## Stereospecific Synthesis of Thymidine Cyclic 3′,5′-($S_P$)- and -($R_P$)-Phosphorothioates[1]

*Sir:*

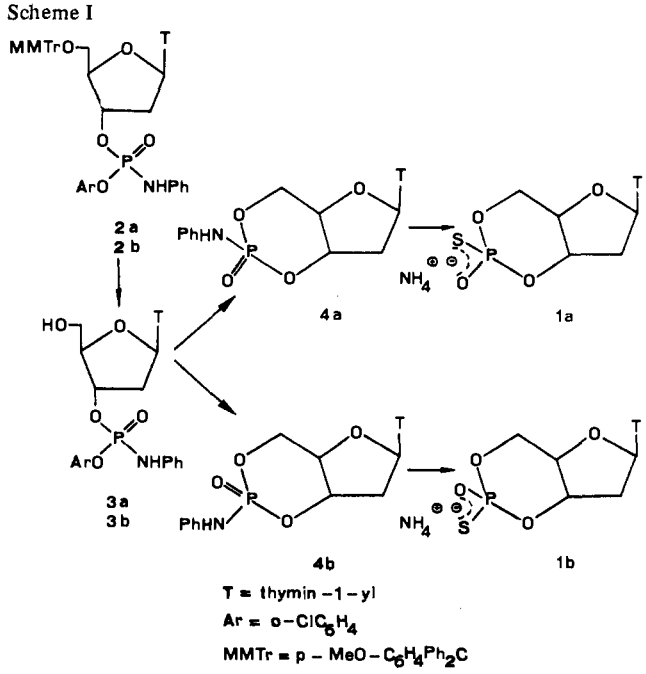
Cyclic nucleoside 3′,5′-phosphorothioates offer considerable potential for the study of enzymatic reactions.[2a] By virtue of the asymmetric phosphorus atom they exist in "endo" and "exo" diastereoisomeric forms,[2b] and knowledge of the stereochemical course of their reactions may deliver valuable information about the role of enzymes responsible for metabolism of cyclic nucleotides. In spite of this, only one nonstereospecific method for the preparation of cAMPS by cyclization of adenosine 5′-*O*,*O*-bis(*p*-nitrophenyl)phosphorothioate has been described so far.[2b] The attempt to separate the diastereoisomeric cyclic nucleoside 3′,5′-phosphorothioates by means of physical methods failed.

In this communication we report a new approach to the stereospecific synthesis of P-enantiomeric diastereoisomers of cyclic nucleoside 3′,5′-phosphorothioates. As a model system we chose cyclic thymidine 3′,5′-phosphorothioates (**1**) starting from the P-enantiomeric *o*-chlorophenyl 5′-*O*-monomethoxytritylthymidine 3′-phosphoranilidates (**2**).[3]

Treatment of **2a** (1 mmol; $R_f$ 0.50 (A); $\delta_{31P}$ +2.25 ppm)[4] with 80% acetic acid (20 mL) caused the removal of monomethoxytrityl group and *o*-chlorophenyl thymidine 3′-phosphoranilidate (**3a**) (yield 90%; $\delta_{31P}$ +2.58 ppm; *m/e* 507 $(M)^+$) was obtained. The same operation, as applied to **2b** ($R_f$ 0.35 (A); $\delta_{31P}$ +2.75 ppm), gave **3b** (yield 89%; $\delta_{31P}$ +2.68 ppm; *m/e* 507 $(M)^+$). Each of diastereoisomers, **3a** and **3b** (0.8 mmol), was converted by means of procedure described by Borden and Smith[5] (*t*-BuOK/$Me_2SO$, 10-fold molar excess) into thymidine cyclic 3′,5′-phosphoranilidates (**4**) which were isolated by means of preparative TLC on silica gel $GF_{254}$, developing system B: **4a** (yield (by weight) 84%; $R_f$ 0.56 (B); $\delta_{31P}$ −0.64 ppm; *m/e* 379 $(M)^+$) and **4b** (yield 90%; $R_f$ 0.45 (B); $\delta_{31P}$ +3.56 ppm; *m/e* 379 $(M)^+$).[6] It has to be emphasized that the 3′,5′-dioxaphosphorinanyl ring closure reaction was fully stereospecific. Removal of anilido group from both **4a** and **4b** according to Ikehara et al.[7] gave thymidine cyclic 3′,5′-phosphate as compared with a genuine sample obtained according to a method described in the literature.[8]

