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New Stereospecific Method of Synthesis of [Sp]- and [Rp]-Dinucleoside-(3′,5′) Methanephosphonates

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Summary: Using a stereoretentive reaction between diastereomerically pure 5′-*O*-DMT-(*N*-protected) nucleoside 3′-*O*-(*Se*-methyl methanephosphonoselenolate)s and 3′-*O*-acetyl-(*N*-protected) nucleosides, diastereomerically pure dinucleoside-(3′,5′) methanephosphonates as well as "all-*Rp*" and "all-*Sp*" trimers, tetramers, and pentamers were synthesized.

"Antisense mRNA" oligo(nucleoside methanephosphonate)s (Oligo-Me) are oligonucleotides of 12–15 bases in length where each internucleotide phosphate is replaced by the methanephosphonate function.[1] Unlike native oligonucleotides, Oligo-Me are nonionic, and their enhanced lipophilicity should facilitate their inter- and extracellular transport.[2] Moreover, as neutral molecules they may be expected to interact with cellular proteins less indiscriminately than phosphorothioates or natural oligonucleotides while maintaining their desired interaction with target mRNA sites comparable with that of natural oligonucleotides.[3] Although the examples of potential protection of cells against viral infections caused by Oligo-Me are numerous, the detailed mechanism of their action still remains obscure.[4]

The complexity of the studies on the molecular mechanism of inhibition of "viral" genes or oncogenes is complicated by the fact that, in all biological tests performed until now, diastereomeric mixtures of the Oligo-Me have been used; moreover, their diastereomeric composition was unknown. All except one of the reported cases in the literature methods of synthesis of Oligo-Me are not stereospecific.[5] Oligo-Me, bearing n methanephosphonate linkages, are composed of 2^n-diastereomers. Each diastereomer is characterized by its own chirality,[6] the property of the molecule which is essential for recognition and interaction with target mRNA and other biomolecules. So far, definitive evidence as to which particular diastereomer, or which population thereof, with predetermined sense of chirality, [*Rp*]- or [*Sp*]-, exerts the most profound desired inhibitory effect on the biosynthesis of "unwanted" proteins, does not exist. The pioneering work of Miller et al. has demonstrated that

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affinities of dodecamers, modified at every second juxtaposed position with methanephosphonate of predetermined sense of chirality, toward complementary oligonucleotides differ notably.[7]

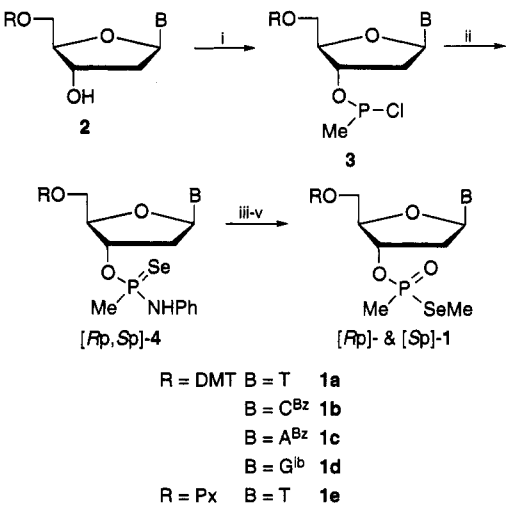
Leśnikowski et al. proved for the first time that the T_m of the heteroduplex formed by [all-but one-*R*p]-octa(thymidine methanephosphonate) and pentadecaadenylic acid is three times higher than for the heteroduplex consisting of the "random mixture" of 128 diastereomeric octa(thymidine methanephosphonate)s and the same template.[8] There is an increasing body of evidence that the interactions between Oligo-Me and DNA or mRNA are dependent on linkage configuration and that the [*R*p]-configuration at each methanephosphonate function is crucial for high stringency of hybridization and maximization of heteroduplex stability,[9] a crucial factor influencing the therapeutic potency of oligonucleotides. Therefore, the problem of practical stereocontrolled synthesis of Oligo-Me is a major challenge for organic chemists and has been the subject of numerous reports.

