Pergamon

Tetrahedron Letters, Vol. 36, No. 24, pp. 4237-4240, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00731-8

Synthesis of Diimidotriphosphoric Acid and Related Esters

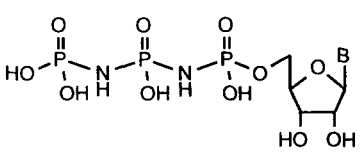
Mourad Saady, Luc Lebeau and Charles Mioskowski

Université Louis Pasteur
Laboratoire de Synthèse Bioorganique associé au CNRS - Faculté de Pharmacie
74, route du Rhin - BP 24 - 67401 Illkirch - France

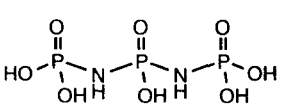
Abstract: The synthesis of diimidotriphosphoric acid and a series of regioselectively protected esters is described. This opens an unprecedented route for the preparation of various nucleotide and dinucleotide analogs and related compounds.

Till the early sixties, much attention has been paid to phosphate-modified nucleotide analogs. Organic chemists have synthesized a series of these compounds that already allowed certain key questions to be answered concerning the role of nucleotides in many biological processes. The first phosphate-modified nucleotide to be prepared was adenylyl methylene diphosphonate (AMP-PCP) and later on, a number of mono- and bis-methylene triphosphate analogs and related haloderivatives have been synthesized and their biological properties studied.[1] However the structural characteristics of the P-C-P group are substantially different from that of the pyrophosphate they replace so that often these analogs are ineffective as substrates, effectors or inhibitors. Other structural modifications of the triphosphate sequence aimed to better mimic the steric, electronic and ionization characteristics of the natural occurring pyrophosphate chain. They led to thiophosphates and β,γ-imido analogs of nucleotide triphosphates.[2,3]

The later compound series (nucleoside-PPNP) showed very interesting biological properties so that we were naturally tempted to investigate toward α,β–β,γ-bis imidotriphosphate compounds **1** (Figure 1).



1



2

Figure 1

Up to now there is no report in the literature on the synthesis of a linear P-N-P-N-P sequence. Here we wish to describe an original synthetic pathway for the preparation of diimidotriphosphoric acid **2** and some of its esters, providing a straightforward access to the synthesis of P-N-P-N-P-nucleosides.[4] Elaboration of the linear P-N-P-N-P skeleton was realized starting from *o*-xylenediamine **3**[5] that was phosphorylated with dibenzyl chlorophosphate (Figure 2).