The procedure previously reported for the stereospecific conversion of *P*-anilidates into *P*-thiolates,[3,9] when applied to both **4a** and **4b**, allowed the ready synthesis of P-enantiomeric **1a** and **1b**, respectively. Thus, treatment of a pyridine (2 mL) solution of **4a** (0.2 mmol) with sodium hydride (2 mmol) followed by carbon disulfide (1 mL) and heating of the resulting mixture at 70 °C during 2.5 h gave **1a**, purified by means of descending paper chromatography on Whatman 3MM paper, developing solvent 2-propanol–aqueous ammonia–water (7:1:2), and isolated as the ammonium salt by elution with diluted ammonium hydroxide solution (yield 53%;[10] $R_f$ 0.54 (C);[4] $\delta_{31P}$ −54.73 ppm; *m/e* 320 $(M - NH_3)^+$). By a similar procedure **4b** was converted to **1b** (yield 56%;[10] $R_f$ 0.51 (C); $\delta_{31P}$ −52.11 ppm; *m/e* 320 $(M - NH_3)^+$). Both **1a** and **1b** gave a positive test with $PdCl_2$[11] and revealed the same electrophoretic mobility (0.53 Up). The overall procedure for preparation of **1a** and **1b** is depicted in Scheme I.

Scheme I



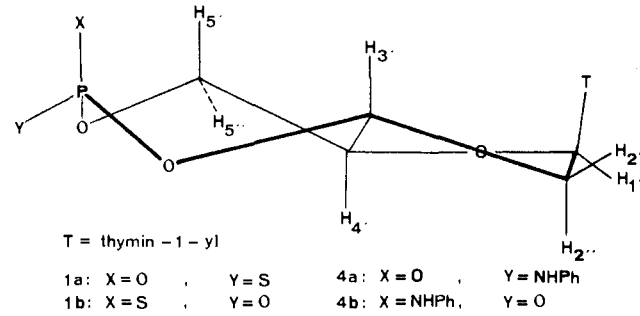




**Figure 1.** Assignment of the spatial orientation of exocyclic P substituents in **1a**, **1b**, **4a**, and **4b**.

On the basis of the known fact that 1,3,2-dioxaphosphorinanyl part of cTMP exists in chair conformation,[12] we assume that the same conformational property is possessed by both cyclic anilidates **4a** and **4b** as well as cyclic phosphorothioates **1a** and **1b**. In our previous work on the synthesis and conformational properties of diastereoisomeric 4-methyl-1,3,2-dioxaphosphorinans we proved that the signal of isomer with the axially oriented exocyclic P–N bond appears in $^{31}P$ NMR spectrum at higher field than that of isomer with the equatorially oriented P–N bond.[13] Using this criterion we were able to assign tentatively the spatial orientation of substituents at the phosphorus atom in both **4a** and **4b**, which is equivalent to assignment of absolute configuration of the phosphorus atom as $S_P$ in **4a** and $R_P$ in **4b**. Because the P–N → P–S conversion was proved to proceed stereospecifically with retention of configuration at the P atom,[9] **1a** has the $R_P$ and **1b** has the $S_P$ configuration (Figure 1). The order of magnitude of chemical shift values for both cyclic phosphorothioates **1a** and **1b** also supports this last conclusion.[14]

Assuming that the ring closure reaction **3** → **4** proceeds with inversion of configuration at the P atom the absolute configuration in **3** should be $S_P$ and $R_P$ in **3a** and **3b**, respectively. However, owing to the known diverse stereochemistry of nucleophilic substitution at the phosphorus atom,[15] this last assignment requires additional proof. The work on conformational and configurational assignments, as well as on application of our approach to cyclic ribonucleoside phosphorothioates, is in progress.

