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First Chemical Synthesis of Deuterated 3'-Azido-3'-Deoxythymidine (AZT)

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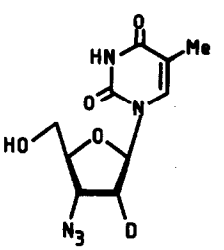
Abstract: The synthesis of 2'(R)d_2-3'-azido-3'-deoxythymidine has been described.

The structure and conformation of 3'-azido-3'-deoxythymidine (AZT) has been most extensively examined among new class of anti-HIV dideoxynucleosides. The X-ray diffraction studies[1] have given two crystallographically independent structures with different geometrical parameters and the one with an unusual C-3' exo/C-4' endo sugar pucker has been proposed to be the anti-HIV active form of AZT[1b]. However our[2] and other[3] studies on NMR of AZT, coupled with NMR[4] and X-ray structure analysis[5] of anti-HIV dideoxynucleosides analogues did not support this hypothesis.

A number of deuterated nucleosides[6] have been synthesised because deuterium NMR has been of tremendous value to provide accurate information about their molecular motions and accessible conformations in liquid and the solid state. However, deuterated AZT, to the best of our knowledge, has not been synthesised so far. We therefore believe deuterated AZT could turnout to be a useful molecule in understanding structure and conformation in light of its anti-HIV activity. We detail herein the first communication on the synthesis of 2'-d_2-3'-azido-3'-deoxythymidine (**1**).



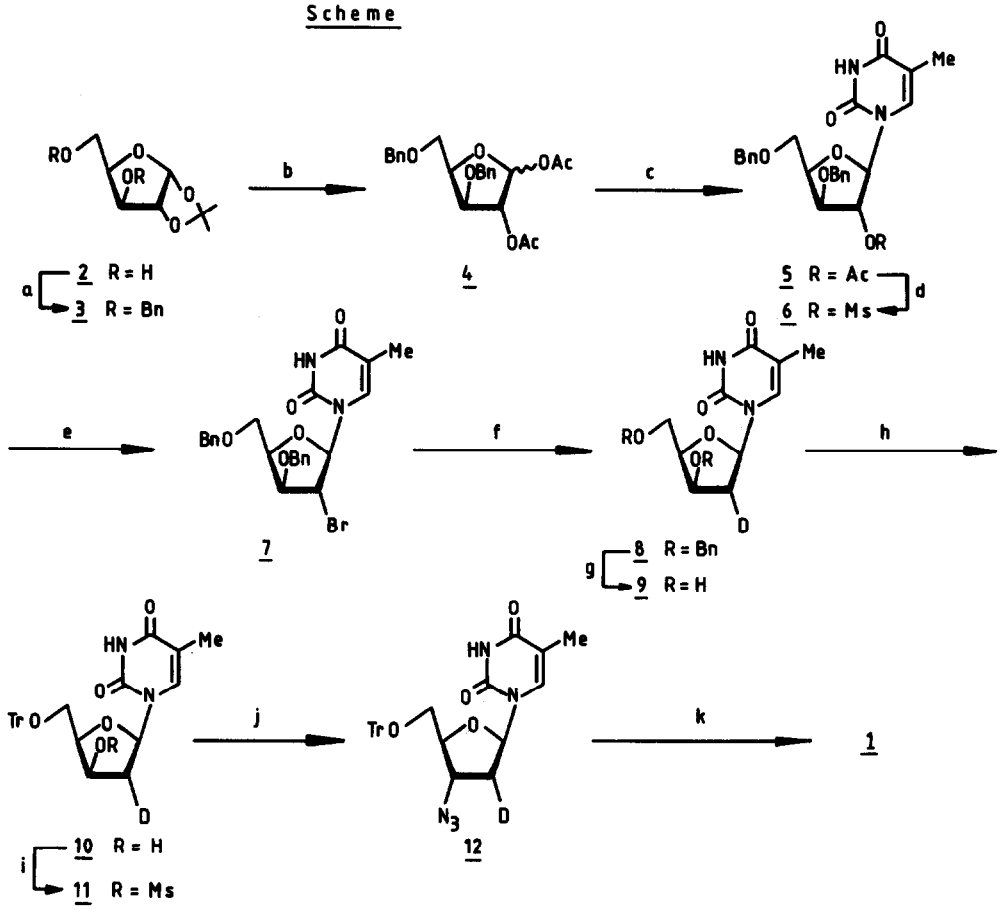
1

The requisite monosaccharide (**4**) was synthesised from the known 1,2-O-isopropylidene-α-D-xylofuranose (**2**)[7] as follows. Benzylation of **2** was effectively carried out by heating with excess of BnCl in the presence of powdered KOH at 80° for 2 h. Subsequent removal of the isopropylidene group with 3N H_2SO_4 in refluxing dioxan followed by conventional acetylation gave **4**[8]. The modified coupling reaction[9] of **4** with thymine in the presence of TMSCl-HMDS-$SnCl_4$ in refluxing CH_3CN gave **5** in 70% yield.

