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The synthesis of unsymmetrical S^1-(3′-*O*-thymidine-*O*-methanephosphonyl)-S^2-*p*-nitrophenyl disulfides and their reactions with triphenylphosphine

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Abstract

The reaction of thymidine 3′-methanephosphonothioic acid with *p*-nitrophenylsulfenyl chloride provides S^1-(3′-*O*-thymidine-*O*-methanephosphonyl)-S^2-*p*-nitrophenyl disulfide which, in the presence of an excess of sulfenyl chloride and triphenylphosphine gives, in a stereospecific manner, thymidine 3′-(*S*-*p*-nitrophenyl methanephosphonodithioate).

Keywords: nucleic acid analogues; phosphonic acids; derivatives; disulfides; stereoselectivity.

Triphenylphosphine is a broadly recognised desulfurizing reagent used for the conversion of dialkyl(diaryl)disulfides into the corresponding dialkyl(diaryl)sulfides.[1] Under specific conditions, triphenylphosphine has also been used for sulfur extrusion from organic sulfides, leading to the formation of C–C bonds (e.g. Eschenmoser contraction).[2]

In our search for efficient methods for the preparation of nucleoside-3′-*O*-(*S*-aryl methanephosphonothioates) (**1**)[3] as potential substrates for the synthesis of dinucleoside (3′,5′)-methanephosphonates,[4] an assumption was made that the reaction of readily available nucleoside-3′-*O*-methanephosphonothioates (**2**)[5] with arylsulfenyl chlorides would provide the corresponding unsymmetrical disulfides **3**. These, under treatment with triphenylphosphine, would give the desired **1** (Fig. 1).

Accordingly, methanephosphonothioic acid **2**[4] was treated in chloroform solution with commercially available *p*-nitrophenylsulfenyl chloride (**4**).[6] Under these conditions, rapid 5′-*O*-detritylation accompanying formation of the mixed disulfide **3** occurred. Thus, for further studies, the separated diastereomers of triethylammonium 5′-*O*-tertbutyldimethylsilyl-thymidine 3′-*O*-methanephosphonothioates† (**5**) were

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† Compound **5**: ^{31}P NMR: 76.76 ppm (predominant); 76.25 ppm (minor); HR FAB MS [M-H]: 497.075, calcd 497.0754.

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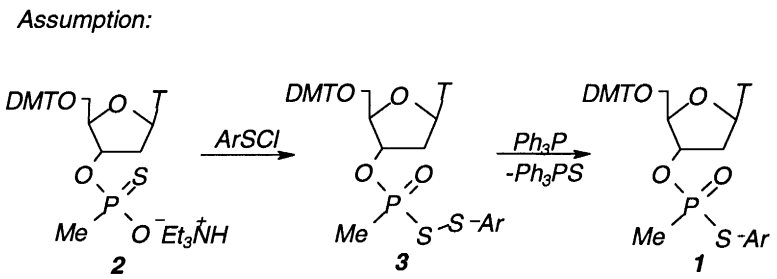
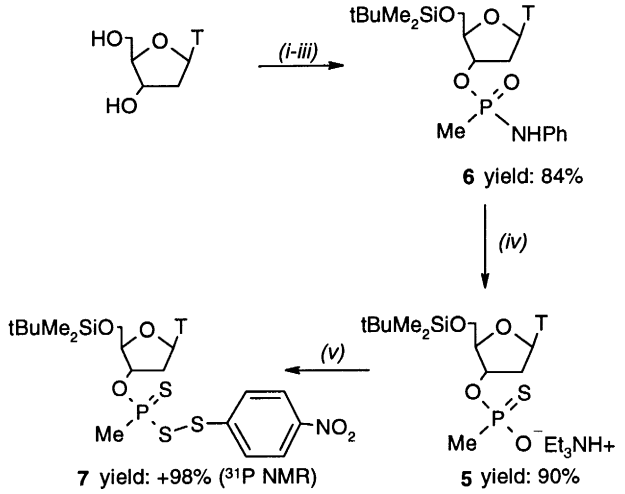


Fig. 1.

prepared by a procedure, depicted in Scheme 1, from the corresponding 5′-*O*-tertbutyldimethylsilyl-thymidine 3′-*O*-methanephosphonanilidates (**6**).‡



