while this is probably not the case for the intermolecular one, this could have a significant effect on α and/or β. Work on this question is in progress in our laboratory.

Somewhat related to this is the uncertainty in pK_a^{XH} and pK_a^{CH}. Our assumption that they lie halfway between their values in the reactant and the product state is certainly not completely correct in every situation and may seriously break down in some cases, particularly for nitroalkanes where C-H bond cleavage/formation and charge development/distribution are very much out of step with each other.[36,38]

Finally, our treatment of carbonyl compounds does not take into consideration the possibility of keto-enol isomerism and is therefore only valid when the enol form is a minor component. A treatment which takes enols into account would lead to a modification of eq 5-7 by changing the denominators (K_2^{XH} + [H^+]) into (K_2^{XH} + [H^+] + K_E^{XH}[H^+]/K_E^{OH} + [H^+]^2/K_E^{OH}) where K_E^{OH} and K_E^{XH} are the acidity constants of the enol for the OH and the XH group, respectively.

In spite of these limitations we believe that our models are very useful in predicting whether an intramolecular pathway should be definitely observable or definitely not observable or whether the situation might be ambiguous; they also predict whether the contribution by the intramolecular pathway would be large or small, and in what approximate pH range this pathway would be most easily detectable. The predictive power of these models is tested in the next section where prediction and experimental observation is compared for nine compounds.

Comparison of Theory with Experimental Results

Table X summarizes the relevant data for **3** and **6-13**. It is apparent from the table that in all cases except for **11** (**11** will be discussed below) the theoretical predictions match with the experimental results. This is true regardless of what EM was chosen (e.g., **3**, **6**, **7**, **12**, **13**) or, in the case of **9** and **10**, regardless of which β value was used.

For **12**, model Ia (EM = 1 M) predicts a slightly positive Δ_{max} of 0.08 which for 50% Me_2SO-50% water is expected to increase to $\Delta_{max} \approx 0.3$. Thus, if EM were 1 M the intramolecular pathway would, in principle, be expected to make a contribution. However, the effect is too small to be detected unequivocally because for definite experimental proof that the intramolecular pathway is significant one usually likes to see at least a 5- to 10-fold rate enhancement (Δ_{max} = 0.7 to 1.0) over the rate which can be accounted for by the external pathways above.

The discrepancy between theory and experiment for **11** is puzzling. The model, based on an EM of 0.1 M, predicts a rather large Δ_{max} of $\sim$2.5 which occurs well within the pH range investigated, and therefore experimental detection should have been easy. We are forced to conclude that perhaps EM is much smaller than assumed and thus much smaller than for most of the other compounds. The reasons for it are not immediately obvious; it might be worthwhile to reinvestigate this compound.

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Supplementary Material Available: Table S1, Model I: Carbonyl Compounds, and Figure S1, Δ_{max} vs. pK^{XH} for benzyl cyanides (4 pages). Ordering information is given on any current masthead page.

S_N2 Substitution with Inversion at a Cyclopropyl Carbon Atom: Formation of 9-Oxatetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecane

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Abstract: The stereoisomeric chlorohydroxypropellanes **2a** and **2b** were prepared by chlorocarbene addition to 4,5,6,7-tetrahydro-2-indanol. The stereochemistry of **2a** and **2b** was established by chemical correlation and by X-ray crystal structure determination of the tosyl derivative **3** of **2b**. On treatment with *t*-BuOK in Me_2SO, **2a** yielded the tetracyclic ether **1**. This remarkable reaction was shown to be an unambiguous case of a genuine S_N2 reaction with inversion at a cyclopropane carbon atom. Alternative mechanisms could be excluded; in particular, a carbene mechanism was excluded by the observation that the stereoisomer **2b** is unchanged under the reaction conditions and that, starting from **2a**-*10-d*, deuterium is retained (inverted) at the carbon atom that undergoes the substitution.

Nucleophilic substitution at cyclopropane rings continues to be an intriguing process. It shows remarkable differences with analogous substitutions at other saturated carbon atoms, cyclopropyl halides being in general much less reactive than normal alkyl halides. This was first observed by Gustavson in 1891[2] and explained by Brown in 1951 by the concept of I strain,[3] i.e., the increase of bond-angle strain at the carbon center when going from the tetracoordinate ground state to the transition state, in which this carbon atom is either tricoordinate and trigonal (S_N1) or pentacoordinate and trigonal bipyramidal (S_N2).

Substitution at cyclopropane rings under solvolytic (S_N1) conditions, first observed by Roberts and Chambers in 1951,[4] has since been intensively investigated and shown to be a concerted process in which ionization is accompanied and assisted by disrotatory ring opening.[5,6]

(1) (a) Vrije Universiteit. (b) Universiteit van Amsterdam.
(2) Gustavson, G. *J. Prakt. Chem.* **1891**, [2]*43*, 396.
(3) Brown, H. C.; Fletcher, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212.
(4) Roberts, J. D.; Chambers, V. C. *J. Am. Chem. Soc.* **1951**, *73*, 5034.
(5) v. R. Schleyer, P.; Sliwinski, W. F.; Van Dine, G. W.; Schöllkopf, U.; Paust, J.; Fellenberger, K. *J. Am. Chem. Soc.* **1972**, *94*, 125.

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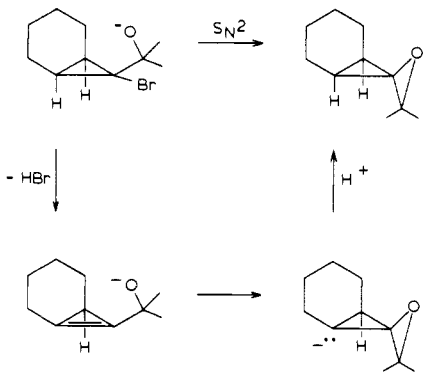
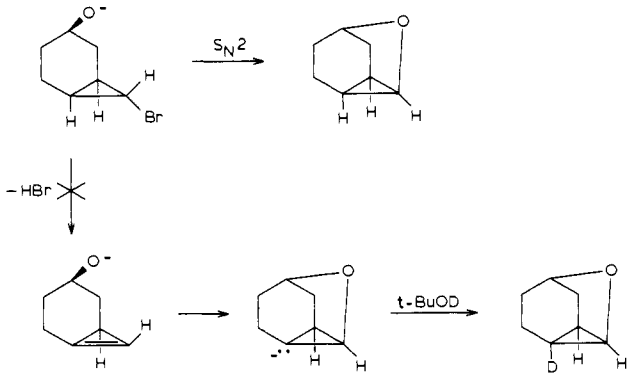
Scheme I



