Tetrahedron Letters,Vol.28,No.31,pp 3623-3626,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NEW SCHEME FOR THE SYNTHESIS OF 5'-NUCLEOTIDE PHOSPHONATE ANALOGS

Nelly Sh. Padyukova, Marat Ya. Karpeisky, Lidiya I. Kolobushkina and Sergey N. Mikhailov*

Institute of Molecular Biology, the USSR Academy of Sciences, Vavilov str. 32, Moscow 117984, USSR

Abstract. A convenient and general method is proposed for the synthesis of 5'-nucleotide phosphonate analogs starting from 5-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranose (1).

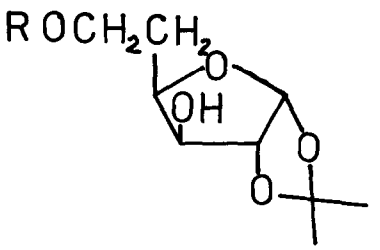
The unique properties of phosphonate analogs of the natural esters of phosphoric acid make them exceptionally well suited for being used in an ever increasing variety of applications. The substitution of the P-O-C fragment in substrate with P-CH_2-C creates an interesting class of compounds which effectively inhibit those enzymes whose substrates are esters of phosphoric acid and its derivatives[1].

The synthesis of phosphonate analogs of 5'- and 3'-nucleotides was reported by many authors[2-6]. Some of the 5'-nucleotide phosphonate analogs were prepared in the Wittig reaction starting from nucleoside 5'-aldehyde derivatives[2].

In the present work we propose a general method for the preparation of 5'-deoxy-5'-dihydroxyphosphinylmethylnucleosides. The method is based on the synthesis of a phosphonate-containing carbohydrate component produced in the Arbuzov reaction with the following glycosylation. The synthesis can be accomplished starting from D-xylo-hexofuranose or D-ribo-hexofuranose 5-deoxy-derivatives. Analysis of literature data implies that the method of homoxylose 1 synthesis developed by Whistler et al.[7] is the most effective one. The starting compound 1 can be prepared in 100 g quantities from D-glucose[7].

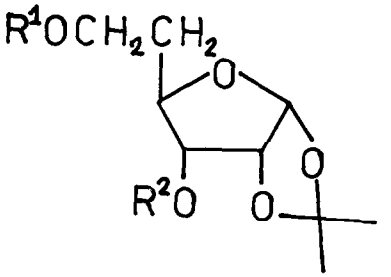
The following tritylation of 1 generated compound 2 in high yield. The configuration at C-3 was reversed using the standard procedure[8]: DMSO and Ac_2O for 1 hr at 70° followed by reduction with $NaBH_4$, the yield of ribo-hexofuranose 3 was 78 %. 5-Deoxy-1,2-O-isopropylidene-3-O-methylthiomethyl-6-O-trityl-α-D-xylo-hexofuranose was a by-product in this reaction.

The reversion of configuration (trasition 2 ⟶ 3) was accompanied by changes in the constants of spin-spin coupling in PMR spectra: $J_{2,3}$ = 0 Hz



1 R = H

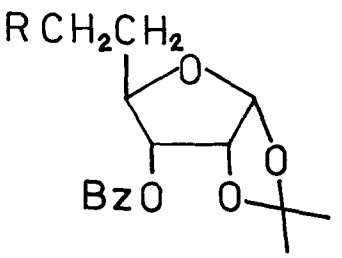
2 R = Tr



3 R^1 = Tr, R^2 = H

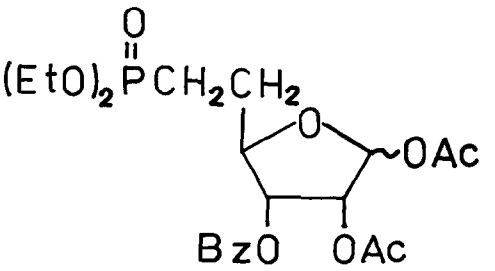
4 R^1 = Tr, R^2 = Bz

5 R^1 = H, R^2 = Bz

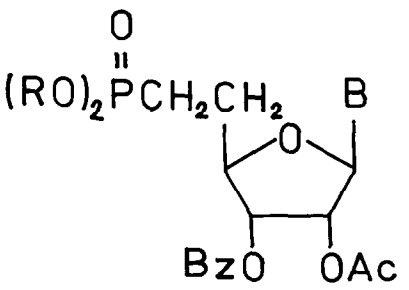


6 R = Br

7 R = P(O)(OEt)$_2$



8

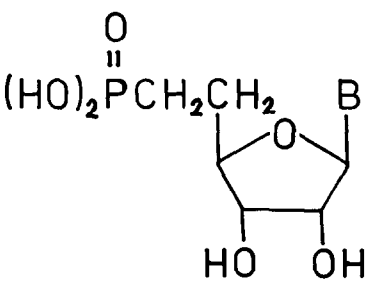


9 R = Et, B = Ura

10 R = Et, B = Ade^{Bz}

11 R = H, B = Ura

12 R = H, B = Ade^{Bz}



13 B = Ura

14 B = Ade

for xylo-derivatives 1 and 2 and $J_{2,3}$ = 4.7-5.1 Hz for their C-3 epimers. Benzoylation with a mixture of BzCN and NEt_3[9] in dioxane followed by detritylation with a 1M $SnCl_4$ solution in dichloroethane[10] produced 5 in high yield. It should be mentioned that derivatives 3-5 are convenient precursors for the preparation of homonucleosides. Bromination of 5 with a mixture of CBr_4 and Ph_3P in DMF[11] gave 6. Phosphonate 7 was synthesized in the Arbuzov reaction by boiling bromide 6 with $(EtO)_3P$, the PMR spectrum of 7 had proton signals from the protecting groups and PCH_2CH_2 group in the region 2.1-1.7 ppm. Acetolysis of phosphonate 7 generated a mixture of β and α anomers 8 at a ratio 2:1 which may be separated using silica gel column chromatography.

