Tetrahedron Letters,Vol.30,No.19,pp 2567-2570,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CLEAVAGE OF A NUCLEOSIDIC OXETANE WITH CARBANIONS: SYNTHESIS OF A HIGHLY PROMISING CANDIDATE FOR ANTI-HIV AGENTS —— A PHOSPHONATE ISOSTERE OF AZT 5'-PHOSPHATE

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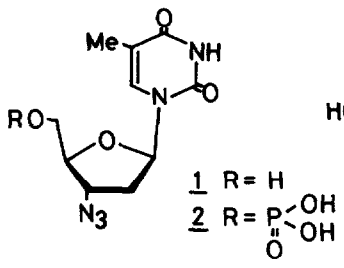
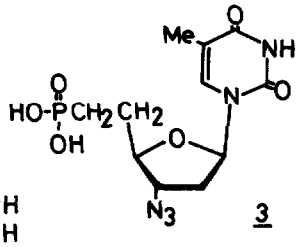
Summary A phosphonate analogue of 3'-azido-3'-deoxythymidine (AZT) 5'-phosphate was synthesized via nucleophilic ring-opening of a nucleosidic oxetane with $(RO)_2POCH_2Li$ as a key reaction step.

Since the finding that 3'-azido-3'-deoxythymidine (AZT, 1) is a chemotherapeutically effective nucleoside to the treatment of acquired immunodeficiency syndrome (AIDS),[1] many 2',3'-dideoxyribonucleosides have been synthesized and tested with the aim to develop more selective agents against human immunodeficiency virus (HIV).[2]

Most nucleoside analogues so far synthesized in this context are modified at either the base moiety or the 3'-position. As AZT is known to be converted to its 5'-phosphate (2) by cellular thymidine kinase and then to the triphosphate to act as a reverse-transcriptase inhibitor,[3] it appeared to us that a phosphonate analogue such as 3, which mimics 2, would be a highly promising candidate for the chemotherapy of AIDS.

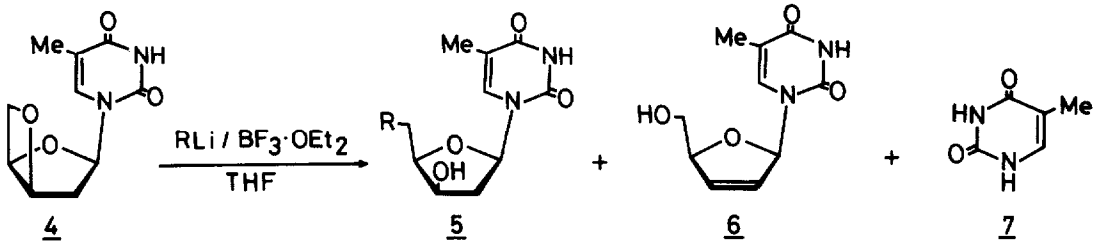




Though the Wittig reaction is well known as a method to effect C-C bond formation at the 5'-position of nucleosides,[4] we would like to report here a highly efficient alternative based on the cleavage of an oxetane ring with organolithiums,[5] which enabled us to synthesize 3.

1-(3,5-Anhydro-β-D-threo-pentofuranosyl)thymine (4), a nucleosidic oxetane, which can be readily prepared from thymidine[6] is obviously the most appropriate starting material for our present study.[7] Results of our preliminary experiments using 4 and simple organolithiums in combination with boron trifluoride etherate in THF are summarized in Table 1.

Although, in the reaction of MeLi (Run 1), the expected product (5a) was accompanied by a by-product (5b) resulting from LiBr in a commercially available ether solution of the reagent, neither the starting material (4) nor elimination products (6 and 7)[8] were detected. More basic alkyllithiums tend to



4 5 6 7

Scheme 1

5a R= Me, 5b R= Br
5c R= Bu
5d R= Bu-t, 5e R= H
5f R= Ph
5g R= C≡CSiMe$_3$

Table 1 Oxetane ring cleavage of 4 with RLi*

Run	R	Isolated yields of products (%)			
		4	5	6	7
1	Me	—	5a/5b=2/1	—	—
2	Bu	9	31	13	18
3	t-Bu	37	26	6/5e=2/3	27
4	Ph	—	92	—	—
5	C≡CSiMe$_3$	—	95	—	—

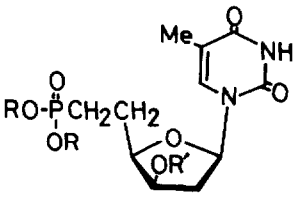
* The following commercially available solutions of organolithiums were used: MeLi/ether, BuLi/hexane, t-BuLi/pentane, and PhLi/ether-benzene. $Me_3SiC{\equiv}CLi$ was prepared from BuLi and $Me_3SiC{\equiv}CH$ in THF.

increase the extent of the elimination pathway (Runs 2 and 3). It seems likely that softer reagents encourage the addition reaction to 4, as can be seen from almost quantitative formations of 5f and 5g (Runs 4 and 5). A typical procedure is illustrated below by the preparation of 5f.

