Journal of Chemical Research (M)

Paper E/143/78 Received 14th August 1978‡

Tetraisopropyldisiloxane-1,3-diyl, a Group for Simultaneous Protection of 3′- and 5′-Hydroxy Functions of Nucleosides

By Wojciech T. Markiewicz

/Department of Stereochemistry of Natural Products, Institute of Organic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznań, Poland/

A new type of silyl protecting group was designed and a reagent for its introduction was synthesized. This reagent, 1,3-dihalo-1,1,-3,3-tetraisopropyldisiloxane allows simultaneous protection of 3′- and 5′-OH groups of nucleosides in high yield. When this reagent is applied to 5′-O-protected nucleosides it blocks 2′- and 3′-OH groups. The properties of the protecting group, including its removal, selective partial cleavage and some applications, are presented.

SELECTIVE protection of different hydroxyl functions is one of the crucial problems in the syntheses involving nucleosides and other polyfunctional compounds. A variety of protecting groups [1] allowing direct protection of nucleoside sugar hydroxyl groups has been worked out: /i/ for 5′-OH: trityl and its derivatives, trialkylsilyl and different acyl groups; /ii/ for 2′- and 3′-OH: benzyl, o-nitrobenzyl and acyl groups; /iii/ for simultaneous protection of 2′- and 3′-OH: alkylidene derivatives, cyclic carbonates, phenyl boronates, cyclic phosphates and dibutylstannylene derivatives.

As far as we knew a reagent for simultaneous protection of 3′- and 5′-hydroxyl functions of nucleoside was not known. +

[1] /a/ C. B. Reese, in "Protective Groups in Organic Chemistry", J. F. W. McOmie, Ed., Plenum Press, London, 1973, pp 95-143. /b/ E. Halsam, ibid., pp 145-182. /c/ V. Amarnath, A. D. Broom, Chem. Rev., 1977, 77, 183-217 and the references cited therein.

+ Only a 3′,5′-cyclic phosphate might be considered as a protecting group introduced in two steps: /i/ 5′-OH phosphorylation followed by /ii/ cyclization with condensing agent.

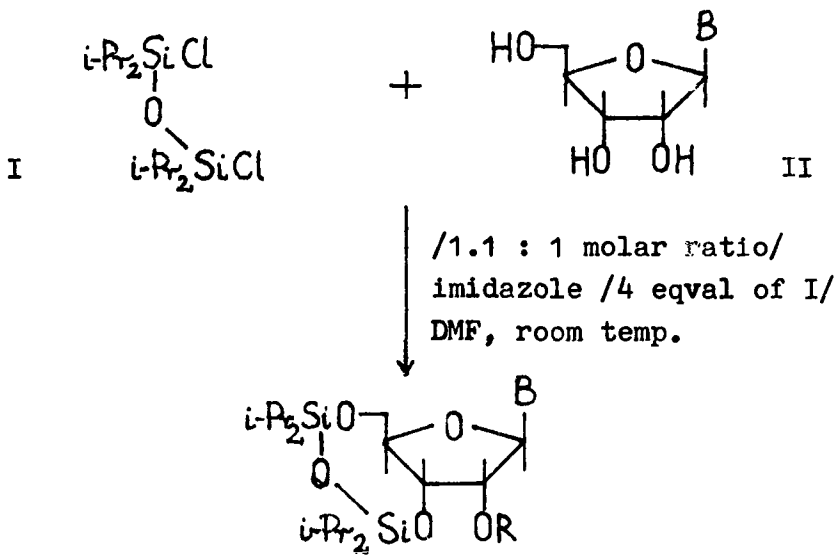
‡ Revised version received 23rd October 1978

A protecting group of such kind would possibly open new routes for the functionalization of nucleoside 2′-position.

Our attention was attracted to silyl protecting groups by the fact that triisopropylsilyl chloride is known to react with 1° alcohol /EtOH/ ca. 10^3 times faster than with 2° alcohol /i-PrOH/.[2] Hopefully, the bifunctional silyl reagent would react rapidly with a chosen hydroxyl group /1°/ and then react intramolecularly with other suitably situated alcoholic function. 1,3-Dihalotetraalkyldisiloxane was expected to fulfil these requirements.