Scheme II



With regard to S_N2 substitutions, the situation is much less clear-cut. Theoretical calculations seem to indicate that such substitutions might occur with retention of configuration at the substituted carbon atom.[7] However, experimental evidence for this or any other type of direct intermolecular S_N2 substitution is lacking. If nucleophilic substitutions are observed, an indirect, multistep mechanism is usually involved.[8,9] Intramolecular substitutions have been intensively investigated, in particular by Seebach and co-workers, and inversion of configuration has been observed in some cases.[8,10] Again, alternative pathways, in particular elimination–addition reactions via cyclopropenes (Scheme I), can so far not be excluded with absolute certainty. While the stereospecificity of these reactions forms a strong argument against cyclopropene intermediates,[8] the recent observation of stereospecific additions to strained cycloalkenes by Seebach and Liesner[11] makes such a conclusion less convincing unless β-hydrogen atoms are absent.[8]

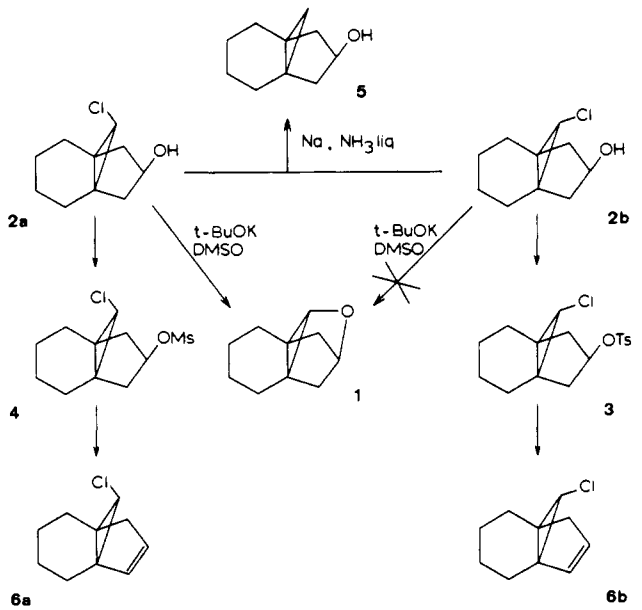
There seems to be only one case (Scheme II) in which the noninvolvement of the β-hydrogens follows from the lack of deuterium incorporation in the presence of *t*-BuOD; a true S_N2 reaction is obviously involved.[10]

We report here a case of direct S_N2 reaction at a cyclopropane carbon atom that is unambiguous. It is intramolecular and occurs with inversion at carbon.

Results and Discussion

Formation and Structure of 1. In the course of our investigations on the preparation of [4]metacyclophane, which so far have led to its Dewar isomer instead,[12] we accidentally obtained an interesting byproduct, which was identified as 9-oxatetracyclo-[6.2.1.$0^{1,6}$.$0^{6,10}$]undecane (**1**). It turned out that **1** was formed in almost quantitative yield when alcohol **2a** was treated for 16 h at room temperature with potassium *tert*-butoxide (*t*-BuOK) in Me_2SO (Scheme III).

Scheme III



The structure of **1** follows from its spectral data (see Experimental Section) and from the fact that it is derived from **2a**, the structure and stereochemistry of which is unambiguously established as follows. Addition of chlorocarbene, prepared from dichloromethane and *n*-butyllithium, to 4,5,6,7-tetrahydro-2-indanol[13] afforded a mixture of the stereoisomeric alcohols **2a** and **2b** (ratio ca. 2:1, total yield 94%). Although there is some precedent for a cis-directing influence of an oxygen function in chlorocarbene additions to cyclopentenols,[14] more reliable information on the stereochemistry was derived from the X-ray crystal structure determination of the tosylate **3** of **2b** (vide infra). While **2a** and **2b** were not easy to separate on a preparative scale, separation was easily achieved by the preparation of their sulfonic acid esters. Surprisingly, **2b**, though having the chlorine and hydroxyl groups syn to each other, was much more rapidly tosylated by tosyl chloride in pyridine than **2a**; **3** was obtained in 90% purity from this reaction and could be further purified by recrystallization from hexane as white crystals, mp 85.5 °C, which were suitable for X-ray diffraction measurements. From the mother liquors of this preparation which contained unreacted **2a**, the mesylate **4** was obtained by reaction with mesyl chloride in pyridine in 91% yield; unfortunately the yellowish crystals, (mp 105–110 °C) could not be purified and obtained in suitable form for crystal structure determination, as **4** appeared to be unstable. However, a structural correlation between **2a** and **2b** was achieved by reduction with sodium in liquid ammonia[15] to alcohol **5**[13] (92%), thereby establishing that the stereochemistry of the hydroxyl group was identical in both compounds. According to the crystal structure, the hydroxyl group is exo. Thus, it had indeed a cis-directing effect on the carbene addition. The difference between **2a** and **2b** must therefore reside in the stereochemistry of the chloro substituent. As **2b** (via **3**) is proven to be the *exo*-chloro derivative by X-ray diffraction, the complete stereochemistry of **2a** can be derived unambiguously to be that of *endo*-10-chloro-*exo*-8-hydroxytricyclo[4.3.1.$0^{1,6}$]decane, as shown in Scheme III. The opposite stereochemistry at C(10) for **2a** and **2b** is further con-