**Acknowledgment.** This work was assisted financially by the Polish Academy of Sciences, Grant No. MR 12-1-7-10.

### References and Notes

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(4) TLC was carried out on precoated plates, silica gel 60 $F_{254}$ (Merck) in the following solvent systems: (A) chloroform–acetone (7:3); (B) chloroform–methanol (85:15). Paper chromatography was performed on What-

man No. 1 paper in solvent system (C) 2-propanol–aqueous ammonia–water (7:1:2). Electrophoresis was carried out on Whatman No. 1 paper in 0.1 M TEAB buffer at 21 V/cm. $^{31}P$ NMR measurements performed in pyridine solutions with $H_3PO_4$ as an external standard. Negative chemical shift values are assigned for compounds absorbing at the lower field than $H_3PO_4$. Field desorption–mass spectrometry was performed on Varian MAT-7 machine.
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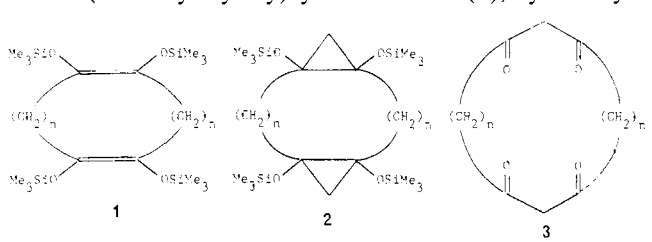
## Macrocyclic Compounds with Two 1,3-Diketone Units in the Ring. Synthesis and Transition Metal Complexation

*Sir:*

The complexation of metal ions by multidentate macrocyclic compounds has been a subject of considerable interest. Recently, Cram and coworkers reported syntheses of cyclic acetylacetone hosts and their affinities for divalent ions.[1] We now wish to report a new and versatile synthesis of macrocyclic compounds (**3**), in which two 1,3-diketone units are symmetrically located in the ring, and their complex formation with transition metal ions such as Cu, Ni, and Co.

The synthesis of the macrocyclic tetraketones **3** started with tetrakis(trimethylsilyloxy)cycloalkadienes (**1**), cyclic silyl-

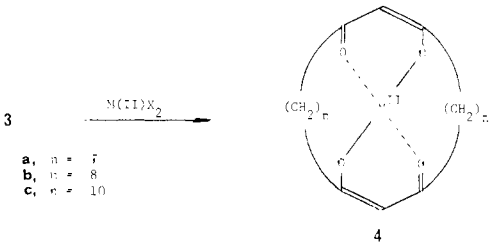


**a**, n = 7
**b**, n = 8
**c**, n = 10
**d**, n = 13

acyloin dimers, which are derived from the silyl-acyloin condensation[2] of aliphatic dicarbo esters such as dimethyl nonanedioate, dimethyl decanedioate, dimethyl dodecanedioate, and dimethyl tetradecanedioate. Cyclopropanation of **1** with diethylzinc and methylene diiodide afforded tetrakis(trimethylsilyloxy)tricycloalkanes (**2**), which were then treated with $Fe^{III}Cl_3$ in DMF[3] to produce the desired macrocyclic tetraketones **3** in satisfactory yields.