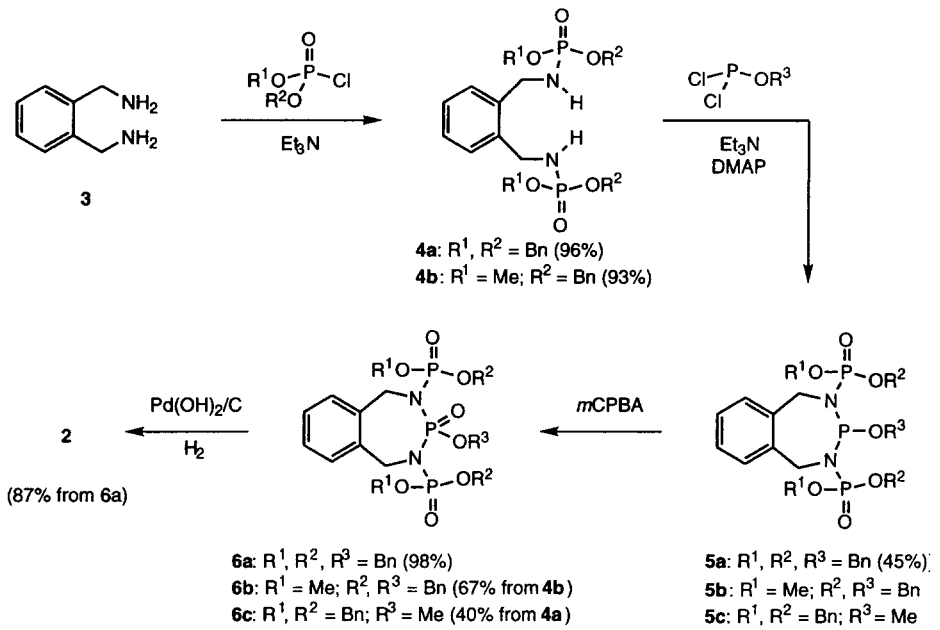


Figure 2

Cyclization of the resulting bis-phosphoramide **4a** was achieved using benzyl dichlorophosphite and gave **5a** that was oxidized as **6a**. Catalytic hydrogenation of **6a** using the Pearlman catalyst[6] in *t*BuOH/water 1:1 under hydrogen pressure (70 psi) afforded diimidotriphosphoric acid **2**.[7]

Regioselectively monodeprotected precursors of **2** could be prepared from compounds **6b** and **6c** using differently substituted chlorophosphates and dichlorophosphites (Figure 3).[8]

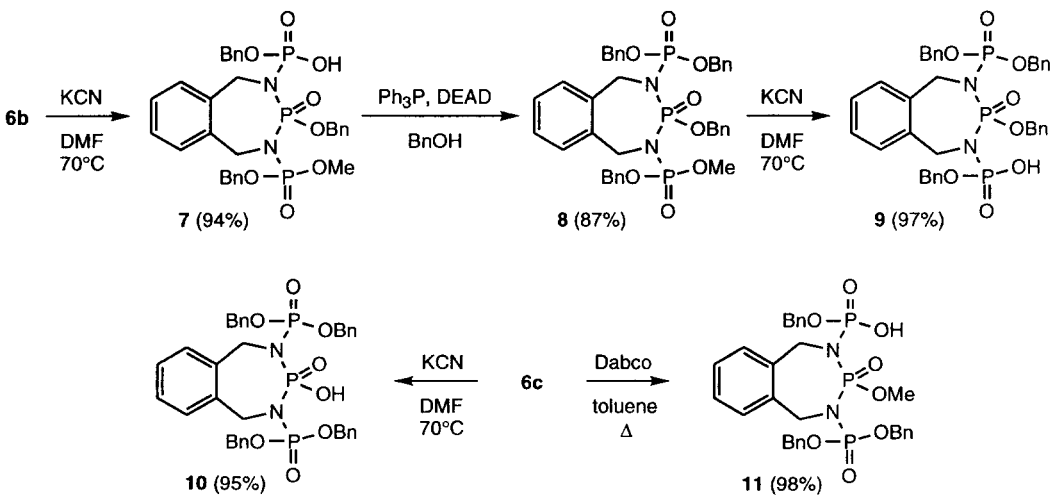


Figure 3

In conclusion, diimidotriphosphoric acid **2** provides a rapid access to P-N-P-N-P-nucleosides extrapolating well established procedures.[1a,9] More interesting are compounds **7**, **9**, **10** and **11**[10] that allow multiple regioselective esterification with nucleosides or any other aglycone moiety (Figure 4). This opens an unprecedented route to a series of new substances, like nucleotide and dinucleotide analogs and related compounds for example. The different chemical transformations can be realized in classical organic solvents without any solubility problems generally met with non-protected polyphosphate analog species and final removal of remaining benzyl groups can be performed by catalytic hydrogenation.

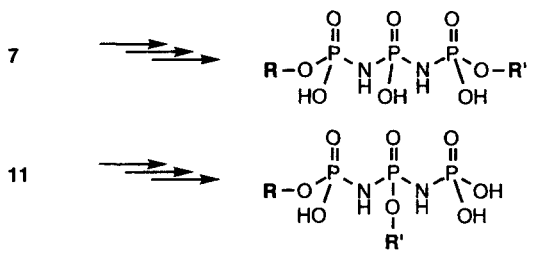


Figure 4

Acknowledgment: This work was supported in part by a grant from Association pour la Recherche sur le Cancer.

References:

(1) For a review see : a) Engel, R. *Chem. Rev.* **1977**, *77*, 349-367. b) Blackburn, G.M. *Chem. & Ind.* **1981**, 134-138.

(2) a) Eckstein, F.; Goody, R.S. *Biochemistry* **1976**, *15*, 1685-1691. b) Eckstein, F. *Ann. Rev. Biochem.* **1985**, *54*, 367-402. c) Ludwig, J.; Eckstein, F. *J. Org. Chem.* **1991**, *56*, 1777-1783.