Scheme 1. *Reagents and reaction conditions*: (i) *t*$BuMe_2SiCl$ (1.15 equiv.), imidazole (4 equiv.), MeCN; (ii) $MeP(O)Cl_2$ (2 equiv.), pyridine, 20 min; (iii) $PhNH_2$, rt, 30 min; (iv) NaH, DMF, CS_2, followed by column chromatography (silica gel) with $CHCl_3$–MeOH–Et_3N (89:10:1); (v) *p*-NO_2–C_6H_4SCl (1.2–2 equiv.), $CHCl_3$, −50°C, 10 min

The reaction of methanephosphonothioic acid **5** (triethylammonium salt, diast. ratio FAST:SLOW=9:1) with *p*-nitrophenylsulfenyl chloride (**4**, 1.2–2 molar equivalents) in chloroform at −50°C§ led to immediate quantitative formation of a new compound which on the basis of ^{31}P NMR [FAST: 56.48 ppm (90%), and SLOW: 55.52 ppm (10%)], and FAB MS analysis¶ was identified as 5′-*O*-tertbutyldimethylsilyl-3′-*O*-(methanephosphonothioyl *p*-nitrophenylsulfanyl)-3′-*O*-thymidine (**7**) (Scheme 1). The ratio of diastereomers **7** was identical with that assigned for the starting methanephosphonothioic acid **5** (9:1). Attempts at isolation of pure **7** from the reaction mixture by means of a silica gel column chromatography failed. Therefore, further attempts at sulfur extrusion from **7** were performed on crude **7** (not isolated from the reaction mixture‖) by addition of

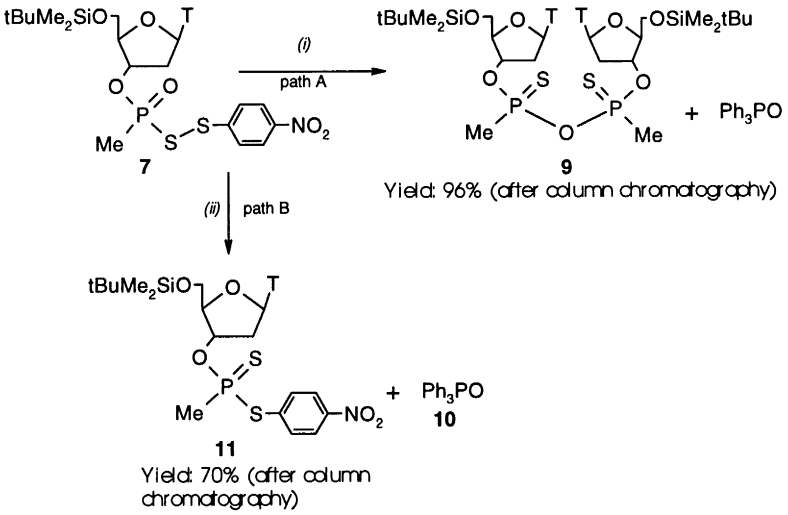
‡ Compound **6**: ^{31}P NMR: FAST: 30.13 ppm; SLOW: 29.49 ppm. HR FAB MS [M-H]: 572.121, calcd 572.121. R_f=0.65 (FAST), and 0.6 (SLOW) (5%EtOH in $CHCl_3$, standard silica gel TLC plates).

§ This reaction was also checked at −90°C, and only compound **7** was observed at that low temperature. None of the P^V or phosphonium type reactive intermediates were detected during low temperature NMR studies.

¶ MS analysis was performed for **7** prepared in the following way: The crude reaction mixture was diluted with chloroform, washed twice with 0.05 M citric acid, dried over $MgSO_4$, and concentrated under vacuum. FAB [M-H]: 603.1, calcd 603.9].

‖ Sample prepared as for MS analysis.

a twofold molar excess of triphenylphosphine (**8**). Two different products were obtained depending on the ratio **5**:**4** used for the generation of disulfide **7**. If 1.2 molar equivalents of **4** were used for condensation with methanephosphonothioate **5**, the major product, obtained in 96% yield after silica gel column chromatography, was identified as pyromethanephosphonodithioate **9**** (Scheme 2, path A). Triphenylphosphine oxide (**10**) (^{31}P NMR 29.7 ppm), instead of the expected triphenylphosphine sulfide, was a second product of this reaction. In contrast, addition of triphenylphosphine to the condensation product of methanephosphonothioic acid **5** (9:1) with 100% molar excess of sulfenyl chloride **4** provided 5′-*O*-tertbutyldimethylsilyl thymidine 3′-(*S*-*p*-nitrophenyl methanephosphonodithioates) (**11**) (ratio of diastereomers 9:1) in a stereospecific manner. Ester **11** was isolated in over 70% yield by means of silica gel column chromatography.†† The structure **11** was elucidated on the basis of the interpretation of ^{31}P and ^{1}H NMR data.



