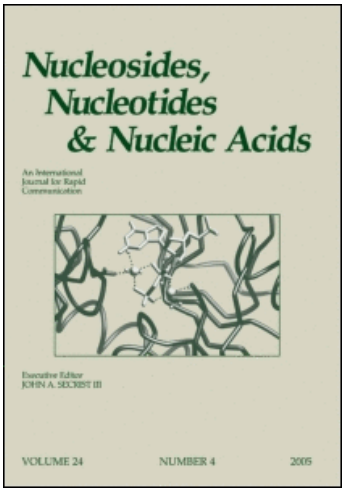

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STEREOSPECIFIC SYNTHESIS OF P-CHIRAL DI(2'-O-DEOXYRIBONUCLEOSIDE)METHANEPHOSPHONATES

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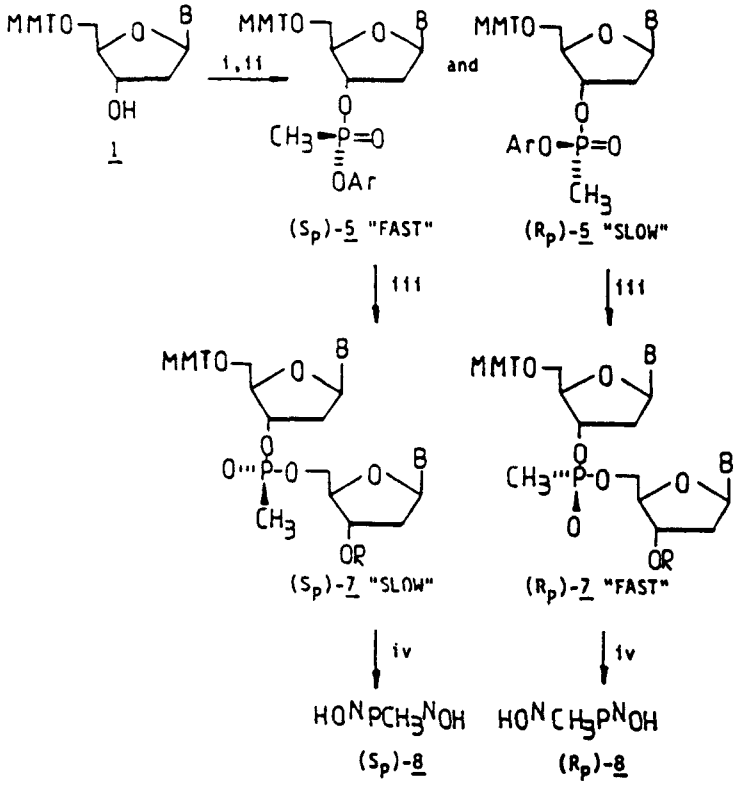
ABSTRACT: Using monomeric 5'-O-monomethoxytrityl(2'-O-deoxyribonucleoside) 3'-O-[O-(4-nitrophenyl)]methanephosphonate of defined absolute configuration at phosphorus and suitably 3'-protected-5'-activated nucleoside components, both (Rp)- or (Sp)-isomers of four di(2'-O-deoxyribonucleoside) methanephosphonates were prepared.

It has been reported that nucleophilic substitution at phosphorus in 5'-MMT-thymidine 3'-[O-(4-nitrophenyl)]methanephosphonate (5,B=Thy) is stereospecific and under appropriate conditions diastereoisomerically pure di-, tri-, and tetra(thymidine methanephosphonates) of predetermined sense of chirality of P-atom can be obtained in multimiligram quantities[1]. In this communication we wish to present further results on the synthesis of 5'-protected deoxyadenosine-, deoxycytidine- and deoxyguanosine-3'-[O-(4-nitrophenyl)] methanephosphonates, (5, B=Ade, Cyt and Gua), respectively, their separation into diastereoisomerically pure compounds, an assignment of absolute configuration at phosphorus, and, finally, the synthesis of diastereoisomerically pure di(deoxyadenylyl)-, di(deoxycytidylyl)- and di(deoxyguanosinylyl)-(3',5')-methanephosphonates (8,B=Ade,Cyt and Gua) respectively.

Since the reaction of 5'-MMT-deoxyadenosine (1,B=Ade), 5'-MMT-deoxycytidine (1,B=Cyt) and 5'-MMT-deoxyguanosine (1,B=Gua) with [O-(4-nitrophenyl)]methanephosphonochloridate (2) designed as new phosphonylating agent for 5(B=Thy) synthesis was inefficient, compound 5(B=Ade) was



i/ $(4\text{-}NO_2C_6H_4O)(CH_3)P(O)Cl$/pyridine (2) or
$(4\text{-}NO_2C_6H_4O)(CH_3)P(O)BT$/THF (3) or
$(4\text{-}NO_2C_6H_4O)(CH_3)P(O)T/CH_3CN$ (4)
ii/ separation of diastereisomers
iii/ 6:T_{Ac},dA_{TBDMS},dC_{TBDMS},dG_{TBDMS}/C_5H_5N/ t-BuMgCl
iv/ 1M TBAF/THF followed by 80% AcOH