Engels demonstrated that the formation of dinucleoside methanephosphonates *via* condensation of 3′-OH and 5′-OH nucleosides with methyldichlorophosphine, followed by oxidation, is a partially stereoselective process and that the stereoselectivity depends on the temperature of condensation and the base composition.[10]

The condensation of 5′-*O*-[4,4′-dimethoxytrityl(DMT)]-nucleoside 3′-*O*-(*N*,*N*-diisopropylmethanephosphonoamidites) with 5′-OH nucleosides is also partially stereoselective, albeit the use of diastereomerically pure substrates indicated that the process of condensation is accompanied by partial epimerization at phosphorus.[11] This result of Lebedev et al. was not unexpected since, as it was demonstrated earlier in the case of diastereomerically pure 5′-*O*-DMT-*N*-benzoylcytidine 3′-*O*-(*O*-methyl-*N*,*N*-diisopropylphosphoroamidite), an excess of tetrazole causes the epimerization *via* phosphorotetrazolidite intermediates.[12] So far, the most successful strategy was based on the condensation of 5′-*O*-(4′-monomethoxytrityl)-nucleoside 3′-*O*-(*O*-4-nitrophenyl methanephosphonate)s with 3′-*O*-protected nucleosides, catalyzed by *tert*-butylmagnesium chloride.[13] Stereoregular tetramers and pentamers were obtained by this method.[14] The above approach was also successful when the *p*-nitrophenoxide leaving group was replaced by 1,1,1,3,3,3-hexafluoro-2-propanoxylate.[15]

In this report we wish to present our results applying a similar strategy of stereocontrolled synthesis of Oligo-Me[13] based on 5′-*O*-DMT-(*N*-protected) nucleoside 3′-*O*-(*Se*-methyl methanephosphonoselenolate)s (**1**) as monomeric substrates. Compounds **1** were obtained according to the sequence of reactions depicted in Scheme 1.

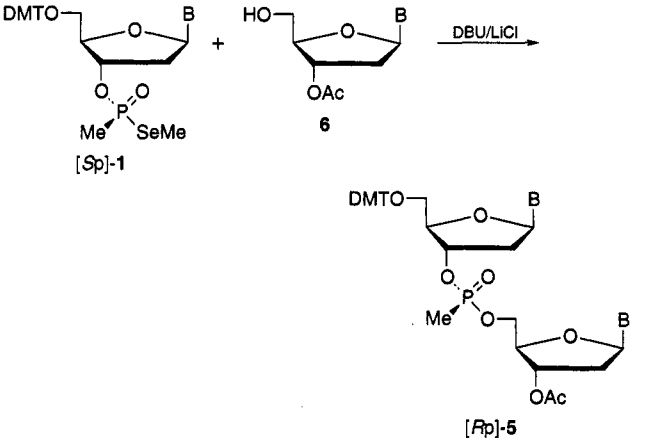
Scheme 1[a]



R = DMT B = T **1a**
B = C^{Bz} **1b**
B = A^{Bz} **1c**
B = G^{ib} **1d**
R = Px B = T **1e**

[a] Key: (i) $MePCl_2$, THF, −40 °C, Et_3N; (ii) aniline, selenium, rt; (iii) NaH/DMF, CO_2, rt; (iv) MeI, CH_2Cl_2, rt; (v) separation of diastereomers, Merck Kieselgel 60, $CHCl_3$–MeOH (1–5%).

Scheme 2[a]



[a] Reaction conditions: **6** (1 equiv, 0.2 M in pyridine, rt); **1** SLOW-[*S*p] or FAST-[*R*p] (1.5–2 equiv), DBU (10 equiv), LiCl (10 equiv).