Thus, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane /TIPDSiCl$_2$, I/ was synthesized starting from isopropylmagnesium bromide and trichlorosilane. The obtained diisopropylsilanol was condensed into disiloxane and chlorinated with Cl_2/CCl_4.

TIPDSiCl$_2$ was allowed to react with uridine /IIa/ to give as a main product 3′,5′-O-/tetraisopropyldisiloxane-1,3-diyl/uridine /IIIa, R=H/.



III, R = H

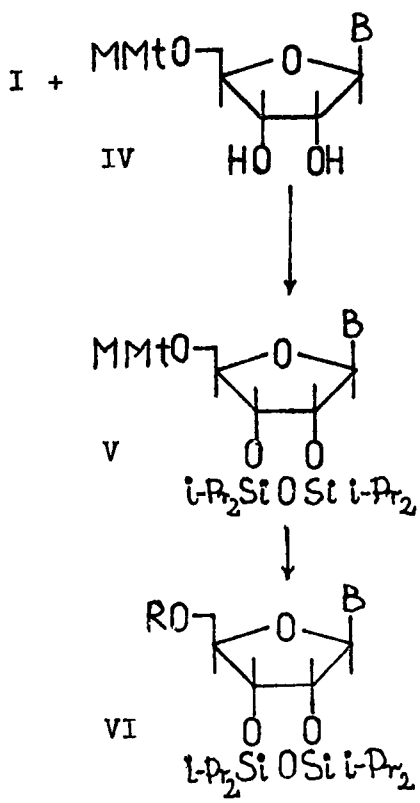
/70 - 80%, after a short column chromatography/

for II and III a, B = uracil-1-yl
b, B = cytosin-1-yl
c, B = 4-N-benzoylcytosin-1-yl
d, B = guanin-9-yl
e, B = adenin-9-yl

[2] A. D. Allen, J. C. Charlton, C. Eaborn and G. Modena, J. Chem. Soc., 1957, 3668.

TIPDSiCl$_2$ was allowed to react with 5′-O-protected nucleoside, namely 5′-O-monomethoxytrityluridine /IV/ in order to check its reactivity towards 2′- and 3′-hydroxyl functions. The reaction was carried out under the same conditions as for an unprotected nucleoside and resulted in 5′-O-monomethoxytrityl-2′,3′-O-/tetraisopropyldisiloxane-1,3-diyl/uridine /V/ as essentially the sole product. The monomethoxytrityl group was removed from V with 0.1 M TsOH in dioxan.

The structure of IIIa /R=H/ was confirmed by: /i/ its pmr spectrum; /ii/ pmr spectrum of its acetyl derivative IIIa /R=Ac//Table 1./. The positions of free hydroxyl groups in each compound described in this paper were estimated by an analysis of pmr spectra of the compound and its acetyl derivative. It is well known that hydrogens attached to the carbon carrying alcoholic function show the largest changes of chemical shifts /downfield/ due to esterification. /iii/ Ms spectrum, M^+ - i-Pr 443.1677 /calc. 443.1612/; /iv/ a TLC comparison of IIIa /R=H/ and VI /ΔR_F ca. 0.1/; /v/ syn-



/1.1 : 1 molar ratio/ imidazole /4 eqval of I/ DMF, room temp.

0.1 M TsOH in dioxan

B = uracil-1-yl, R = H
MMt = monomethoxytrityl

Table 1. Pmr chemical shifts for protected nucleoside derivatives in $CDCl_3$, /ppm/ ± 0.05