B = Thy, Ade, Cyt, Gua
R = Ac(B=Thy),TBDMS(B=Ade, Cyt, Gua)
Ar= $4\text{-}NO_2C_6H_4$-
BT=1-hydroxybenzotriazolyl
T = triazolyl

obtained via methanephosphonylation of 1(B=Ade) with prepared *in situ* [O-(4-nitrophenyl)-O-(1-benzotriazolyl)] methanephosphonate (3), while compounds 5(B=Cyt) and 5(B=Gua) were prepared via methanephosphonylation of 1(B=Cyt) and 1(B=Gua) with prepared *in situ* [O-(4-nitrophenyl)]methanephosphonotriazolidate (4). Corresponding compounds 5(B=Ade,Cyt and Gua) were obtained as a mixture of Rp and Sp-diastereoisomers in 45, 43 and 73 percent yield, respectively. Separation of diastereoisomers was feasible by means of silica gel column chromatography with eluting systems 3% CH_3OH in $CHCl_3$ (v/v) for 5(B=Ade) and 5(B=Cyt), and $CH_3COOH/CH_3OH/CHCl_3$ (0.3:0.3:10, v/v) for 5(B=Gua), respectively.

	Monomers (5)							Dimers (7)							
B	Configuration	TLC [Rf]	UV [nm]^{e} λ_{max}	λ_{min}	^{31}P NMR^{f} [ppm]	^{1}H NMR^{f} P-CH$_3$ δ[ppm]	J[Hz]	Yield^{a} [%]	Configuration	HPTLC [Rf]	UV [nm]^{e} λ_{max}	λ_{min}	^{31}P NMR^{f} [ppm]	^{1}H NMR^{f} P-CH$_3$ δ[ppm]	J[Hz]	HPLC^{g} [Rt] [min]	Yield [%]
Thy	Sp	0.48^{b}	269	248	28.65	1.69	17.7	53	Sp	0.12^{b}	264	245	31.72	1.57	17.6	12.59	66
	Rp	0.38^{b}	272	248	29.81	1.75	17.8		Rp	0.16^{b}	265	245	32.14	1.49	17.5	11.84	66
Ade	Sp	0.39^{b}	263	246	28.99	1.78	17.7	45	Sp	0.35^{c}	259	241	31.87	1.49	17.6	12.07	50
	Rp	0.34^{b}	262	245	28.97	1.73	17.7		Rp	0.37^{c}	258	241	31.83	1.49	17.6	10.94	50
Cyt	Sp	0.24^{b}	270	252	29.15	1.77	17.7	43	Sp	0.07^{c}	272	255	32.34	1.52	17.1	7.44	60
	Rp	0.17^{b}	272	251	29.34	1.71	17.2		Rp	0.16^{c}	271	255	32.41	1.52	16.9	7.44	60
Gua	Sp	0.56^{c}	257	-	29.11	1.71	17.7	74	Sp	0.53^{d}	256	-	31.94 (CsDsN)	1.80	17.6	7.30	20
	Rp	0.46^{c}	257	-	29.03	1.80	17.7		Rp	0.61^{d}	253	-	33.96 (CsDsN)	1.85	16.8	7.30	17

a) yield of FAST + SLOW isomers;
b) developing system: 6% MeOH in $CHCl_3$;
TLC was performed on silica gel 60 F_{254} plates (MERCK), HPTLC was performed on silica gel 60 F_{254} plates (MERCK)
c) developing system: 10% MeOH in $CHCl_3$
d) developing system: 10% H_2O in CH_3CN
e) in 96% C_2H_5OH
f) in $CDCl_3$ (except $G_{PH_2}G$)
g) Rt parameters for 3'- and 5'-deprotected compounds 8, ODS hypersil 5μ, 4.6/300mm column, gradient 5-20% CH_3CN in 0.1 M TEAB; 1.0% CH_3CN/min.

Assignment of absolute configuration at phosphorus in diastereoisomers 5(B=Ade,Cyt and Gua) like in the case of diastereoisomers of 5(B=Thy), was possible via 5'-deprotection of 5, and the conversion of resulting nucleoside 3'-[O(4-nitrophenyl)] methanephosphonate to nucleoside (3',5') cyclic methanephosphonates, which is stereospecific and occurs with inversion of configuration[2]; since the absolute configuration at P-atom in cyclic methanephosphonates could be determined by means of ^{31}P NMR[3,4], the stereochemical correlation allowed us to assign the absolute configuration in diastereoisomers of 5(B=Ade,Cyt,Gua).

Each diastereoisomer of 5(B=Ade) was reacted with 3'-(t-butyl dimethylsilyl)deoxyadenosine 6(B=Ade), while diastereoisomers of 5(B=Cyt,Gua), were exposed on the reaction of 3'-(t-butyldimethylsilyl)-deoxycytidine 6(B=Cyt) or -deoxyguanosine 6(B=Gua), respectively. t-Butyl magnesium chloride, as originally proposed by Hayakawa[5], was used for activation of 5'-hydroxyl function of nucleosides. Compounds 7 were obtained as diastereoisomerically pure species and were characterised by means of TLC, UV, ^{31}P- and ^{1}H-NMR. After deprotection by means of 1M TBAF/THF and 80% CH_3COOH diastereoisomers of 8 were isolated and characterised by means of HPLC (see TABLE).

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