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(13) Starr, J. E.; Eastman, R. H. *J. Org. Chem.* **1966**, *31*, 1393.
(14) Fleming, I.; Thomas, E. J. *Tetrahedron* **1972**, *28*, 5003.
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Table I. Fractional Coordinates $\times 10^4$ and Equivalent Thermal Parameters ($Å^2 \times 10^3$) with Esd's in Parentheses

	x	y	z	U_{eq}[a]
C(1)	6309 (6)	3520 (2)	5531 (3)	59 (1)
C(2)	6288 (10)	3372 (2)	6818 (4)	94 (2)
C(3)	8117 (12)	3006 (3)	7286 (5)	137 (2)
C(4)	9262 (14)	2682 (5)	6586 (6)	186 (4)
C(5)	9670 (7)	2871 (2)	5404 (4)	84 (2)
C(6)	7982 (6)	3266 (2)	4833 (3)	58 (1)
C(7)	8537 (6)	3731 (2)	3956 (4)	69 (1)
C(8)	7480 (6)	4305 (2)	4300 (3)	58 (1)
C(9)	5839 (7)	4146 (2)	5116 (4)	71 (1)
C(10)	5838 (6)	3031 (2)	4690 (3)	65 (1)
C(11)	9131 (6)	4671 (2)	1723 (3)	57 (1)
C(12)	11201 (6)	4571 (2)	2066 (3)	69 (1)
C(13)	12351 (6)	4206 (2)	1421 (4)	70 (1)
C(14)	11492 (6)	3939 (2)	410 (3)	65 (1)
C(15)	9438 (7)	4062 (2)	57 (4)	71 (1)
C(16)	8250 (6)	4428 (2)	693 (3)	65 (1)
C(17)	12779 (9)	3529 (2)	−254 (5)	92 (2)
Cl	4210 (2)	3141 (1)	3399 (1)	104 (1)
S	7599 (2)	5090 (1)	2594 (1)	67 (1)
O(1)	6437 (4)	4613 (1)	3290 (2)	57 (1)
O(2)	5953 (5)	5363 (1)	1885 (3)	91 (1)
O(3)	8900 (5)	5438 (1)	3377 (2)	88 (1)

[a] $U_{eq} = {}^1/_3 \Sigma_{ij} U_{ij} a_i^* a_j^* \bar{a}_i \bar{a}_j$.

firmed by the fact that **3** and **4** on treatment with *t*-BuOK in Me_2SO gave rise to the isomeric elimination products **6a** and **6b** (Scheme III).

Molecular and Crystal Structure of 3. Crystals of **3** are monoclinic, space group $P2_1/c$ with 4 molecules in a unit cell of dimensions $a = 6.459$ (1) Å, $b = 22.497$ (3) Å, $c = 11.568$ (2) Å, and $\beta = 94.92$ (2)°. A total of 2850 intensities were collected on a Nonius CAD4 automatic diffractometer with graphite-monochromatized Cu Kα radiation. A total of 667 of these were below the 2.5σ level and were treated as unobserved. No absorption correction was applied (crystal dimensions $0.3 \times 0.3 \times 0.15$ mm; $\mu = 32.7$ cm^{-1}). The positions of Cl and S were derived from an E^2 Patterson synthesis; the C and O atoms were located in a subsequent ΔF synthesis. Refinement proceeded by anisotropic block-diagonal least-squares calculations. The refinement was not altogether satisfactory in that C(3) and C(4) obtained very large thermal parameters while the distances involving C(3) and C(4) were rather short. Also a ΔF synthesis at this stage revealed all H atoms except those attached to C(3) and C(4); near these atoms several peaks of about 0.3 e/Å^3 occurred, but these could not be ascribed to H. Probably disorder is responsible for all this, different conformations of the six-membered ring C(1)–C(6) being present in the crystal. C(1), C(2), C(5), and C(6) are coplanar (deviations ≤0.004 Å; see Table III), C(2) and C(5) having somewhat larger thermal parameters than C(1) and C(6). These four atoms will be more or less fixed by the three- and five-membered rings in which C(1) and C(6) participate. The refined coordinates of C(3) and C(4) represent average positions. Probably two extreme conformations make large contributions to the average electron density with, in each case, C(3) and C(4) at opposite sides of the plane of C(1), C(2), C(5), and C(6). Continued refinement after inclusion of isotropic H atoms (except those at C(3) and C(4)) converged to an R value of 0.057. The final coordinates are listed in Table I. Table II gives the bond distances and angles. In Table III the distances of the relevant atoms from the best planes through C(1)–C(2)–C(5)–C(6) (I), C(1)–C(6)–C(7)–C(9) (II), and C(11)–C(16) (III) are indicated. The angles between planes I, II, and that of the cyclopropane ring (IV) are as follows: I–II 143.0°, I–IV 73.8°, and II–IV 69.2°. C(17) and S are deviating significantly in the same direction from the plane of the benzene ring, which is slightly boat shaped.

Stereochemistry and Reactivity of 2a and 2b. As pointed out above, it was initially unexpected that **2b** is tosylated with much greater ease than **2a**. While a detailed analysis of the conformational aspects of these and other [*n*.3.1]propellanes will be the subject of a future publication, it is sufficient in the present context

Table II. Bond Lengths (Å) and Bond Angles (Deg) with Esd's in Parentheses

C(1)–C(2)	1.527 (6)	C(2)C(1)C(6)	120.3 (4)
C(1)–C(6)	1.515 (6)	C(2)C(1)C(9)	119.7 (4)
C(1)–C(9)	1.510 (6)	C(2)C(1)C(10)	117.4 (4)
C(1)–C(10)	1.483 (6)	C(6)C(1)C(9)	108.4 (4)
C(2)–C(3)	1.502 (9)	C(6)C(1)C(10)	59.1 (3)
C(3)–C(4)	1.355 (12)	C(9)C(1)C(10)	117.3 (3)
C(4)–C(5)	1.477 (9)	C(1)C(2)C(3)	113.5 (5)
C(5)–C(6)	1.514 (6)	C(2)C(3)C(4)	122.1 (6)
C(6)–C(7)	1.521 (6)	C(3)C(4)C(5)	123.2 (8)
C(6)–C(10)	1.478 (6)	C(4)C(5)C(6)	113.2 (5)
C(7)–C(8)	1.529 (6)	C(1)C(6)C(5)	120.6 (3)
C(8)–C(9)	1.521 (6)	C(1)C(6)C(7)	108.4 (4)
C(8)–O(1)	1.471 (4)	C(1)C(6)C(10)	59.4 (3)
C(10)–Cl	1.769 (4)	C(5)C(6)C(7)	119.5 (4)
C(11)–C(12)	1.380 (6)	C(5)C(6)C(10)	118.1 (4)
C(11)–C(16)	1.388 (5)	C(7)C(6)C(10)	116.3 (3)
C(11)–S	1.748 (5)	C(6)C(7)C(8)	105.7 (4)
C(12)–C(13)	1.370 (6)	C(7)C(8)C(9)	108.3 (4)
C(13)–C(14)	1.388 (6)	C(7)C(8)O(1)	112.0 (3)
C(14)–C(15)	1.382 (6)	C(9)C(8)O(1)	107.9 (3)
C(14)–C(17)	1.497 (7)	C(1)C(9)C(8)	106.5 (4)
C(15)–C(16)	1.380 (6)	C(1)C(10)C(6)	61.6 (3)
S–O(1)	1.571 (3)	C(1)C(10)Cl	121.6 (3)
S–O(2)	1.425 (4)	C(6)C(10)Cl	121.9 (3)
S–O(3)	1.417 (3)	C(12)C(11)C(16)	119.9 (4)
		C(12)C(11)S	120.3 (3)
		C(16)C(11)S	119.8 (3)
		C(11)C(12)C(13)	119.9 (4)
		C(12)C(13)C(14)	121.5 (4)
		C(13)C(14)C(15)	117.8 (4)
		C(13)C(14)C(17)	120.0 (4)
		C(15)C(14)C(17)	122.2 (4)
		C(14)C(15)C(16)	121.7 (4)
		C(11)C(16)C(15)	119.1 (4)
		C(11)SO(1)	104.2 (2)
		C(11)SO(2)	109.4 (2)
		C(11)SO(3)	109.4 (2)
		O(1)SO(2)	102.9 (2)
		O(1)SO(3)	109.5 (2)
		O(2)SO(3)	120.1 (2)

