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STEREOSELECTIVITY IN RADICAL REACTIONS OF 2'-DEOXYNUCLEOSIDES. A SYNTHESIS OF AN ISOSTERE OF 3'-AZIDO-3'-DEOXYTHYMIDINE-5'-MONOPHOSPHATE (AZT-5' MONOPHOSPHATE)

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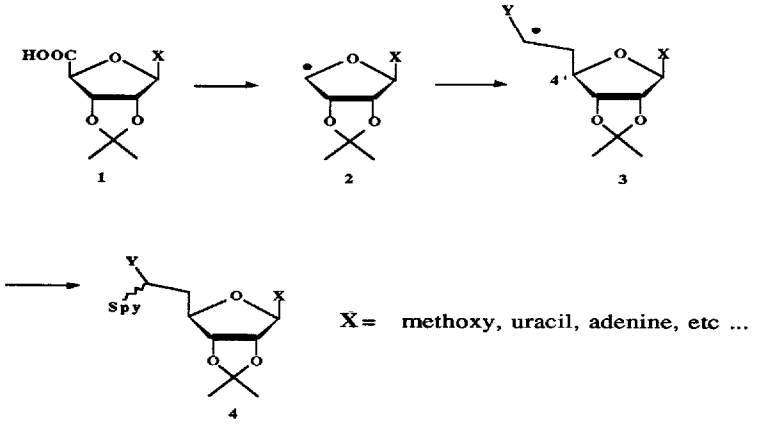
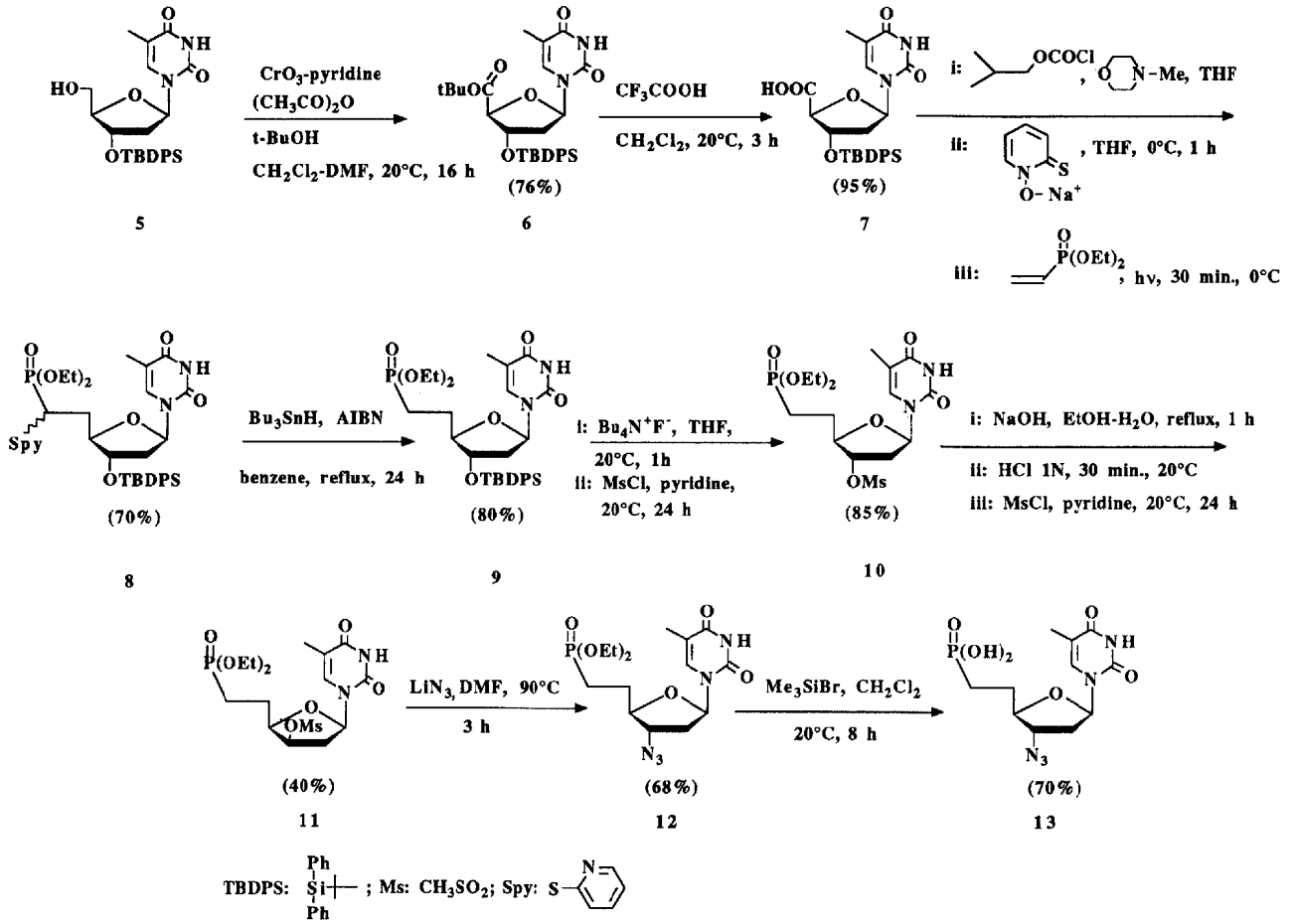
Abstract - The bulky *t*-butyldiphenylsilyl group, attached to the 3'-hydroxyl of the uronic acid from thymidine, permits a stereoselective formation of a carbon-carbon bond using the 4' carbon radical. Taking advantage of this stereoselectivity an isostere of 3'-azido-3'-deoxythymidine-5'-monophosphate (AZT 5'-monophosphate) has been synthesised.