The use of bis-trimethylsilyluracil and $F_3CSO_2OSiMe_3$[12] as a catalyst in the reaction of glycosylation resulted in nucleotide 9 (30 %) and N-1-ethyluracil[13](36 %). A similar side reaction was reported earlier[6]. That is why bis-trimethylsilyluracil and bis-trimethylsilyl-N^6-benzoyladenine were glycosylated in the presence of $SnCl_4$[12]. The yields of protected nucleotides 9 and 10 were 83 % and 80 % respectively. The signals of ethyl groups were diastereotopic in the PMR spectra of 7-10[14].

The ethyl groups were selectively removed by treatment with Me_3SiBr in dichloroethane[5,15]. The resultant derivatives 11 and 12 can be used for the synthesis of oligonucleotides.

The PMR spectra of phosphonates 11 and 12 lacked proton signals from the ethyl groups, but showed signals from benzoyl and acetyl protecting groups. Elimination of these groups with an ammonia solution in methanol led to phosphonates 13[16] and 14[17] in high yields. Their UV spectra were identical with those of UMP and AMP, which confirmed the site of glycosylation.

All the steps in this synthesis have a high yield (78-95 %), which allows one to run 2-3 steps in succesion without isolating the products. This scheme is suitable for synthesizing the phosphonate analogs of 5'-nucleotides in preparative quantities and, being universal, has certain advantages over traditional approaches.

References and Notes.

1. R.Engel, Chem. Rev., 77, 349 (1977).
2. G.H.Jones and J.G.Moffatt, J. Am. Chem. Soc., 90, 5337 (1968).
3. A.Hampton, F.Kappler and F.Perini, Bioorg. Chem., 5, 31 (1976).
4. H.P.Albrecht, G.H.Jones and J.G.Moffatt, Tetrahedron, 40, 79 (1984).
5. A.Mazur, B.E.Tropp and R.Engel, Tetrahedron, 40, 3949 (1984).
6. M.Morr, L.Ernst and L.Grotjahn, Z. Naturforsch., 38B, 1665 (1983).
7. R.E.Gramera, T.R.Ingle and R.L.Whistler, J. Org. Chem., 29, 207 (1964).

8. J.D.Stevens in "Methods in Carbohydrate Chemistry", vol. VI, p.123, Academic Press, New York, London, 1972.
9. A.Holý and M.Souček, Tetrahedron Lett., 185 (1971).
10. L.N.Beigelman, B.S.Ermolinsky, G.V.Gurskaya, E.N.Tsapkina, M.Ya.Karpeisky and S.N.Mikhailov, Carbohydr. Res., (1987).
11. J.P.H.Verheyden and J.G.Moffatt, J. Org. Chem., 37, 2289 (1972).
12. H.Vorbrüggen in "Nucleoside Analogues. Chemistry, Biology and Medical Applications", NATO ASI Series A, vol. 26, p. 35, Plenum Press, New York, London, 1980.
13. M.p. 146-147°. Reported m.p. 146-147.5°: T.Tanabe, K.Yamauchi and M.Kinoshita, Bull. Chem. Soc. Japan, 50, 3021 (1977).
14. For example, 100 MHz PMR spectrum of compound 9 ($CDCl_3$): δ 8.60 bs (1H, NH), 8.01-7.91 m (2H, Bz), 7.54-7.30 m (3H, Bz), 7.22 d (1H, $J_{6,5}$ 8.0, 6-H), 5.92 d (1H, $J_{1',2'}$ 4.8, 1'-H), 5.73 dd (1H, $J_{5,6}$ 8.0, $J_{5,NH}$ 2.0, 5-H), 5.41 dd (1H, $J_{2',1'}$ 4.8, $J_{2',3'}$ 6.0, 2'-H), 5.33 dd (1H, $J_{3',2'}$ 6.0, $J_{3',4'}$ 5.0, 3'-H), 4.20 m (1H, 4'-H), 4.08 dq (2H, $J_{H,Me}$ 7.0, $J_{H,P}$ 8.0, $POCH_2Me$), 4.07 dq (2H, $J_{H,Me}$ 7.0, $J_{H,P}$ 8.0, $POCH_2Me$), 2.14-1.73 m (4H, PCH_2CH_2), 2.01 s (3H, Ac), 1.30 t (3H, J_{H,CH_2} 7.0, $POCH_2Me$), 1.29 t (3H, J_{H,CH_2} 7.0, $POCH_2Me$).
15. T.Morita, Y.Okamoto and H.Sakurai, Bull. Chem. Soc. Japan, 51, 2169 (1978).
16. 100 MHz PMR spectrum of compound 13 (D_2O): δ 7.56 d (1H, $J_{6,5}$ 8.0, 6-H), 5.88 d (1H, $J_{5,6}$ 8.0, 5-H), 5.84 d (1H, $J_{1',2'}$ 4.8, 1'-H), 4.45-4.00 m (3H, 2',3',4'-H), 2.14-1.80 m (4H, PCH_2CH_2). ^{31}P NMR (D_2O): +23.0 (external 85 % H_3PO_4).
17. 100 MHz PMR spectrum of compound 14 (D_2O): δ 8.31 s (1H, 8-H), 8.22 s (1H, 2-H), 6.05 d (1H, $J_{1',2'}$ 6.0, 1'-H), 4.70-4.20 m (3H, 2',3',4'-H), 2.20-1.53 m (4H, PCH_2CH_2). ^{31}P NMR (D_2O): +24.8 (external 85 % H_3PO_4)

(Received in UK 26 May 1987)