Table III. Distances (Å) from Various Planes

I (C(1), C(2), C(5), C(6))		II (C(1), C(6), C(7), C(9))		III (C(11)–C(16))	
C(1)	0.004 (4)	C(1)	−0.006 (4)	C(11)	−0.021 (4)
C(2)	−0.002 (5)	C(6)	0.006 (3)	C(12)	0.012 (4)
C(5)	0.002 (5)	C(7)	−0.004 (4)	C(13)	0.005 (4)
C(6)	−0.004 (3)	C(9)	0.004 (4)	C(14)	−0.013 (4)
				C(15)	0.005 (4)
C(3)	0.085 (6)	C(8)	0.251 (4)	C(16)	0.012 (4)
C(4)	−0.238 (9)			C(17)	−0.061 (4)
				S	−0.138 (2)

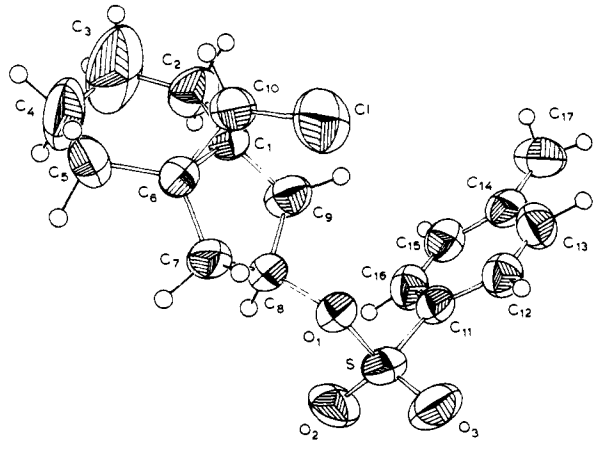
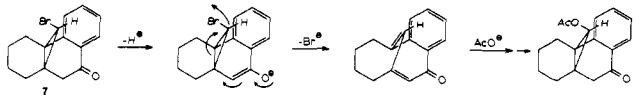


Figure 1. ORTEP drawing and numbering of **3**.

Scheme IV



to point out that according to the crystal structure (Figure 1), the five-membered ring in **3** has an envelope conformation that is slightly bent away from the three-membered ring. This brings the tosyloxy group into a pseudoequatorial position. The NMR spectra (see Experimental Section) indicate that the same conformation applies to both **3** and **2b**, whereas representatives of the **a** (i.e., *endo*-chloro) series, **2a** and **4**, as well as **1** (conformationally fixed) and **5** (conformationally unbiased by a chloro substituent), have a different conformation with the envelope pointing toward the three-membered ring (note the small couplings between H(8) and H(7,9)).

Our preliminary interpretation is as follows. In the "natural" conformation, a [4.3.1]propellane apparently has the envelope of the five-membered ring preferentially pointing to the smaller, three-membered ring; this tendency is already present in the bicyclo[3.1.0]hexane system[16] and is probably enhanced in the [4.3.1]propellanes by the conformationally mobile (cf. the large elipsoids of C(3) and C(4) in the crystal structure) and space-filling tetramethylene chain of the six-membered ring. In this conformation, the pseudoaxial hydroxyl group of **2a** is sterically hindered by the *exo*-hydrogen of the three-membered ring, so that approach by the tosylating reagent is impeded. In **2b**, the large *exo*-chlorine at C(10) pushes the five-membered ring down; as a consequence, the *exo*-hydroxyl group is pseudoequatorial and therefore accessible in a more or less normal fashion.

The Mechanism of Formation of 1. The transformation of **2a** to **1** by base fulfills the geometric requirements of a S_N2 reaction with inversion of configuration (Williamson ether synthesis). However, possible alternative mechanism must a priori be considered.

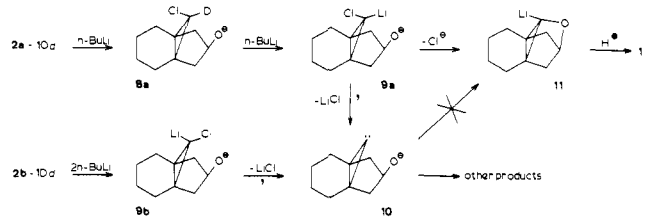
In the first place, it was of interest to investigate the possibility of an S_N2 reaction with retention. As mentioned in the introduction, calculations predict the possibility of this mechanism, in particular for substitutions at small rings.[7] When **2b** was subjected to treatment with *t*-BuOK in Me_2SO under identical conditions as **2a**, it was recovered unchanged and no trace of **1** could be detected by GLC. This result proves that S_N2 substitution by front-side attack does not occur; it does not disprove the possibility of substitution with retention by attack of the nucleophile in the plane of the three-membered ring—the pathway predicted by the calculations—because geometric restraints in **2b** make such a lateral approach of the alkoxide toward C(10) impossible.