Table 1

substrate **1**[a]	dimer **5**	config	yield[b] (%)	^{31}P NMR (ppm)
1a-SLOW	$T_{PMe}T^c$	FAST [*R*p]	92	33.00
1a-FAST		SLOW [*S*p]	86	33.14
1b-SLOW	$C^{Bz}{}_{PMe}C^{Bz}$	FAST [*R*p]	80	32.98
1b-FAST		SLOW [*S*p]	60	33.06
1c-SLOW	$A^{Bz}{}_{PMe}A^{Bz}$	FAST [*R*p]	40	32.57
1c-FAST		SLOW [*S*p]	45	32.71
1d-SLOW	$G^{ib}{}_{PMe}G^{ib}$	FAST [*R*p]	65	33.13
1d-FAST		SLOW [*S*p]	30	33.33
1a-SLOW	$T_{PMe}G^{ib}$	FAST [*R*p]	70	33.11
1a-FAST		SLOW [*S*p]	93	33.17

[a] Diastereomeric purity was higher than 99%, as estimated by ^{31}P and ^{1}H NMR. [b] After column chromatography, silica gel 230–400 mesh, gradient 0–5% MeOH in $CHCl_3$. Yields have not been optimized. [c] PMe: methanephosphonate internucleotide bond.

The condensation of appropriate 5′-*O*-DMT-*N*-protected nucleosides (except thymidine) **2** with methyldichlorophosphine gave 5′-*O*-DMT-nucleoside 3′-*O*-methanephosphonochloridites **3**, which without isolation were condensed with aniline in the presence of elemental

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Table 2

compd[a]	absolute config	FAB-MS [M − H]⁻	^{31}P NMR (ppm)	HPLC[b]
$T_{PMe}G$ (**5**)	*Rp*	983, 984	32.11	5.17
	Sp	983, 984	33.51	6.15
$C_{PMe}T_{PMe}G$ (**7**)	*Rp*,*Rp*	1373, 1374	32.80, 32.07	15.13
	Sp,*Sp*	1374, 1375	33.87, 33.75	17.19
$C_{PMe}C_{PMe}T_{PMe}G$ (**8**)	*Rp*,*Rp*,*Rp*	1764, 1765	33.54, 33.36, 33.30	18.94
	Sp,*Sp*,*Sp*	1764, 1765	33.72, 33.54, 33.44	20.59
$T_{PMe}C_{PMe}C_{PMe}T_{PMe}G$ (**9**)	*Rp*,*Rp*,*Rp*,*Rp*	2024.1, 2025.0 [M − Ac]⁻	32.72,[c] 32.82, 33.22[e]	21.35
	Sp,*Sp*,*Sp*,*Sp*	2024.7, 2025.7 [M − Ac]⁻	34.22,[e] 34.28, 34.37[d]	21.55

[a] 5′-*O*-DMT-3′-*O*-acetyl-base-protected oligomers. [b] Retention time (in min) after deprotection [conditions: 80% acetic acid, 30 min, ethylenediamine/EtOH (1:1), 6 h, 25 °C]; RP ODS-Hypersil column, gradient 16% MeCN−48% MeCN in water, 1.6% MeCN/min, flow 1.5 mL/min. [c] In DMSO-d_5. [d] In MeOD-Py (2:3 v/v). [e] Double intensity.

selenium.[16] The resulting 5′-*O*-DMT-nucleoside 3′-*O*-(methanephosphonoanilidoselenoate)s (**4**) were isolated and purified by column silica gel chromatography and, under treatment with sodium hydride/carbon dioxide,[17] were converted into the corresponding 5′-*O*-DMT-nucleoside 3′-*O*-(methanephosphonoselenoate)s. These were alkylated with methyl iodide without isolation, and the resulting **1** were purified and separated into FAST- and SLOW-eluted diastereomers by silica gel chromatography.[18] Their condensation with 3′-*O*-protected nucleosides resulted in formation of the desired dinucleoside-(3′,5′) methanephosphonates (**5**) (Scheme 2).