At this stage the substitution of 2'-OH group with deuterium was considered. Removal of the acetate group in **5** under Zemplen conditions and consequent mesylation with MsCl-Et_3N

afforded **6** in 85% yield. By virtue of steric and electronic factors[10], the restrictions to displace secondary sulfonate group, particularly present at position 2 of a furanose ring, with conventional nucleophiles are well documented. However, with pyridine-HBr salt in pyridine as a solvent under reflux, **6** underwent smooth displacement reaction to provide **7**[11] in 75% yield. The retention of configuration at C-2' was demonstrated by the ^{1}H-NMR spectrum in which the characteristic singlet due to H-1' was located at 6.08 ppm. This could be explained by considering the formation of an intermediary 2,2'-anhydro ring formation[12].

Scheme



a) BnCl, KOH, Δ, 80°, 2h; b) (i) 3N H_2SO_4, Dioxan, Δ, 0.5 h, (ii) Ac_2O, Et_3N, RT, 2h; c) Thymine, HMDS, TMS-Cl, $SnCl_4$, CH_3CN, Δ, 0.5h; d) (i) NaOMe, MeOH, 1h, (ii) MsCl, Et_3N, CH_2Cl_2, 1h; e) Py-HBr, Py, Δ, 3h; f) Bu_3SnCl (cat.), $NaBD_4$, MeOH, h ν, 3h; g) 10% Pd-C, MeOH, H_2 (3 atm), 8h; h) TrCl, Py, 90°C, 1h; i) MsCl, Py, 1h; j) LiN_3, DMF, 90°C, 4h; k) aq. AcOH (80%), 90°C, 1h.

For reductive debromination of **7**, we have utilised the Corey's procedure[13] in which **7** was treated with 1 molar % of Bu_3SnCl and 1 eq. of $NaBD_4$ in MeOH while irradiating the

reaction mixture with 500w tungsten lamp. The product **8** showed in its ^{1}H-NMR spectrum the small coupling constant ($J_{H-1',H-2'}$ = 2.6 Hz) for H-1', thus clearly proving the R configuration at C-2'[8,9,12]. The delivery of the deuterium radical taking place from the less hindered α-face was predictable[14].

The next set of reactions involved hydrogenolysis of **8** in the presence of 10% Pd-C in MeOH at 45 psi to give the diol (**9**) which with 1.2 eq. of TrCl in pyridine at 90°C for 1 h was selectively converted into 5'-O-trityl ether (**10**) in 65% overall yield[15]. Subsequently **10** was transformed into the mesylate derivative **11** and then subjected to displacement reaction with LiN_3 in DMF at 90° for 4 h to provide **12** in 90% yield. Finally **12** was detritylated with 80% aq. AcOH at 90° for 1 h to give the target molecule **1**.[16]

In this report we have demonstrated the first synthesis of a first deuterated AZT whose nmr studies are being planned in these laboratories.