compound	base protons		ribose ring protons				
	6or8	5or2	1′	2′	3′	4′	5′
IIIa /R=H/	7.87	5.76	5.81	4.3	4.3	4.3	4.2
IIIa /R=Ac/	7.81	5.77	5.91	5.47	4.42	4.0	4.1
VI /R=H/	7.75	5.78	5.74	4.61	4.61	4.21	3.93
VI /R=Ac/	7.65	5.78	5.82	4.3	4.3	4.5	4.42
VIIa /R=R′=H, X=OH/	8.06	5.65	5.88	4.28	4.28	4.28	4.12
VIIa /R=R′=Ac, X=OH/	7.82	5.74	6.27	5.36	5.41	4.21	4.04
VIIIa /R=R′=H, X=OH/	7.87	5.74	5.82	?	?	?	3.94
VIIIa /R=R′=Ac, X=OH/	7.46	5.76	5.92	5.34	4.69	4.27	4.37
IXa /R=R′=H, X=OH/	8.00	5.74	5.82	?	?	?	3.94
IXa /R=R′=Ac, X=OH/	7.65	5.82	5.97	4.77	5.12	4.4	4.42
VIIa /R=R′=H, X=F/	7.96	5.63	5.88	4.25	4.25	4.25	4.08
VIIIa/R=Ac, R′=H, X=OH/	7.82	5.72	5.89	5.39	4.82	4.14	3.96
IIIb /R=H/[+]	7.72	5.68	5.57	4.05	4.05	4.05	4.05
IIIb /R=Ac/[++]	8.22	7.46	5.88	5.44	4.37	4.15	4.15
IIIc /R=H/	8.32	?	5.88	4.3	4.3	4.3	4.3
IIIc /R=Ac/	8.25	?	5.93	5.48	4.42	4.2	4.2
IIId /R=H/[+]	7.80	-	5.73	4.35	4.35	4.05	4.05
IIId /R=Ac/	7.74	-	5.91	5.75	4.71	4.1	4.1
IIIe /R=H/[§]	8.36	8.07	6.05	4.61	5.04	4.12	4.12
IIIe /R=Ac/[§]	8.33	8.05	6.08	5.83	5.07	4.1	4.13
VIIe /R=H/[§]	8.32	8.12	6.13	4.55	4.55	4.55	4.2
VIIe /R=Ac/	8.31	8.31	6.33	5.75	5.67	4.30	4.10

? No assignment of this signal was done due to overlapping with other ones. [+] In d_6-DMSO. [++] During acetylation of IIIb /R=H/ O- and N-acetylation took place to give III /B=4-N-acetylcytosin-1-yl, R=Ac/. [§] No assignment of H-2 and H-8 signals of adenine moiety was done.

thesis of previously obtained 2′-O-methoxytetrahydropyranyluridine [3] starting from IIIa /R=H/. Other unprotected nucleosides containing free or N-acylated amino group /IIb-e/ were found to

[3] C. B. Reese, R. Saffhill and J. E. Sulston, Tetrahedron, 1970, 26, 1023.

react in the same way as uridine /Scheme 1/ to give 3',5'-O-protected nucleosides [+] in high yields /70 - 80%/.[++] Thus the general importance of $TIPDSiCl_2$ for simultaneous protection of nucleoside 3'- and 5'-OH groups was proved. Furthermore, we have found that $TIPDSiCl_2$ reacts with nucleosides in pyridine as both a solvent and base in exactly the same way as in the presence of imidazole in DMF, although the reaction times were slightly longer. Dibromo analogue of the reagent was obtained as well, i.e. 1,3-dibromotetraisopropyldisiloxane /$TIPDSiBr_2$/. It reacted with uridine in the same way as $TIPDSiCl_2$, but the reaction was much quicker and was finished within minutes.

Stability. Properties of the TIPDSi group at 3' and 5'-positions.

The properties of the TIPDSi group differ slightly depending on which positions of sugar moiety it protects. The properties of this group in 3',5'-positions of nucleoside were primarily investigated with respect to its stability and compatibility with other protecting groups.

We have found that the nucleoside protected by the TIPDSi group is unaffected by: /i/ water; /ii/ ca. 0.3 M TsOH in dioxan; /iii/ 10% F_3CCO_2H in $CHCl_3$ /by vol./; /iv/ 5 M NH_3 in dioxan-water /4:1, by vol./ and i-$BuNH_2$-MeOH /1:9, by vol./; /v/ tertiary amines /pyridine, Et_3N/.

Thus, the TIPDSi group is stable under the conditions of introduction of tetrahydropyranyl [4] and methoxytetrahydropyranyl [3] groups, acyl,[1] arylsulphonyl [1] groups, introduction and removal of trityl groups.[1, 5]

Removal.