Stereoselectivity in radical reactions can be secured by a steric control of the new centre of chirality. Recently,[1] we showed that uronic acids **1** (X = methoxyl, uracil, adenine etc...), derived from furanose ketals gave, by acylation with *N*-hydroxy-2-thiopyridone and photolysis, the corresponding 4'-radicals **2**. These then reacted very stereoselectively with electrophilic olefins to give the radical **3**, which was quenched by thiopyridyl transfer.[2] This furnished stable products **4** as a mixture of stereoisomers at the side chain thiopyridyl function. The high stereoselectivity in the step **2** -> **3** was attributed to the steric bulk of the dimethylketal function. Of course, an anomeric effect may also be involved.[3] In any case the high degree of stereoselecivity in step **2** -> **3** contrasts with the lack of stereoselectivity in the step **3** -> **4** .



A number of other observations in the literature confirm the importance of steric bulk in controlling the stereoselectivity of radical reactions in carbohydrates and other structures.[4]


HO
OTBDPS
5
CrO_3-pyridine
$(CH_3CO)_2O$
t-BuOH
CH_2Cl_2-DMF, 20°C, 16 h
tBuOC
OTBDPS
(76%)
6
CF_3COOH
CH_2Cl_2, 20°C, 3 h
HOOC
OTBDPS
(95%)
7
i: OCOCl, N-Me, THF
ii: , THF, 0°C, 1 h
O- Na^+
iii: $P(OEt)_2$, hv, 30 min., 0°C
$P(OEt)_2$
Spy
OTBDPS
(70%)
8
Bu_3SnH, AIBN
benzene, reflux, 24 h
OTBDPS
(80%)
9
i: $Bu_4N^+F^-$, THF, 20°C, 1h
ii: MsCl, pyridine, 20°C, 24 h
OMs
(85%)
10
i: NaOH, EtOH-H_2O, reflux, 1 h
ii: HCl 1N, 30 min., 20°C
iii: MsCl, pyridine, 20°C, 24 h
OMs
(40%)
11
LiN_3, DMF, 90°C
3 h
N_3
(68%)
12
Me_3SiBr, CH_2Cl_2
20°C, 8 h
$P(OH)_2$
N_3
(70%)
13
TBDPS: Ph, Si, Ph ; Ms: CH_3SO_2; Spy: S-N

The same efficient stereoselectivity was recently seen[5] for the reaction of radicals of type **2** with diethylvinylphosphonate to afford compounds **4** (Y = P(O)(OEt)$_2$). Reductive removal of the thiopyridyl function and removal of the protecting groups afforded phosphonates, isosteric with the corresponding naturally occurring 5'-monophosphates.