Elimination–addition reactions as alternatives to a S_N2 reaction can be excluded in our case. Formation of a cyclopropene[8-10] is impossible as there is no β-hydrogen relative to the leaving-group chloride. Elimination via a bridgehead olefin, which has been demonstrated for the nucleophilic substitution of **7**[11] (Scheme IV), is also impossible for **2a** and is, moreover, excluded by the lack of reaction with **2b**.

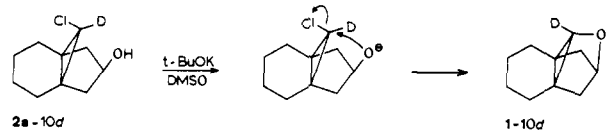
Finally and most seriously, a carbene mechanism has to be excluded. Therefore, **2a** and **2b** were treated with a 10–15-fold excess of *n*-butyllithium (*n*-BuLi) in ether/hexane (ca. 2:1) at room temperature for 16 h. **2b** was recovered essentially unchanged (a few percent decomposition may have occurred), and **2a** afforded 2–5% of **1**. When the reaction was repeated with the deuterated compounds, **2a**-*10-d* gave 2% **1** containing less than 0.6% deuterium; recovered **2a**-*10-d* or **2b**-*10-d* had completely retained the label.

These results reveal that the carbene route from **2a** to **1** is possible but not very efficient, contrary to the S_N2 process with *t*-BuOK. It is furthermore striking that **1** is not formed from **2b**. One reason may be that metalation of **2a** is favored relative to

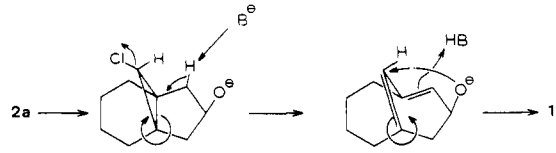
Scheme V



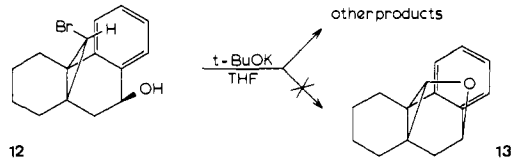
Scheme VI



Scheme VII



Scheme VIII



that of **2b** by complexation of the organolithium reagent to the negatively charged oxygen in **8a** and "intramolecular" abstraction of the proton at C(10).[17] It is also conceivable that carbenoid **9a** behaves in a way different from **9b**. Rather than reacting via the free carbene **10**, **9a** may undergo nucleophilic substitution of the activated chloride,[10] leading to **11**, which is subsequently protonated to **1**; in **9b**, the substitution process is not favorable, and other decomposition pathways may prevail (Scheme V). Convincingly, the reaction of **2a**-*10-d* (99.3 ± 1% D) with *t*-BuOK in Me_2SO under standard conditions gave **1**-*10-d* (60% yield, 98.8 ± 1% D) with virtually complete retention of the label; when the reaction was performed with **2a** and *t*-BuOK in Me_2SO-d_6, no incorporation of deuterium was observed in **1** (Scheme VI).

The last result simultaneously excludes a sequence of ring-opening[18] and ring-closure[19] reactions depicted in Scheme VII.[20] Such a course of events may be considered unlikely in view of the high strain involved in the intermediate diene and the rather high energy required for the inversion of its pyramidalized olefinic carbon atom[21] when it is attacked by the negatively charged oxygen. But whatever the argument may be, the nonincorporation of deuterium is incompatible with this pathway.

These results complete the argumentation in favor of a "normal" backside nucleophilic substitution with inversion of configuration of the S_N2 type at a cyclopropyl carbon atom. Upon reflection of the reasons why a genuine S_N2 reaction at a cyclopropane carbon atom is so rare, the following favorable circumstances come to mind. Of great importance is the nonavailability of escape reactions. Equally important appear to be intramolecularity of the reaction[10] and a favorable symmetrical arrangement of nucleophilic and leaving groups. A slight deviation from the ideal alignment prevents substitution, as is illustrated by the observation

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that in the reaction of **12** with *t*-BuOK no **13** is formed[11] (Scheme VIII).

Experimental Section

Proton and ^{13}C magnetic resonance spectra were recorded on a Bruker WH-90 spectrometer. Data are reported as follows: chemical shifts (δ, relative to tetramethyl silane as an internal standard), multiplicity, coupling constants, and integral. Mass spectral data were obtained with a Varian CH-5 DF mass spectrometer at an ionization energy of 70 eV. Infrared spectra were recorded on a Beckman 580B spectrometer. All melting points are uncorrected. Microanalyses were performed at the Organisch Chemisch Instituut TNO, Zeist, The Netherlands, under the supervision of W. L. Buis.

***endo*- and *exo*-10-Chloro-*exo*-8-hydroxytricyclo[4.3.1.0^{1,6}]decane (2a and 2b, Respectively).** 4,5,6,7-Tetrahydro-2-indanol[13] (6.9 g, 50 mmol) was dissolved in a mixture of 180 mL of dry ether and 180 mL of dichloromethane. The solution was cooled to −60 °C and stirred. At this temperature 200 mL of a 1.48 M solution of *n*-butyllithium in hexane (296 mmol) was added in 0.5 h. The mixture was slowly warmed to room temperature and quenched with water. The layers were separated, the water layer was extracted twice with ether, and the combined organic layers were washed with water, brine, and water, dried over $MgSO_4$, and concentrated at reduced pressure. The residual oil, 9.81 g, contained some polymeric material and **2a** and **2b** in a ratio 2:1. For analytical purposes separation of the products was achieved by preparative GLC (1.5 m, 15% Carbowax-20M on Chromosorb WHP, 185 °C). The approximate total yield was 94%.

For **2a**: white solid, mp 55–57 °C; ^1H NMR ($CDCl_3$) 4.32 (t of t, J = 4.0, 3.6 Hz, 1 H), 3.50 (s, 1 H), 2.02–2.01 (2 × d, J = 4.0 Hz, J = 3.6 Hz, 4 H), 1.8–1.65 (m, 4 H + OH); 1.31 (m, 4 H); ^{13}C NMR ($CDCl_3$, 22.63 MHz) 72.27 (d, J = 141 Hz, C(8)), 46.99 (t, J = 131 Hz, C(7,9)), 45.56 (d, J = 190 Hz, C(10)), 28.86 (s, C(1,6)), 23.85 (t, J = 126 Hz, C(2,5)/C(3,4)), 21.51 (t, J = 129 Hz, C(3,4)/C(2,5)); IR (10% solution in CCl_4) 3630, 3380, 3060, 2930, 2850, 1445, 1050 cm^{-1}; mass spectrum, m/z 186/188 ($C_{10}H_{15}ClO^{+\cdot}$, 53% and 18%, calcd for $C_{10}H_{15}{}^{35}ClO^{+\cdot}$ 186.0811, obsd 186.0813), 133 ($C_{10}H_{13}^{+\cdot}$, 100%).