The TIPDSi group can be removed quantitatively with ca. 1 M tetra-n-butylammonium fluoride /TBAF/ in THF at room temp. /less than 10 min./ as with other described silyl groups [1, 6, 7] and with a

[+] The method is a matter of Polish Patent application.

[++] The reaction conditions were not optimized.

4 M. Smith, H. G. Khorana, J. Am. Chem. Soc., 1959, 81, 2911.

5 /a/ M. Smith, D. H. Rammler, I. H. Goldberg and H. G. Khorana, J. Am. Chem. Soc., 1962, 84, 430. /b/ H. Schaller, G. Wiemann, B. Lerch and H. G.Khorana, J. Am. Chem. Soc., 1963, 85, 3821.

6 E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 1972, 94, 6190.

7 K. K. Ogilvie, Can. J. Chem., 1973, 51, 3799.

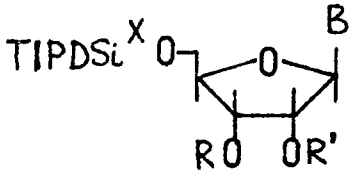
new fluoride reagent, tri-n-butylammonium fluoride /TBAHF, see below/ in ca. 2 hr. This group can also be removed by treatment with 0.2 M HCl in dioxan-water /4:1, by vol./ in ca. 24 hr, with 0.2 M HCl in MeOH in ca. 9 hr, and with 0.2 M NaOH in dioxan-water /4:1, by vol./ in ca. a week.

The partial cleavage of the TIPDSi group which converts it into a protecting group of a single alcoholic function would extend the range of applications of this group. We have found conditions allowing the partial cleavage of the TIPDSi group at the 3′-end as well as at the 5′-end.

/i/ 3′-End cleavage.

When IIIa /R=H/ was dissolved and stirred in dioxan-1 M NaOH aq /4:1, by vol., 10 ml per 1 mmole of III/ at room temp. partial cleavage took place selectively at the 3′-end and VIIa /R=R≠H,X=OH/ was isolated in ca.95% yield. The same results were obtained for other 3′,5′-O-TIPDSi derivatives /IIIb-e, R=H/.

TBAF is too reactive for partial cleavage of the TIPDSi group. Therefore we made a new fluoride reagent which is ca. 50 times less reactive than TBAF, namely tri-n-butylammonium fluoride /TBAHF/. TBAHF /1 M, 1 eqval/ in THF reacts with IIIa /R=H/ in 0.5 hr at room temp. and the attack takes place mainly at the 3′-end. Thus, VIIa /R=R≠H, X=F/ was obtained in ca. 60% yield and it could be hydrolyzed into hydroxy analogue, VIIa /R=R≠H, X=OH/ with aqueous pyridine.

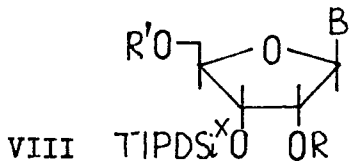


VII

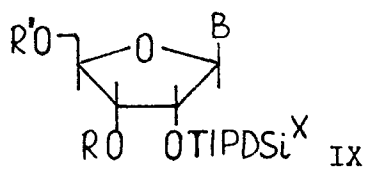
$TIPDSi^X$ = XSi/i-Pr/$_2$OSi/i-Pr/$_2$-

/ii/ 5′-End cleavage.

Treatment of IIIa /R=H/ with 0.2 M HCl in dioxan-water /4:1, by vol./ at room temp. for 2.5 hr gave the mixture of VIIa, VIIIa and IXa /R=R≠H, X=OH/ in the ratio 2 : 5 : 3, respectively, thus showing that the reaction was accompanied by 3′⟶2′ isomerization. 2′-O-Acetyl group was found to be stable under the conditions