Scheme 2. *Reagents and reaction conditions*: (i) Ph_3P (2 equiv.), $CHCl_3$, rt, 10 min; (ii) NO_2–C_6H_4SCl, Ph_3P (2 equiv.), $CHCl_3$, rt, 10 min.

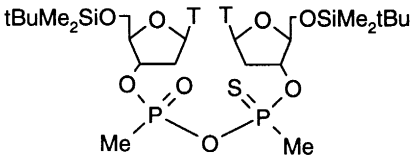
In an analogous sequence of reactions for the SLOW diastereomer of methanephosphonate **5** (^{31}P NMR 76.25 ppm) the diastereomeric disulfide **7** of opposite absolute configuration at phosphorus was formed (^{31}P NMR 55.55 ppm)**.** Consequently, the second isomer **11** was obtained in 72% yield (^{31}P NMR 97.3 ppm).‡‡

** Compound **9**: ^{31}P NMR 87.82 ppm, 87.3 ppm; $^{2}J_{P-P}$=26.5 Hz (major isomer); FAB MS [M-H] 882.2, calcd 883.8; R_f=0.5 (5%EtOH in $CHCl_3$ on standard TLS plates).

†† Into **5**, dissolved in $CHCl_3$, and cooled to −50°C a solution of 2 molar equiv. of **4** in $CHCl_3$ was poured in a single portion. The reaction mixture was warmed up gradually to an ambient temperature within 15 min, and Ph_3P (2 equiv.) in $CHCl_3$ was added to this solution. After 15 min the reaction mixture was worked-up in a standard way, and a final product **11** was purified by a silica gel chromatography. FAST **11** (predominant): ^{31}P NMR: 97.5 ppm, ^{1}H NMR 2.36 ppm (3H, P–CH_3,$^{2}J_{P-CH3}$=15.41 Hz); SLOW **11** (minor): 97.3 ppm, ^{1}H NMR: 2.37 ppm (3H, P–CH_3,$^{2}J_{P-CH3}$=15.34 Hz).

‡‡ Attempted synthesis of thymidine 3′-*O*-(*S*-phenyl methanephosphonodithioate)s in an analogous reaction of FAST-**5** with 2–4-fold molar excess of phenylsulfenyl chloride gave the expected mixed disulfide in a stereospecific manner, in 85% yield (^{31}P NMR: 59.13 ppm in $CDCl_3$), but treatment of the crude reaction mixture with Ph_3P led to formation of thymidine 3′-*O*-(*S*-phenyl methanephosphonodithioate) in the yield ca. 20% only (^{31}P NMR:97.34 ppm). Silica gel chromatography led to isolation of P^1,P^2-dithymidyl pyromethanephosphonodithioates and pyromethanephosphonomonothioates (mixtures of diastereomers- data not shown) as the main products.

Hydrolysis of crude **7** under basic conditions (twofold molar excess of DBU, large excess of water) led to isolation of pyromethanephosphomonothioate **12**[§§] (70%) and the recovery of the starting methanephosphonothioic acid **5** (30%). If the same reaction product **7** (^{31}P NMR: 56.48 ppm) resulting from the condensation of **4** with **5** was treated with $Et_3N \cdot 3HF$, the corresponding 5′-*O*-tertbutyldimethylsilyl-*O*-thymidine-3′-*O*-methanephosphonofluoridate (**13**)[¶¶] was isolated by precipitation in 85% yield.



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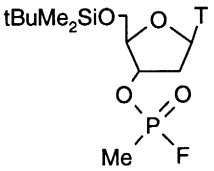

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In conclusion, we have demonstrated an efficient stereospecific method for the one-pot synthesis of pure *S*-aryl methanephosphonodithioates **11** from the separated diastereomers of methanephosphonothioic acids **5**. Formation of an intermediate, unsymmetrical disulfide **7**, was proven by spectroscopic and chemical methods.

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[§§] Compound **12**: ^{31}P NMR: FAST: 88.28–87.25 (m) ppm and 24.8–24.08 (m) ppm. The experiments with $H_2{}^{18}O$ proved that the incorporation of ^{18}O into the isolated **5** did not occur.

[¶¶] Compound **13**: ^{31}P NMR: 30.91.5 ppm, J_{P-F}=1060 Hz; ^{19}F NMR: −50.36 ppm, J_{P-F}=1060 Hz.