For **2b**: pale yellow oil; ^1H NMR ($CDCl_3$) 4.57 (t of t, J = 9, 6.5 Hz, 1 H, X part of A_2B_2X system), 3.34 (s, 1 H), 2.10 (A_2B_2 [X], δ_A 2.28, δ_B 1.93, J_{AB} = 14 Hz, J_{AX} = 9.0 Hz, J_{BX} = 6.5 Hz, 4 H), 1.8–1.65 (m, 4 H), 1.60 (br s, OH), 1.23 (m, 4 H); mass spectrum, m/z 186/188 ($C_{10}H_{15}ClO^{+\cdot}$, 9% and 3%, calcd for $C_{10}H_{15}{}^{35}ClO$ 186.0811, obsd 186.0822), 91 ($C_7H_7^+$, 100%).

***exo*-10-Chloro-*exo*-8-(tosyloxy)tricyclo[4.3.1.0^{1,6}]decane (3).** The 2:1 mixture (7.2 g, 45 mmol) of the isomeric alcohols **2a** and **2b** was dissolved in 50 mL of dry pyridine and added dropwise to a stirred ice-cooled solution of 5.7 g (30 mmol) of *p*-toluenesulfonyl chloride in 50 mL of dry pyridine. After the addition, the mixture was stirred for another hour at 0 °C and then kept in the refrigerator at 3–5 °C for 24 h. The reaction was quenched by adding 540 μL (30 mmol) of H_2O. A precipitate was formed and discarded, and the mother liquor was poured into 300 mL of ice water and extracted 3 times with 40-mL portions of ether. The combined ether layers were washed with a $CuSO_4$ solution until no Cu–pyridine complex was formed any more, dried over $MgSO_4$, and concentrated at reduced pressure. To the remaining oil was added 50 mL of hexane; the mixture was shaken vigorously and kept at −20 °C for several days. The crystalline tosylate was collected by suction filtration. The mother liquor, containing **2a**, was, after evaporation of the solvent, used for the preparation of **4** (vide infra). The crude product contained about 90% **3** and about 10% of the tosylate of **2a**. Recrystallization from hexane afforded **3** (yield 70%, from **2b**): white solid, mp 85.5 °C; ^1H NMR ($CDCl_3$) 7.56 (A_2B_2, δ_A 7.77, δ_B 7.34, J_{AB} = 8.5 Hz, 4 H), 5.19 (quint J = 9 Hz, 1 H), 3.27 (s, 1 H), 2.45 (s, 3 H), 2.09 (d, J = 9 Hz, 4 H), 1.8–1.6 (m, 4 H), 1.22 (m, 4 H).

Anal. Calcd for $C_{17}H_{21}ClO_3S$: C, 59.90; H, 6.21; O, 14.08. Found: C, 60.00; H, 6.00; O, 13.97.

***endo*-10-Chloro-*exo*-8-(mesyloxy)tricyclo[4.3.1.0^{1,6}]decane (4).** **4** was prepared by mixing 2 equiv (7.33 g, 64 mmol) of methanesulfonyl chloride and 5.97 g (32 mmol) of the alcohol **2a**, obtained from the mother liquor of the previous reaction, under similar conditions as in the tosylation reaction. The workup was identical with that of **3**. 4 was obtained as a pale yellow solid, which could not be purified by crystallization, probably due to its instability (yield 91%, from **2a**): pale yellow solid, mp 105–110 °C dec; ^1H NMR ($CDCl_3$) 5.13 (t of t, J = 5.5, 1 Hz, 1 H, X part of A_2B_2X system), 3.21 (s, 1 H), 2.98 (s, 3 H), 2.31 (A_2B_2[X], δ_A 2.39, δ_B 2.23, J_{AB} = 15 Hz, J_{AX} = 1 Hz, J_{BX} = 5.5 Hz, 4 H), 1.8–1.7 (m, 4 H), 1.31 (m, 4 H).

Anal. Calcd for $C_{11}H_{17}ClO_3S$: C, 49.90; H, 6.47; O, 18.13. Found: C, 49.60; H, 6.68; O, 17.64.

***exo*-8-Hydroxytricyclo[4.3.1.0^{1,6}]decane (5).** The 2:1 mixture (1.01 g, 5.41 mmol) of **2a** and **2b** was treated with sodium in liquid ammonia analogous to the method described by Closs and Closs.[15] After workup and crystallization from pentane, 0.76 g (5 mmol) of a white crystalline material (**5**) was obtained (yield, 92%): white solid, mp 55–63 °C (lit.[13] mp 61–68 °C); ^1H NMR ($CDCl_3$) 4.29 (quint, J = 3.75 Hz, 1 H), 1.87 (d, J = 3.75 Hz, 4 H), 1.7–1.5 (m, 4 H), 1.62 (br s, OH), 1.3–1.1 (m, 4 H), 0.83 (d, J = 4 Hz, H(10), anti), 0.31 (d, J = 4 Hz, H(10), syn); mass spectrum, m/z 152 ($C_{10}H_{16}O^{+\cdot}$, 14%, calcd for $C_{10}H_{16}O$ 152.1201, obsd 152.1202), 93 ($C_7H_9^{+\cdot}$, 100%).

***endo*- and *exo*-10-Chlorotricyclo[4.3.1.0^{1,6}]dec-7-ene (6a and 6b, Respectively).** The elimination reactions of **3** and **4** were performed in the same manner. To the dry reactant was added 3 equiv of freshly sublimed *t*-BuOK; then 15 mL of dry Me_2SO was added, the reaction vessel was closed and sealed, and the solution was stirred for 16 h at room temperature. The reactions were performed with ca. 4 mmol of reactant. The reaction was stopped by pouring the mixture into a 5-fold quantity of ice water, followed by extraction with pentane. The organic layers were washed with water (2×) and brine (2×), dried over $MgSO_4$, and concentrated at reduced pressure. From **3**, **6b** was isolated as a pale yellow oil in 35% yield; it was purified by preparative GLC (1.5 m, 10% Carbowax 20-M on Chromosorb-WHP, 100 °C). From **4**, **6a** was isolated as a yellow oil in 82% yield; it contained almost no impurities and was not purified by GLC.