VIII

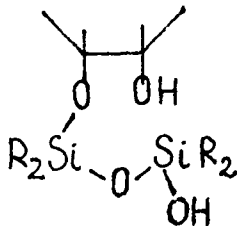


IX

$TIPDSi^{X}$ = $XSi/i\text{-}Pr/_2OSi/i\text{-}Pr/_2$-

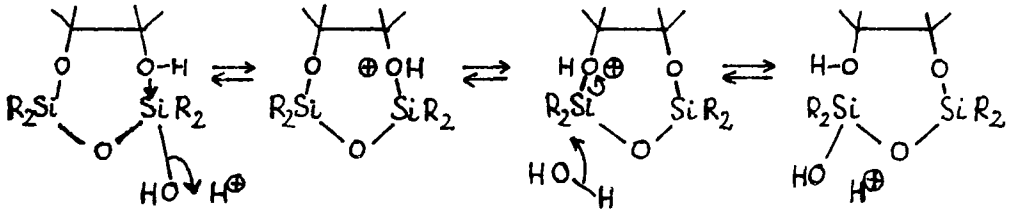
of acidic partial cleavage. IIIa /R=Ac/ underwent 5′-end cleavage without 3′-end cleavage and gave VIIIa /R=Ac, R=H, X=OH/ as essentially the sole product. Unfortunately, the isomerization took place during the removal of the acetyl group under alkaline [+] conditions, as judged from pmr spectrum of the product.

There is little known about isomerization of alkylsilyl groups. Little, if any, migration of silyl groups was observed under acidic conditions /50% F_3CCO_2H aq - dioxan/. [8] The easy isomerization of silyl groups observed by us might be possibly explained if one assumes the participation of a hydroxyl group at silicon.



Two hypothetical mechanisms of the isomerization catalyzed by acid /A/ and by base /B/ are shown below.

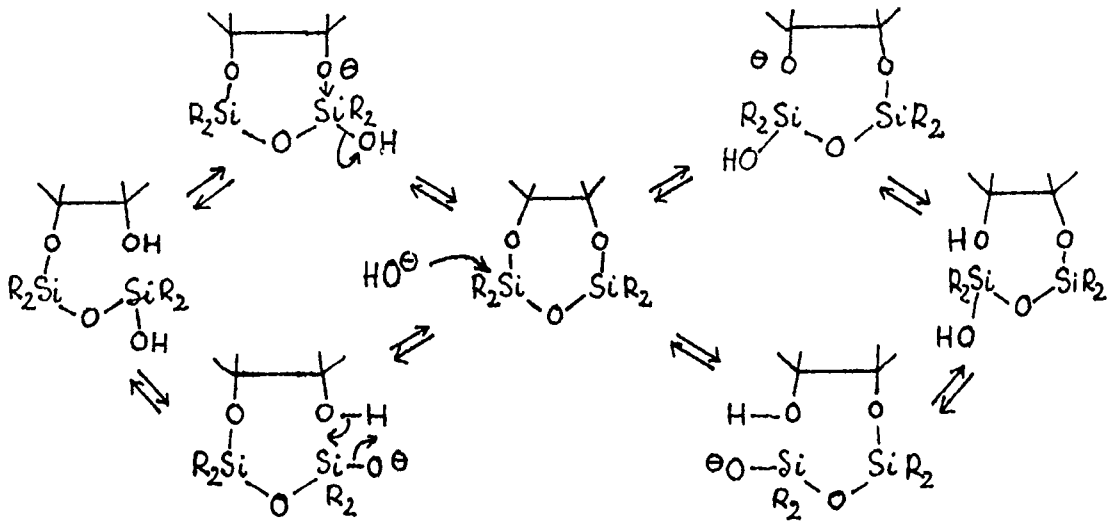
A



[+] Some loss of the $TIPDSi^{OH}$ group /ca. 20%/ was observed during removal of 2′-O-acetyl group with $i\text{-}BuNH_2$-MeOH /1:9/.

[8] S. Hanessian and P. Lavallee, Can. J. Chem., 1975, 53, 2975.

B



This problem requires further investigations and we hope to get some insight into the problem by studying other TIPDSi^{X} derivatives.+

Properties of the TIPDSi group at 2′ and 3′-positions.

As one can expect these properties are similiar to properties of the 3′,5′-O-TIPDSi group as far as the reactions at the 3′-end are considered.

Thus, the TIPDSi group is easily cleaved under alkaline conditions and by-products, namely 2′/3′/-O-TIPDSi nucleoside derivatives, are present in small amounts /ca. 1 - 3%/ during the course of the deprotection.