In this article we turn to the interesting question of stereoselective radical reactions in the biologically important 2'-deoxy-series. Following our initial ideas we decided to make one face of the molecule as hindered as possible. The known[6] *t-b*utyldiphenylsilyl derivative of thymidine **5** was converted *via* the *t*-butyl ester **6** into the protected uronic acid **7** in good overall yield. Using the mixed anhydride method[7] the *N*-hydroxy-2-thiopyridone derivative was formed and photolysed in the presence of diethylvinylphosphonate[5] to give the adduct **8**. Removal of the thiopyridyl function gave a single isomer **9**. Clearly the radical addition reaction was highly stereoselective. Since this is due to the bulky silyl derivative, there will be other applications for this group in controlling radical stereoselectivity.

Desilylation of **9** and mesylation gave the mesylate **10**. Treatment with alkali gave the cyclic imino-ether,[8] which on acid catalysed hydrolysis, afforded the inverted alcohol. Mesylation in the usual way gave mesylate **11**. Reaction of this with lithium azide in *N,N'*-dimethylformamide[9] gave azide **12**. The latter, on treatment with trimethylsilyl bromide, provided the desired azide phosphonate **13**. This is isosteric with the 5'-monophosphate of the well known 3'-azido-3'-deoxythymidine (AZT) **14**.

As this article was being written, a report on the synthesis of the same compound **13** by an entirely different method using ionic chemistry appeared.[10] The phosphonate **13** is said[10] to be a highly promising candidate as an anti-HIV drug.

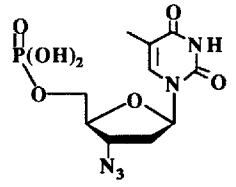


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Table 1: Selected physical data and NMR analysis of compounds 7, 9, 10, 11, 12 and 13.

7: m.p.: 240°C (methanol), $[\alpha]_D^{20}$=+ 58° (c= 1, DMF), MS: (I.C., m/z): 495 $(MH)^+$

^{1}H RMN (200 MHz, DMSO-D6): δ ppm: 7,72, 7,55 (m, 10H, Ph); 7,53 (s, 1H, H_6); 6,57 (dd, 1H, $H_{1'}$, $J_{1'2'}$= 5 Hz, $J_{1'2''}$= 10 Hz); 4,75 (sl, 1H, $H_{3'}$); 4,60 (s, 1H, $H_{4'}$); 2,13 (m, 2H, $H_{2'}$, $H_{2''}$); 1,87 (s, 3H, CH_3); 1,18 (s, 9H, $C[CH_3]_3Si$).

9: m.p.: 150-154°C (ether-pentane), $[\alpha]_D^{20}$=+33° (c= 0,5, $CHCl_3$), MS: (F.A.B., m/z): 615 $(MH)^+$

^{1}H RMN (200 MHz, $CDCl_3$): δ ppm: 9,03 (s, 1H, NH); 7,66, 7,45 (m, 10H, Ph); 6,98 (s, 1H, H_6); 6,38 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 7 Hz); 4,06 (m, 5H, $H_{3'}$, $[CH_3\underline{CH_2}O]_2PO$); 3,38 (m, 1H, $H_{4'}$); 2,33 (m, 1H, $H_{2'}$); 1,9 (s, 3H, CH_3); 1,83-1,36 (m, 5H, $H_{2''}$, $H_{5'}$, $H_{5'gem}$, $H_{6'}$, $H_{6'gem}$); 1,26 (t, 6H, $[\underline{CH_3}CH_2O]_2PO$); 1,1 (s, 9H, $[CH_3]_3CSi$).