(3) Yount, R.G.; Babcock, D.; Ballantyne, W.; Ojala, D. *Biochemistry* **1971**, *10*, 2484-2489.

(4) a) Saady M., Lebeau L., Mioskowski C. "Analogues stables, non-hydrolysables, de diphosphates ou de triphosphates et leurs procédés de fabrication". **Fr. 94 08091**, june 30, 1994. b) Lebeau, L.; Saady, M.; Mioskowski, C.; Grassi, J.; Pradelles, P.; Creminon, C. "Conjugués d'analogues de diphosphates ou triphosphates avec des enzymes ou des porteurs antigéniques et dosage immunologique utilisant de tels conjugués". **Fr. 94 08086**, june 30, 1994.

(5) a) Ing, H.; Manske, H. *J. Chem. Soc.* **1926**, 2348. b) Brasted, R.C.; O'brien, T.D.; Heino, W.L. *Inorg. Chem.* **1964**, *3(4)*, 503-505. c) Gibson, M.S.; Bradshaw, R.W. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 919-930. d) Analytical data of *o*-xylenediamine have never been reported: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.34-7.22 (4 H, m); 3.91 (4 H. s); 2.16 (4 H. s). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 140.50; 128.56; 127.25; 43.88.

(6) Pearlman, M.W. *Tetrahedron Lett.* **1967**, 1663-1664.

(7) Selected analytical data. **4a**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.32-7.15 (24 H, m); 4.93 (8 H, AB part of ABX syst., J_{AB}=11.8, J_{AX}=7.5, J_{BX}=7.5 Hz, υ_A=4.98, υ_B=4.88); 4.06-3.96 (6 H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 137.21 (d, J=6.2 Hz); 136.33 (d, J=7.3 Hz); 129.10; 128.24; 127.93; 127.58; 67.79 (d, J=5.1 Hz); 42.24. ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 9.72 (s). **4b**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.40-7.11 (14 H, m); 4.96 (8 H, AB part of ABX syst., J_{AB}=11.7, J_{AX}=7.7, J_{BX}=8.6 Hz, υ_A=5.01, υ_B=4.91); 4.14-4.04 (4 H, m); 3.64 (3 H, d, J=11.3 Hz); 3.56-

3.50 (2 H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 137.25 (d, *J*=6.4 Hz), 136.45 (d, *J*=7.3 Hz); 129.13; 128.44; 128.17; 128.00; 127.74; 67.95 (d, *J*=4.9 Hz); 53.07 (d, *J*=5.5 Hz); 42.42. ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 10.65 (s). **5a**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.37-7.09 (29 H, m); 5.25-4.79 (10 H, m); 4.61 (2 H, dd, *J*=6.5, *J*=11.6 Hz); 4.12 (2 H, m). ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 8.36 (2 P, s); 7.51 (1 P, s). **6a**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.29-7.08 (29 H, m); 5.04 (2 H, d, *J*=7.5 Hz); 4.99-4.83 (8 H, m); 4.81-4.52 (4 H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 135.84; 135.67; 135.06; 128.92; 128.44; 128.40; 128.28; 128.00; 127.91; 127.83; 69.16; 69.09; 68.83; 49.01. ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 8.11 (1 P, t, *J*=18.9 Hz); 4.09 (2 P, d, *J*=18.9 Hz). **6b** (mixture of diastereomers): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.50-7.14 (19 H, m); 5.44-4.46 (10 H, m); 3.68, 3.63, 3.56 and 3.44 (6 H, 4d, *J*=11.8 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 135.97-135.11 (m); 129.01-128.90 (m); 128.5-127.73 (m); 69.15-68.88 (m); 54.10, 54.04, 53.85 and 53.80 (4d, *J*=5.3 Hz); 48.96 (m). ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 8.15, 7.67, 7.09 and 7.18 (1 P, 4t, *J*=17.6, 19.1, 18.1 and 18.1 Hz resp.); 5.38, 5.36, 5.32 and 5.26 (2 P, 4d, *J*=18.1, 19.1, 17.6 and 18.1 Hz resp.). **6c**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.35-6.81 (24 H, m); 5.03 (4 H, *AB part of ABX syst.*, J_{AB}=11.8, J_{AX}=7.9, J_{BX} = 7.7 Hz, υ_A=5.08, υ_B=4.99); 4.86 (4 H, m); 4.77-4.47 (4 H, td, *J*=31.0, *J*=16.3 Hz); 3.69 (3 H, d, *J*=11.7 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 135.90 (d, *J*=7.5 Hz); 135.69 (d, *J*=7.9 Hz); 135.05; 128.85; 128.38; 128.32; 128.25; 128.19; 127.95; 127.79; 69.11 (d, *J*=5.7 Hz); 68.88 (d, *J*=5.5 Hz); 53.86 (d, *J*=5.5 Hz); 48.91. ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 9.25 (1 P, t, *J*=18.9 Hz); 4.14 (2 P, d, *J*=18.9 Hz). **2**: ^{31}P-NMR (D_2O/H_3PO_4, 81.015 MHz) δ 4.01 (2 P, m); 0.23 (1 P, m). MS (FAB$^-$, TEA): 254.9 [M-H$^-$].