This group is also readily removed with fluoride reagents /TBAF, TBAHF/ but it is more stable against acid /$t_{1/2}$ ca. 2.7 hr, 0.2 M HCl in dioxan-water, 4:1, by vol./ than when it is present at 3′,5′-O-positions of nucleoside /$t_{1/2}$ ca. 0.4 hr/.

The TIPDSi group might be a useful protecting group for 2′ and 3′-positions of nucleosides as well.

+ IIIa /R=H/ and IIIa /R=Ac/ in MeOH containing anh. HCl afforded crystalline VIIIa /R=R≠H, X=OCH_3/ and VIIIa /R≠H, X=OCH_3/ in ca. 30 and 55% yields, respectively.

ref.3
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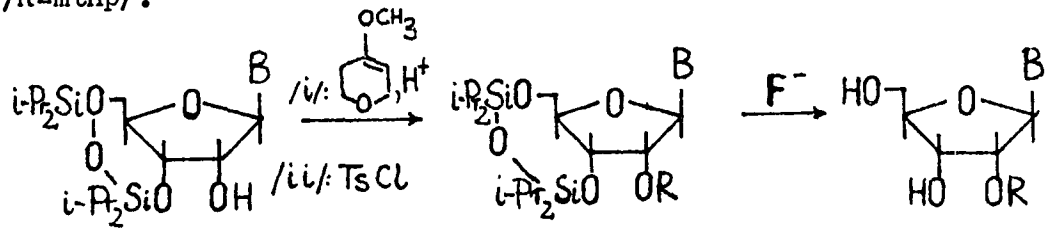
Applications.

Two examples, synthesis of described in literature: /i/ 2'-O-methoxytetrahydropyranyluridine [3] /Xa, R=mthp/ and /ii/ 2'-O-tosyladenosine [9] /Xe, R=Ts/, illustrate the usefulness of 3',5'-O--TIPDSi protection.

IIIa /R=H/ reacted with 4-methoxy-5,6-dihydro-2H-pyran [10] in dioxan in the presence of toluene-p-sulphonic acid to give IIIa /R=mthp/.



/i/: IIIa	IIIa /R=mthp/	Xa /R=mthp/
/ii/: IIIe	IIIe /R=Ts/	Xe /R=Ts/

The TIPDSi group from this compound was removed with TBAF and Xa /R=mthp/ was obtained in ca. 77% yield.

Similiarly, IIIe /R=H/ was converted into IIIe /R=Ts/ with TsCl in pyridine in ca. 90% yield, and after removal of the TIPDSi group with TBAF gave Xe /R=Ts/ in ca. 80% yield.

Conclusions.

The differences in reactivity of the TIPDSi group towards nucleophilic /OH^-, F^-/ and electrophilic /H^+/ reagents leading to its selective 3'- and/or 5'-end cleavage pressumably do not arise from its cyclic character and are in agreement with data for acyclic silyl ethers. Studies on hydrolysis of $Et_3SiOC_6H_4X$ compounds had shown [11] that electron-withdrawing groups markedly facilitate the alkali-catalysed reaction and that the acid-catalysed process is facilitated by electron-releasing substituents although not very

[9] /a/ M. Ikehara, M. Kaneko, Tetrahedron, 1970, 26, 4251. /b/ M. Kaneko, M. Kimura, T. Nishimura and B. Shimizu, Chem. Pharm. Bull., 1977, 25, 2482.

[10] C. B. Reese, R. Saffhill and J. E. Sulston, J. Am. Chem. Soc., 1967, 89, 3366.

[11] /a/ E. Akerman, Acta chem. scand., 1957, 11, 373. /b/ C. Eaborn, "Organosilicon Compounds", Butterworths Scientific Publications, London, 1960, p 303.

significantly. This means in other words that the more acidic is a hydroxylic component formed during the hydrolysis of silyl ether, the easier is alkali-catalysed reaction and slower acid--catalysed reaction. Therefore, the above data could account for the behaviour of the TIPDSi protected nucleosides in reactions of partial cleavage of the TIPDSi group as ribonucleoside 2^{o} hydroxyl functions are more acidic than 1^{o} ones.[12]

The experiments with other types of substrates in order to estimate scope and limitations of the TIPDSi group are in progress.

Experimental.