As the most effective catalyst for condensation of **1** with 5′-OH-nucleosides (**6**) we have used, among other strong organic bases, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[19]

Because it has been discovered that this condensation process is not stereospecific,[20] we have used the tandem catalyst consisting of DBU/LiCl.[21] The presence of LiCl was demonstrated earlier to enhance the basicity of amines used in Horner−Wadsworth−Emmons-type reactions and has proved to be effective in DBU-catalyzed transesterifications of peptides.[22] It appeared that the condensation of diastereomerically pure (dp >99%) 5′-*O*-DMT [or *O*-9-phenylxantheneyl]nucleoside 3′-*O*-(*Se*-methyl methanephosphonoselenolate)s **1** with 3′-*O*-acetyl nucleosides **6** is completed within 10−60 min and results in formation of **5** with a good yield and with **full stereospecificity**. Characterization of the corresponding dinucleoside (3′,5′)-methanephosphonates **5** has been based on the results of mass spectrometry. Their diastereomeric purity has been ascertained by ^{1}H and ^{31}P NMR spectroscopy and RP HPLC analysis. Pertinent data are collected in Table 1.

This methodology has been successfully extended to the synthesis of trimer **7**, tetramer **8**, and pentamer **9**, each of [*Rp*,*Rp*]-, [*Rp*,*Rp*,*Rp*]-, [*Rp*,*Rp*,*Rp*,*Rp*]- and [*Sp*,*Sp*]-, [*Sp*,*Sp*,*Sp*]-, and [*Sp*,*Sp*,*Sp*,*Sp*]-configuration at phosphorus atoms, respectively. 5′-*O*-Deprotection is easily achieved by acid treatment.[23] Therefore, 5′-*O*-deprotected dimers, trimers, and tetramers, respectively, were condensed with monomer **1** in the presence of DBU/LiCl (Table 2).

All compounds **7**−**9** were also analyzed by MS, ^{1}H, and ^{31}P NMR spectroscopies, and their purities were confirmed by means of HPLC. Since the corresponding **5**, **7**, **8**, and **9** are isolated as fully protected species and their selective 3′-*O*- or 5′-*O*-deprotection is simple, these constructs can be condensed together in a desired fashion. Such a possibility is rather excluded for "shortmers" prepared by our previous method, where bases are not protected.[19] Attempts to adapt the presented methodology to the requirements of solid-phase synthesis are in progress.

Another feature of the present methodology is the high stereospecificity of the coupling process. To establish the stereochemistry of the reaction between **1** and **6** we have assigned the absolute configuration of 5′-*O*-pixyl-thymidine 3′-*O*-(*Se*-methyl methanephosphoselenolate) (FAST-eluted **1e**). Its condensation with 3′-*O*-acetylthymidine gives, after removal of 3′-*O*- and 5′-*O*-protective groups, [*Sp*]-dithymidylyl-(3′,5′) methanephosphonate of known absolute configuration.[24]

In order to describe the stereochemistry of the displacement of selenomethyl by oxygen, it is necessary to define the absolute configuration of the starting materials **1**.

Crystals of the FAST-eluted **1e** were grown in CH_2Cl_2−hexane solution (by diffusion of hexane) and selected for X-ray analysis, which shows its configuration to be [*Rp*]. Since the absolute configuration of the product, namely $T_{PMe}T$, has been assigned formerly to be [*Sp*],[24] it follows that the process of nucleophilic substitution of selenium occurs with retention of configuration (Scheme

(16) Compounds **4** were obtained in the reaction of 5′-*O*-protected nucleoside with $MePCl_2$ (−40 °C) (1 equiv) in THF solution in the presence of triethylamine (2 equiv), followed by aniline (2 equiv) and elemental selenium (2.5 equiv). The resulting 5′-*O*-protected nucleoside 3′-(methanephosphonoanilidoselenoate)s **4** were isolated as mixtures of diastereomers in a ratio of approximately 1:1 by silica gel column chromatography. ^{31}P NMR δ: **4a** 76.57 and 76.36, $^1J_{PSe}$ = 812, 814 Hz; **4b** 76, 65 and 76, 29; $^1J_{PSe}$ = 820, 820 Hz; **4c** 76, 56 and 76, 39; J_{PSe} = 828, 828 Hz; **4d** 76, 62 and 76, 37; $^1J_{PSe}$ = 823, 825 Hz ($CDCl_3$) (correct MS data for all compounds).