(8) Selected analytical data. **7** (mixture of diastereomers): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 11.32 (1 H, s broad); 7.44-7.05 (19 H, m); 5.37-4.40 (10 H, m); 3.63-3.28 (3 H; m). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 135.86-134.80 (m); 128.97-127.51 (m); 69.02-68.29 (m); 54.07; 48.83-48.40 (m). ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 11.19-10.83 (m); 9.46-7.76 (m); 7.03-5.85 (m); 5.54-5.04 (m); 4.85-3.13 (m); 2.70-2.41 (m); 1.57-1.42 (m). **8** (mixture of diastereomers): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.31-7.26 (24 H, m); 5.08-4.86 (12 H, m); 3.60 and 3.48 (3 H, 2d, *J*=11.5 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 136.01; 135.81; 135.65; 135.35; 135.19; 135.07; 133.87; 132.21; 132.01; 128.99; 128.91; 128.57; 128.43; 128.37; 128.33; 128.30; 128.24; 128.09; 128.00; 127.90; 127.84; 69.21; 69.10; 69.03; 68.99; 68.93; 68.88; 53.98; 53.87; 53.32; 48.95. ^{31}P-NMR ($CDCl_3/H_3PO_4$, 81.015 MHz) δ 8.12-7.26 (1 P, m); 5.50-5168 (1 P, m); 4.15-3.60 (1 P, m). **9** (mixture of diastereomers): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.37-7.01 (24 H, m); 5.12-4.82 (8 H, m); 4.80-4.57 (4 H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 135.93-134.81 (m); 128.87-127.19 (m); 69.32-68.33 (m); 48.83-48.48 (m). ^{31}P-NMR ($CDCl_3$, 81.015 MHz) δ 11.88 and 10.47 (1 P, 2 t, *J*=19.7 Hz); 5.72 and 3.81 (1 P, 2 d, *J*=20.4 Hz); -0.05 and -0.96 (1 P, 2 d, *J*=19.7 Hz). **10**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.26-7.03 (24 H, m); 4.90 (8 H, *AB part of ABX syst.*, J_{AB}=11.7, J_{AX} =5.6, J_{BX}=8.0 Hz, υ_A=4.91, υ_B=4.86); 4.66 (4 H,*t* , *J*=15.2 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 135.38; 135.22; 135.07; 129.07; 128.37; 128.32; 127.88; 69.06 (d, *J*=5.2 Hz); 48.69. ^{31}P-NMR ($CDCl_3$, 81.015 MHz) δ 6.36 (1 P, *t*, *J*=23.4 Hz); 4.57 (2 P, *d*, *J*=23.4 Hz).

(9) Myers, T.C.; Nakamura, K.; Danielzadeh, A.B. *J. Org. Chem.* **1965**, *30*, 1517-1520.

(10) Saady, M.; Lebeau, L.; Mioskowski, C. *J. Org. Chem.* **1995** (in press).

(*Received in France* 16 *March* 1995; *accepted* 12 *April* 1995)