References

1. a) Gursakaia, G.V.; Tsapkina, E.N.; Skaptsova, N.V.; Kraevskii, A.A.; Lindeman, S.V.; Struchkov, I.T.; Akad. Nauk, SSR, 1986, **291**, 899; b) Birnbaun, G.T.; Giziewicz, J.; Gabe, E.T.; Lin, T-S.; Prusoff, W.H. Can. J. Chem., 1987, **65**, 2135; c) Camerman, A.; Mastropaolo, D.; Camerman, N.; Proc. Natl. Acad. Sci., USA, 1987, **84**, 8239; d) Dyer, I.; Low, J.N.; Tollin, P.; Wilson, H.R.; Howie, R.A. Acta. Crystallogr. Sect. C.; 1988, **44**, 767.
2. Swapna, G.V.T.; Jagannadh, B.; Gurjar, M.K.; Kunwar, A.C.; Biochem. Biophy. Res. Comm.; 1989, **164**, 1086.
3. a) Hicks, N.; Howarth, O.W.; Hutchinson, D-W.; Carbohydr. Res., 1991, **216**, 1; b) Plavec, J.; Koole, L.H.; Sandstrom, A.; Chattopadhyaya, J.; Tetrahedron, 1991, **47**, 7363.
4. Jagannadh, B.; Reddy, D.V.; Kunwar, A.C.; Biochem. Biophy. Res. Comm., 1991, **179**, 386.
5. a) Van Roey, P.; Salerno, J.M.; Duax, W.L.; Chu, C.K.; Ahn, M.K.; Schinazi, R.F. J. Am. Chem. Soc. 1988, **110**, 2277; b) Van Roey, P.; Salerno, J.M.; Chu, C.K.; Schinazi, R.F.; Proc. Natl. Acad. Sci. USA; 1989, **86**, 3929.
6. a) Roy, S.; Hiyama, N.; Torchia, D.A.; Cohen, J.C.; J. Am. Chem. Soc., 1986, **108**, 1675; b) Berger, M.; Shaw, A.; Cadet, J.; Jones, J.; Nucleosides. Nucleotides, 1987, **6**, 395; c) Pathak, T.; Chattopadhyaya, J.; Tetrahedron, 1987, **43** , 4227; d) Hiyama, Y.; Roy, S.; Cohen, J.C.; Torchia, D.A.; J. Am. Chem. Soc.; 1989, **111**, 8609; e) Fuji, T.; Saito, T.; Kizu, K.; Hayashibara, H.; Kumazawa, Y.; Nakajima, S.; Fujisawa, T.; Chem. Pharm. Bull. 1991, **39**, 301.
7. Baker, B.R.; Schuab, R.E.; J. Am. Chem. Soc., 1955, **77**, 5900.
8. Benhaddou, R.; Czernecki, S.; Valery, J.M.; Bellosta, V.; Bull. Chem. Fr., 1991, **127**, 108.
9. Gosselin, G.; Bergogne, M.C.; deRudder, J.; DeClercqe, E.; Imbach, J.L.; J. Med. Chem.; 1986, **29**, 203.
10. a) Richardson, A.C.; Carbohydr. Res. 1989, **10**, 395; b) Ball, D.H.; Parrish, F.W.; Adv. Carbohydr. Chem.; 1969, **24** 139; c) Wu, M.C.; Anderson, L.; Slefe, C.W.; Jensen, L.J.; J. Org. Chem.; 1974, **39**, 3014.

11. New compounds showed satisfactory HRMS or elemental analysis.
12. Hrebabecky, H.; Holy, A.; Carbohydr. Res., 1991, **216**, 179.
13. Corey, E.J.; Suggs, J.W.; J. Org. Chem.; 1975, **40**,, 2254.
14. Hartwig, W.; Tetrahedron, 1983, **39**, 2609.
15. Herwitz, J.P.; Hrbanski, J.A.; Chua, J.; J. Org. Chem. 1962, **27**, 3300.
16. ^{1}H-NMR (200 MHz) data and optical rotation of some selected compounds:-

Compound 7 ($CDCl_3$): δ 1.51 (s, 3H), 3.66 (m, 2H), 4.08 (bs, 2H), 4.42 (m, 5H), 6.08 (s, 1H), 7.2 (m, 11H), 8.06 (s, 1H).

$[\alpha]_D$ -4.6°C (c 1.3, $CHCl_3$).

Compound 8 ($CDCl_3$): δ 1.66 (s, 3H), 2.19 (d, 1H, J=2.6 Hz), 3.85 (m, 2H), 4.14 (m, 2H), 4.45 (ABq, 2H), 4.57 (ABq, 2H), 6.23 (d, 1H, 2.6 Hz), 7.25 (m, 10H), 7.50 (s, 1H), 8.95 (bs, 1H).

$[\alpha]_D$ -18.3° (c 1.3, $CHCl_3$).

Compound 9 ($CDCl_3$+CD_3OD): δ 1.90 (s, 3H), 2.03 (bs, 1H), 3.92 (m, 3H), 4.43 (bs, 1H), 6.10 (d, 1H, J=2.6 Hz), 7.86 (s, 1H).

$[\alpha]_D$ -7.2° (c 1.2, MeOH).

Compound 11 ($CDCl_3$): δ 1.80 (s, 3H), 2.44 (d, 1H, J=2.3 Hz), 2.73 (s, 3H), 3.85 (dd, 1H, J=7.0 Hz, J=10.4 Hz), 3.63 (dd, 1H, J=5.8 Hz, J=10.4 Hz), 4.12 (m, 1H), 5.26 (d, 1H, J=4.6 Hz), 6.23 (d, 1H, J=2.3 Hz), 7.30 (m, 16 Hz).

$[\alpha]_D$ -25.1° (c 1.1, $CHCl_3$).

Compound 1 ($CDCl_3$): δ 1.90 (s, 3H), 2.50 (t, 1H, J=6.2 Hz), 3.70-4.05 (m, 3H), 4.40 (m, 1H), 6.05 (d, 1H, J=6.2 Hz), 7.38 (s, 1H), 9.22 (bs, 1H).

$[\alpha]_D$ +44.2° (c 1.4, MeOH).

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