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(18) **1a**-FAST: ^{31}P NMR δ = 49.72, $^1J_{PSe}$ = 428 Hz; MS FAB [M − H]⁻ 697, 698, 700. **1a**-SLOW: ^{31}P NMR δ = 49.76, $^1J_{PSe}$ = 430 Hz; MS FAB [M − H]⁻ 697, 698, 700. **1b**-FAST: ^{31}P NMR δ = 50.21, $^1J_{PSe}$ = 429 Hz; MS FAB [M − H]⁻ 786, 788, 789. **1b**-SLOW: ^{31}P NMR δ = 50.43, $^1J_{PSe}$ = 431 Hz; MS FAB [M − H]⁻ 786, 788, 789. **1c**-FAST: ^{31}P NMR δ = 49.79, $^1J_{PSe}$ = 430 Hz; MS FAB [M − H]⁻ 809, 812, 813. **1c**-SLOW: ^{31}P NMR δ = 50.24, $^1J_{PSe}$ = 432 Hz; MS FAB [M − H]⁻ 809, 812, 813. **1d**-FAST: ^{31}P NMR δ = 50.56, $^1J_{PSe}$ = 431 Hz; MS FAB [M − H]⁻ 793, 794, 795. **1d**-SLOW: ^{31}P NMR δ = 51.27, $^1J_{PSe}$ = 434 Hz; MS FAB [M − H]⁻ 793, 794, 795.

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(20) Coupling reaction was much slower; after 4 h only about 10% of the required, albeit epimerized, product was obtained. Substrate **1** is diastereomerically stable in a presence of DBU.

(21) Examples of LiCl/DBU catalytic systems: Seebach, D. *Aldrichim. Acta* **1992**, *25*, 59. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1991**, *32*, 7161. Kanemasa, S.; Uchida, O.;Wada, F. *J. Org. Chem.* **1990**, *55*, 4411. Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384. Rosen, T.; Heathock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.

(22) Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102.

(23) Detritylation of **5**−**7** was performed in 80% acetic acid at rt, followed by purification by means of precipitation from hexane, or column chromatography.

(24) Stec, W. J.; Zon, G.; Egan, W.; Byrd, R. A.; Phillips, L. R.; Gallo, K. A. *J. Org. Chem.* **1985**, *50*, 3908.

2). It has to be mentioned that in the literature there are some known examples of nucleophilic substitution at phosphorus in MeP(O)(OR)(SMe) occurring with retention of configuration,[25] which has been interpreted by De Bruin[26] in terms of a kinetic preference of nucleophile to attack from the side opposite to the most electronegative (but not the most apicophilic) substituent. Such a process requires a single pseudorotation before the leaving group dissociates from a trigonal bipyramidal intermediate. In our case the problem seems to be even more complex since at present one cannot exclude a double-inversion scenario, with primary substitution of selenalkyl group by DBU, followed by the next replacement of DBU ligand by nucleoside. However, this second possibility seems to be less likely, since the exposure of 5′-*O*-DMT-thymidine-3′-*O*-(*Se*-methyl methanephosphonate) to DBU/LiCl, followed by ^{31}P NMR did not shown any substantial evidence for a DBU-onium phosphorane. Also, repeated displacement of DBU by DBU would lead to epimerization at phosphorus. The only indication for an interaction between monomer **1** and DBU is reflected in a minor change of the $^{1}J_{PSe}$ value.[27]

Further studies on the mechanism of the investigated reaction are in progress, but it is reasonable to assume that the presence of LiCl causes the complexation of phosphonyl PO ligands around a lithium cation, enhancing the process of nucleophilic substitution at phosphorus, while DBU facilitates the dissociation of H—O bond of the attacking alcohol.

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Supplementary Material Available: General experimental procedures and characterization data (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(26) DeBruin, K. E.; Tang, C. W.; Johnson, D. M.; Wilde, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 5871.

(27) ^{31}P NMR spectra were recorded for the solution 1-SLOW and DBU/LiCl (10 equiv) in pyridine-d_5 at temperatures between −40 to 20 °C; $\delta = 50.63$, $^{1}J_{PSe} = 423$ Hz (−40 °C); $\delta = 49.11$, $^{1}J_{PSe} = 421$ Hz (25 °C).