To a mixture of $BF_3{\cdot}OEt_2$ (0.32 ml, 2.5 mmol) and PhLi/ether-benzene (5.2 ml, 2.5 mmol) in THF (3 ml), a THF (5 ml) solution of 4 (112 mg, 0.5 mmol) was added dropwise under positive pressure of dry argon, while maintaining the temperature at below −70 °C. The resulting solution was stirred for 1 h and quenched with saturated aqueous $NaHCO_3$. The whole mixture was evaporated to dryness and chromatographed through a silica gel column. Elution with 1% EtOH in $CHCl_3$ gave 5f, which was crystallized from EtOH-H_2O to furnish an analytically pure sample (139 mg, 92%, mp 129-130 °C). Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.44; H, 6.28; N, 9.04. UV absorption in MeOH: max 267 nm (ε 10000), min 233 nm (ε 2100). MS m/z: 302 (M^+), 177 (M^+− B), and 126 (B+1). PMR ($CDCl_3$) δ: 1.91 (3H, d, 5-Me), 2.44 (2H, m, CH_2-2'), 3.16 (2H, d, CH_2-5'), 3.36 (1H, br, 3'-OH), 4.05 (1H, m, H-4'), 4.23 (1H, m, H-3'), 5.99 (1H, dd, J= 3.2 and 7.1 Hz, H-1'), 7.63 (1H, d, H-6), 9.45 (1H, br, NH).[9]

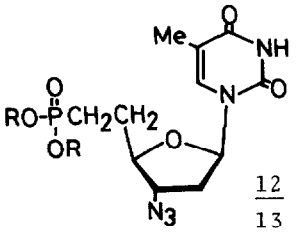
We also examined the amounts of $BF_3 \cdot OEt_2$ needed for this cleavage using PhLi. Quite interestingly, even the presence of 1 equiv of the Lewis acid gave rise to the formation of 5f in 71% yield, whereas the use of PhLi alone led to the complete recovery of 4.

On the basis of these results, our approach to 3 was initiated by the $BF_3 \cdot OEt_2$ mediated cleavage of 4 with lithium dimethyl methylphosphonate, $LiCH_2PO(OMe)_2$, which was prepared from the corresponding ester and BuLi in THF.[10] When 4 was treated with this lithiated species under similar conditions to the above, the desired phosphonate derivative 8 was obtained in 53% yield along with 4 (36%) and a highly polar by-product, which showed one negative charge on paper electrophoresis at pH 7.4. Replacement of the ester to diethyl methylphosphonate gave 9 in a higher yield of 73%.



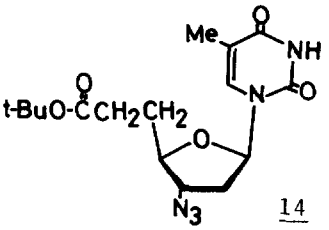
8 R= Me, R'= H
9 R= Et, R'= H
10 R= Me, R'= Ms
11 R= Et, R'= Ms

Subsequent treatment of 8 and 9 with MsCl in pyridine in the presence of DMAP gave 10 (77%) and 11 (84%), respectively, which were then converted to the 3'-azido derivatives 12 (55%) and 13 (77%) (1 equiv of NaN_3/DMF, 80 °C, 11 h). During the latter reaction, especially in the case of 10, it was observed that NaN_3 could bring about not only the desired S_N2 reaction at the 3'-position but also cleavage of the phosphonate ester moiety. Thus, only 24% yield of 12 was isolated when 3 equiv of the reagent were used in the reaction of 10. In a similar manner, starting from 4 and $LiCH_2CO_2Bu$-t, a carboxylate derivative (14) was also synthesized.



12 R= Me
13 R= Et

Finally, hydrolysis of 12 was carried out with TMSBr in DMF (40 °C, 5 h). An aqueous work-up followed by ion-exchange column chromatography furnished 3 in 93% yield as its disodium salt.[11]



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Optimization of the reaction conditions and preparation of 3's triphosphate analogue are currently under investigation and will be published elsewhere together with their anti-HIV activity.

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8) From a view point of the reported instability of 2',3'-didehydro-2',3'-dideoxyribonucleosides, we assume 7 would derive from 6: see ref. 6.

9) All new compounds involved in the present study gave physical data consistent with their structures.

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11) PMR (400 MHz) and IR data of 3 (disodium salt) are shown below. PMR (D_2O, DSS) δ: 1.57 (2H, m, CH_2-6'), 1.90 (3H, s, 5-Me), 1.91 (2H, m, CH_2-5'), 2.48 (2H, m, CH_2-2'), 3.96 (1H, m, H-4'), 4.23 (1H, m, H-3'), 6.19 (1H, t, J= 6.6 Hz, H-1'), 7.50 (1H, s, H-6). IR (KBr) ν: 2120 cm^{-1} ($-N_3$).

(Received in Japan 9 March 1989)