10: $[\alpha]_D^{20}$=+21° (c=0,83, $CHCl_3$)

^{1}H RMN (200 MHz, $CDCl_3$): δ ppm: 9,53 (s, 1H, NH); 7,10 (s, 1H, H_6); 6,20 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 7 Hz); 5,06 (m, 1H, $H_{3'}$, $J_{3',4'}$= $J_{3',2''}$= 3 Hz, $J_{3',2'}$= 6 Hz); 4,11 (m, 5H, $H_{4'}$, $[CH_3\underline{CH_2}]_2PO$); 3,11 (s, H, CH_3SO_2); 2,63 (m, 1H, $H_{2'}$, $J_{2',2''}$= 15 Hz, $J_{2',3'}$= 6 Hz); 2,36 (m, 1H, $H_{2''}$, $J_{2'',1'}$= 7 Hz); 2,15-1,86 (m, 4H, $H_{5'}$, $H_{5'gem}$, $H_{6'}$, $H_{6'gem}$); 1,95 (s, 3H, CH_3); 1,33 (t, 6H, $[\underline{CH_3}CH_2]_2PO$).

11: $[\alpha]_D^{20}$=-14,4° (c= 1, $CHCl_3$), **IR:** vmax ($CHCl_3$): 3400, 1700 cm^{-1}

^{1}H RMN (200 MHz, $CHCl_3$): δ ppm: 9,56 (s, 1H, NH); 7,31 (s, 1H, H_6); 6,21 (dd, 1H, $H_{1'}$, $J_{1',2'}$= 8 Hz, $J_{1',2''}$= 2,5 Hz); 5,18 (dd, 1H, $H_{3'}$, $J_{3'2'}$= 5 Hz, $J_{3',4'}$= 2 Hz); 4,11 (m, 5H, $H_{4'}$, $(CH_3\underline{CH_2}O)_2PO$); 3,1 (s, 3H, CH_3SO_3); 2,85 (m, 1H, $H_{2'}$, $J_{2',1'}$= 8 Hz, $J_{2',3'}$= 5 Hz, $J_{2',2''}$= 16 Hz); 2,17 (dd, 1H, $H_{2''}$, $J_{2'',2'}$= 16 Hz, $J_{2'',1'}$= 2,5 Hz); 2,02-1,86 (m, 4H, $H_{5'}$, $H_{5'gem}$, $H_{6'}$, $H_{6'gem}$); 1,95 (s, 3H, CH_3); 1,33 (t, 6H, $[\underline{CH_3}CH_2O]_2PO$).

12: $[\alpha]_D^{20}$= +44° (c= 0,5, $CHCl_3$), **MS:** (I.C., m/z): 402 $(MH)^+$, **IR:** vmax ($CHCl_3$): 2100, 1690, 1260, 1060, 960 cm^{-1}

^{1}H RMN (400 MHz, $CHCl_3$): δ ppm: 9,08 (s, 1H, NH); 7,18 (s, 1H, H_6); 6,15 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 6,5 Hz); 4,18 (m, 4H, $[CH_3\underline{CH_2}O]_2PO$); 4,01 (dd, 1H, $H_{3'}$, $J_{3',4'}$= $J_{3',2'}$= 6 Hz); 3,85 (m, 1H, $H_{4'}$); 2,43 (m, 2H, $H_{2'}$, $H_{2''}$); 2,1-1,83 (m, 4H, $H_{5'}$, $H_{5'gem}$, $H_{6'}$, $H_{6'gem}$); 1,98 (s, 3H, CH_3); 1,36 (t, 6H, $[\underline{CH_3}CH_2O]_2PO$).

13: **MS:** (F.A.B., m/z): 346 $(MH)^+$

^{1}H RMN (200 MHz, D_2O): δ ppm: 7,1 (s, 1H, H_6); 5,98 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 6 Hz); 4,05 (m, 1H, $H_{3'}$), 3,75 (m, 1H, $H_{4'}$); 2,65, 2,28 (m, 2H, $H_{2'}$, $H_{2''}$); 1,7 (s, 3H, CH_3); 1,61 (m, 4H, $H_{5'}$, $H_{5'gem}$, $H_{6'}$, $H_{6'gem}$).

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