For **6a**: ^1H NMR ($CDCl_3$) 5.62 (AB[XX′], δ_A 5.77, δ_B 5.47, J_{AB} = 5.5 Hz, J_{AX} = $J_{AX'}$ = J_{BX} = $J_{BX'}$ = 2 Hz, 2 H), 2.62 (s, 1 H), 2.57 ([AB]XX′, δ_X 2.63, $\delta_{X'}$ 2.50, $J_{XX'}$ = 18 Hz, J_{XA} = $J_{X'A}$ = J_{XB} = $J_{X'B}$ = 2 Hz, 2 H), 1.95–1.8 (m, 4 H), 1.4–1.25 (m, 4 H); mass spectrum, m/z 168/170 ($C_{10}H_{13}Cl^{+\cdot}$, 3% and 1%, calcd for $C_{10}H_{13}{}^{35}Cl$ 168.0706, obsd 168.0707), 91 ($C_7H_7^{+\cdot}$, 100%).

For **6b**: ^1H NMR ($CDCl_3$) 5.63 (AB[XX′], δ_A 5.72, δ_B 5.54, J_{AB} = 5.5 Hz, J_{AX} = $J_{AX'}$ = J_{BX} = $J_{BX'}$ = 2 Hz, 2 H), 3.33 (s, 1 H), 2.50 ([AB]XX′, δ_X 2.63, $\delta_{X'}$ 2.38, $J_{XX'}$ = 18 Hz, J_{XA} = $J_{X'A}$ = J_{XB} = $J_{X'B}$ = 2 Hz, 2 H), 2.0–1.85 (m, 4 H), 1.3–1.15 (m, 4 H); mass spectrum, m/z 168/170 ($C_{10}H_{13}Cl^{+\cdot}$, 1.3% and 0.4%, calcd for $C_{10}H_{13}{}^{35}Cl$ 168.0706, obsd 168.0701), 91 ($C_7H_7^{+\cdot}$, 100%).

9-Oxatetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecane (1). **2a** (42 mg, 0.225 mmol), purified by preparative GLC, was dissolved in 5 mL of dry Me_2SO. To this solution was added 0.14 g (1.25 mmol) of freshly sublimed *t*-BuOK. The reaction vessel was closed and sealed, and the solution was stirred for 16 h at room temperature. The reaction was quenched by adding ice water to the mixture; organic products were extracted 3 times with pentane, and the organic layers were washed with water (2×) and brine (2×), dried over $MgSO_4$, and concentrated at reduced pressure. The product was an oil, which was submitted to preparative GLC (1.5 m, 10% SE-30 on Chromosorb WHP, 100 °C) to give **1** as a colorless liquid in 95% yield: ^1H NMR ($CDCl_3$) 4.14 (br s, 1 H at C(8)), 3.41 (s, 1 H at C(10)), 1.95–1.8 (m, 4 H), 1.39 (br s, 4 H at C(7) and C(11)), 1.3–1.15 (m, 4 H); ^{13}C NMR ($CDCl_3$, 22.63 MHz) 71.84 (d, J = 169 Hz, C(8)), 60.77 (d, J = 195 Hz, C(10)), 38.31 (t, J = 135 Hz, C(7,11)), 22.88 (t, J = 129 Hz, C(2,5)/C(3,4)), 22.51 (t, J = 129 Hz, C(3,4)/C(2,5)), 21.00 (s, C(1,6)); mass spectrum, m/z 150 ($C_{10}H_{14}O^{+\cdot}$, 67%, calcd for $C_{10}H_{14}O$ 150.1045, obsd 150.1046), 79 ($C_6H_7^{+\cdot}$, 100%); IR (10% solution in CCl_4) 3060, 3020, 2930, 2860, 1450, 1255, 1108, 1060, 1048, 998 cm^{-1}.

Reactions of 2a with *n*-BuLi. To an ice-cooled solution of 22 mg (0.12 mmol) **2a** in 5 mL of dry ether was added dropwise a 10-fold excess of *n*-BuLi (solution in hexane). After the addition, the mixture was warmed to room temperature and stirred for 16 h. After this period, the mixture was cooled to −20 °C and quenched with water. The layers were separated, the aqueous layer was extracted twice with ether, and the organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated at reduced pressure. The resulting mixture of products was separated by preparative GLC (1.5 m, 10% SE-30 on Chromosorb WHP, 100–150 °C), and the products (**2a** and **1**) were identified by their ^1H NMR spectra.

2a-*10-d* and 2b-*10-d*. The carbene addition reaction (vide supra) for **2a** and **2b** was performed with 10 mmol of 4,5,6,7-tetrahydro-2-indanol, 25 g of CD_2Cl_2 (99.9% D atom), 50 mL of dry ether, and 70 mmol of *n*-BuLi. The products were formed in about 50% yield and purified by preparative GLC. The NMR spectra of **2a-*10-d*** and **2b-*10-d*** were identical with those of **2a** and **2b** but missed resonances at 3.50 and 3.34 ppm, respectively. The percentage of deuterium, 99.3 ± 1 and 97.6 ± 2%, respectively, was calculated from the mass spectra.

Reaction of 2a-*10-d* with *t*-BuOK. The cyclization reaction was performed in a manner analogous to the reaction of **2a** with *t*-BuOK (vide supra) on a 0.08-mmol scale. **1-*10-d***, obtained in about 60% yield, was identical with **1** except for a missing resonance at 3.41 ppm in its ^1H NMR spectrum. The percentage of deuterium, 98.8 ± 1%, was calculated from the mass spectrum.

Reaction of 2 with *t*-BuOK in Me_2SO-d_6. The reaction was performed as described before, with 70 mg (0.37 mmol) of a 3:1 mixture of **2a** and

2b in 2.5 mL of Me_2SO-d_6 and 200 mg (1.8 mmol) of *t*-BuOK. After the solution was stirred at room temperature for 16 h, the reaction mixture was worked up, yielding 50 mg of a mixture of **1**, **2a**, and **2b** in a ratio of 35:40:25, as was shown by GC-MS. Neither in **1** nor in **2a** or **2b** was deuterium incorporated.

