H-6), 11.27(1H, bs, NH, exchangeable). Anal. Calcd. for $C_9H_{11}N_5O_4.1/4\ H_2O$: C, 41.94; H, 4.46; N, 27.18. Found: C, 41.95; H, 4.55; N, 27.08.

(Received in USA 6 June 1988)