A typical experimental procedure for the preparation of the macrocyclic tetraketones **3** is as follows. Under a nitrogen atmosphere, 40.2 g (150 mmol) of methylene diiodide was added dropwise to a stirring mixture of 16.5 g (26 mmol) of **1b** and 15.7 g (130 mmol) of diethylzinc in 100 mL of benzene at room temperature. The mixture was then heated at reflux for 3 h. The standard workup of the reaction mixture[4] gave 12.5 g of a viscous liquid (**2b**), whose IR spectrum exhibited an absorption band at 3050 $cm^{-1}$ characteristic of cyclopropane ring at the expense of a band at 1665 $cm^{-1}$ ascribable to the carbon–carbon double bond of the starting material of **1b**. The viscous liquid of **2b** without further purification was subjected to the $Fe^{III}Cl_3$ induced ring enlargement reaction;[3] i.e., 12.5 g (19 mmol) of **2b** was added dropwise to a solution of 12.4 g (76 mmol) of anhydrous $Fe^{III}Cl_3$ in 40 mL of DMF at room temperature, and, then, the mixture was heated with stirring at 65 °C for 4 h. The reaction mixture was poured into 10% HCl aqueous solution and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel eluting with chloroform to furnish 4.4 g of 22-membered cyclic tetraketone **3b** (47% yield based on **1b** used) as a keto-enol tautomer mixture. The structure of **3b** was confirmed by elemental analysis[5] and spectral data: IR (neat) 1710, 1610 $cm^{-1}$; UV ($CHCl_3$) 275 nm ($\epsilon$ 5500); NMR ($CDCl_3$ with $Me_4Si$) $\delta$ 0.90–2.00 (br s, 24 H), 2.00–2.60 (m, 8 H), 3.55 (s) + 5.55 (s) + 15.0 (br s) = 4 H; mass spectrum $M^+$ 364. Similarly, 20-, 26-, and 30-membered cyclic tetraketones **3a, 3c,** and **3d** were synthesized in 33, 43, and 35% isolated yields from tetrakis(trimethylsilyloxy)cycloalkadienes **1a, 1c,** and **1d,** respectively.

CPK molecular model indicated that the macrocyclic tetraketones **3** thus prepared are capable of taking a conformation in which the four carbonyl oxygens are directed toward the inside of the ring and are on a same plane with a cavity large enough to take up some transition metals. Now it was found that 1:1 chelating metal complexes (**4**) were isolated in the reaction of **3a, 3b,** and **3c** with transition metals such as



**a**, n = 7
**b**, n = 8
**c**, n = 10

$Cu^{II}$, $Ni^{II}$, and $CO^{II}$. To a solution of 100 mg (0.55 mmol) of anhydrous $Cu^{II}(OAc)_2$ in 10 mL of ethyl alcohol was added 200 mg (0.55 mmol) of **3b** in 3 mL of ethyl alcohol at room temperature and the mixture was stirred for 1 h under nitrogen. A precipitated light blue solid (230 mg) was collected and recrystallized from benzene. The solid was assigned to be 1:1 chelating $Cu^{II}$ complex (**4b**·Cu) by the following spectral data and elemental analysis.[5] IR ((KBr disk) 1565, 1515 $cm^{-1}$)) and UV (($CHCl_3$ solvent) $\lambda_{max}$ 295 nm ($\epsilon$ 9500), 250 (9000)) spectra are similar to those of $Cu^{II}(acac)_2$. Mass spectrum exhibited four parent peaks at 425, 426, 427, and 428 with relative intensity of 100:23.86:47.68:10.51 due to the isotopic distribution, which is consistent with calculated value[6] based on the 1:1 chelating $Cu^{II}$ complex **4b**·Cu. According to the same procedure, 1:1 chelating $Cu^{II}$ complexes **4a**·Cu and **4c**·Cu were prepared.

The related nickel(II) and cobalt(II) complexes (**4**·Ni and **4**·Co) were prepared by the reaction of **3** with anhydrous $Ni^{II}Cl_2$ and with anhydrous $Co^{II}Cl_2$ in the presence of triethylamine.

Detailed structure of the 1:1 chelating metal complexes **4**·Cu, **4**·Ni, and **4**·Co must await x-ray analysis.

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