Registry No. 1, 81387-93-1; **1**-*10-d*, 81387-94-2; **2a**, 74543-53-6; **2a**-*10-d*, 81387-95-3; **2b**, 74561-81-2; **2b**-*10-d*, 81444-71-5; **3**, 74543-54-7; **4**, 74543-55-8; **5**, 81444-72-6; **6a**, 74543-56-9; **6b**, 74561-82-3; 4,5,6,7-tetrahydro-2-indanol, 6010-79-3.

Supplementary Material Available: Table IV (thermal parameters), Table V (hydrogen atom parameters) (2 pages). Ordering information is given on any current masthead page.

Synthesis of Chiral [^{18}O]Phosphorothioate Analogues of Adenine Nucleotides

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Abstract: Syntheses of R_P-ATPγS,$\gamma^{18}O_2$, R_P- and S_P-ADPβS,β^{18}O, and R_P- and S_P-AMPS,^{18}O are described. Coupling of 2′,3′-(methoxymethylidene)-AMP, **1**, with S_P-ADPαS,$\alpha^{18}O_2$ produced P^1-5′-adenosyl P^3-2′,3′-(methoxymethylidene)-5′-adenosyl 1-thio[1-tri$^{18}O_2$]phosphate, **3**. Upon cleavage of the unprotected ribose ring with IO_4^-, reduction of IO_3^- by $HPSO_3^{2-}$, removal of the 2′,3′-methoxymethylidene protecting group at pH 2, and alkaline elimination of the product from the IO_4^--cleaved dialdehyde, R_P-ATPγS,$\gamma^{18}O_2$ was produced and isolated by chromatography in 55-58% yield based on S_P-ADPαS,$\alpha^{18}O_2$. Coupling of AMPS,$^{18}O_2$ with **1** produced (R_P)- and (S_P)-P^1-5′-adenosyl P^2-2′,3′-(methoxymethylidene)-5′-adenosyl 1-thio[1-^{18}O]pyrophosphate, **4a** and **4b**, which were separated by ion-exchange chromatography through DEAE-Sephadex A-25. Periodate cleavage, deprotection, and alkaline elimination of **4a** and **4b** analogous to that described above for **3** produced S_P- and R_P-ADPβS,β^{18}O, respectively. Coupling of AMPS,$^{18}O_2$ with AMP produced (R_P)- and (S_P)- P^1,P^2-bis(5′-adenosyl) 1-thio[1-^{18}O]pyrophosphate, **5a** and **5b**, which were separated by ion-exchange chromatography through DEAE-Sephadex A-25. Nucleotide pyrophosphatase catalyzed hydrolysis of **5a** and **5b** produced R_P- and S_P-AMPS,^{18}O, respectively. These chiral nucleoside and nucleotide [^{18}O]phosphorothioates are useful as substrates for stereochemical studies of phosphotransferases. These compounds and their precursors should also serve as important synthetic precursors of ADP and ATP stereospecifically enriched with heavy isotopes of oxygen at any desired position in the phosphoanhydride system.

The efficacy of chirally substituted phosphorothioates in studies of the stereochemical courses of enzymatic phosphoryl group transfer has been demonstrated in a number of studies of reactions catalyzed by phosphohydrolases, phosphotransferases, and nucleotidyltransferases.[3] An essential prerequisite for such studies is the capability to synthesize phosphorothioates that are both acceptable substrates and chirally substituted at the phosphorus atoms that undergo nucleophilic substitution. The sulfur analogue of ATP used in determining the stereochemical courses of the actions of phosphotransferases has one of the three equivalent oxygen atoms bonded to P_γ replaced by a sulfur atom and another enriched in ^{18}O to produce a chiral phosphorus center at P_γ.

We have recently determined the stereochemical courses of phosphoryl group transfer catalyzed by adenylate kinase,[3d] nucleoside phosphotransferase,[4] nucleoside diphosphate kinase,[3j] and adenosine kinase.[5] In these studies R_P- and S_P-AMPS,^{18}O, R_P- and S_P-ADPβS,β^{18}O, and R_P-ATPγS,γ^{18}O were synthesized and used either as substrates or as reference compounds for the assignment of configurations to products of enzymatic [^{18}O]thiophosphoryl transfer.

The chiral [^{17}O]- and [^{18}O]phosphorothioate analogues of nucleotides are important as starting materials for a number of isotopically enriched nucleotides as well as for stereochemical studies in which they serve as substrates for enzymes. They serve as precursors for nucleotides whose α or β phosphorus atoms are chiral by virture of stereospecific ^{17}O and ^{18}O enrichments. They are also key intermediates in the synthesis of nucleotides having exclusively α-β or β-γ-bridging ^{17}O or ^{18}O. This paper describes in detail the syntheses and configurational analyses of the chiral [^{18}O]phosphorothioate analogues of adenine nucleotides including R_P- and S_P-AMPS,^{18}O (adenosine 5′-[^{18}O]phosphorothioate), R_P- and S_P-ADPβS,β^{18}O (adenosine 5′-(2-thio[2-^{18}O]diphosphate)), and R_P-ATPγS,γ^{18}O (adenosine 5′-(3-thio[3-^{18}O]triphosphate)]. Some of the procedures have been reported briefly in Communications.[3d,6]

Materials and Methods

Enzymes, Coenzymes, and Chemicals. The following enzymes were purchased from Sigma Chemical Co. and used without additional purification: rabbit muscle pyruvate kinase, rabbit muscle adenylate kinase, rabbit muscle lactate dehydrogenase, *E. coli* alkaline phosphatase, *E. coli* acetate kinase, yeast hexokinase, and snake venom (*Crotalus atrox*) nucleotide pyrophosphatase. All nucleotides and nucleosides were purchased from Sigma Chemical Co., as were phosphoenol pyruvate, acetyl phosphate, and DEAE-Sephadex A-25. Thiophosphoryl trichloride and sodium thiophosphate were purchased from Ventron. Deuterium oxide (99.7% enriched) and $H_2{}^{18}O$ (99% enriched) were purchased from BioRad Laboratories. All other chemicals were reagent grade and were obtained from commercial sources.

^{31}P NMR and Mass Spectral Analyses. ^{31}P NMR spectra were obtained on a Bruker HX-90 spectrometer operating at 36.43 MHz and equipped with Fourier transform and proton noise decoupler accessories

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