All melting points were taken on a Kofler hot stage and are uncorrected. Boiling points are uncorrected. Nuclear magnetic resonance spectra were taken on a Varian Associates Model EM360 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken on a Jeol Model JMS D-100 spectrometer. UV-spectra were taken on Carl Zeiss Specord UV Vis spectrometer in methanol. Anhydrous sodium sulphate was used to dry the organic layer. Trichlorosilane was purchased from Polskie Odczynniki Chemiczne and redistilled prior to use. 5'-O-Monomethoxytrityluridine /IV/ was obtained according to Lohrmann.[13] 4-N-Benzoylcytidine /IIc/ was prepared according to Watanabe.[14] 4-Methoxy-5,6-dihydro-2H-pyran was prepared according to Reese [3] and its concentration was 5 mmoles/ml. 1 M TBAF in THF was prepared according to Ogilvie.[7] If not stated otherwise, solutions were evaporated at 35^{o}/15 mm. Satisfactory microanalytical data have been obtained for all new crystalline compounds described. TLC analysis was performed on silicagel 60 F_{254} plates /Merck/ with chloroform containing methanol /2 - 10%/. The short column chromatography was performed on TLC silicagel type H /Merck/ in chloroform containing methanol /0 -5%/.

ref.3 0184

ref.7 0185

[12] /a/ P. A. Levene and L. W. Bass, in "Nucleic Acids", J. J. Little and Ives Co., New York, 1931, p 212. /b/ R. M. Izatt, L. D. Hansen, J. H. Rytting and J. J. Christensen, J. Am. Chem. Soc., 1965, 87, 2760. /c/ J. J. Christensen, J. H. Rytting and R. M. Izatt, Biochemistry, 1970, 9, 4907.

[13] R. Lohrmann, H. G. Khorana, J. Am. Chem. Soc., 1964, 86, 4188.

[14] K. A. Watanabe and J. J. Fox, Angew. Chem., 1966, 78, 589.

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane /I/.

Isopropylmagnesium bromide was prepared in a 2 l round-bottomed flask equiped with a stirrer, a reflux-condenser and a dropping funnel, starting from magnesium /19.5 g, 0.8 mole/ and isopropyl bromide /78 ml, 0.8 mole/ in diethyl ether /250 ml/ under exclusion of moisture. Trichlorosilane /28 ml, 0.28 mole/ in diethyl ether /350 ml/ was added slowly. The reaction mixture was then refluxed for 6 hr and ca. 10% hydrochloric acid was slowly added /300 ml/. The ether layer was separated and an aqueous layer was extracted with ether /3x200 ml/. Combined organic layers were washed with water, dried and concentrated. The residue was heated for 3 hr at ca. 100° with a drying agent /molecular sieves/ and distilled under reduced pressure to give 1,1,3,3-tetraisopropyldisiloxane /29.8 g, 0.12 mole, 85%/ as colourless liquid: bp 95°C /15 mm/; pmr /CCl_4/ δ 4.28 /s, 2, Si-H/, 1.00 /28, 4xSi--i-Pr/; ir /neat/ cm^{-1} ν_{Si-H} 2110; ms M^+ 246, M^+- i-Pr 203.

Cl_2/CCl_4 /saturated at room temp./ was dropped into magnetically stirred 1,1,3,3-tetraisopropyldisiloxane /12.3 g, 0.05 mole/ under exclusion of moisture until the reaction mixture stayed yellow. Hydrogen chloride was vigorously evolved. The reaction can be followed by the disappearance of ir ν_{Si-H} band /2110 cm^{-1}/. The reaction mixture was concentrated and distilled under reduced pressure and exclusion of moisture to give 1,3-dichloro-1,1,3,3--tetraisopropyldisiloxane /I, $TIPDSiCl_2$/ /14.2 g, 0.045 mole, 90%/ as colourless liquid: bp 120° /15 mm/; ms M^+- i-Pr 271.

1,3-Dibromo-1,1,3,3-tetraisopropyldisiloxane /$TIPDSiBr_2$/.

Br_2/CCl_4 /ca. 1:20, by vol./ was slowly added into magnetically stirred 1,1,3,3-tetraisopropyldisiloxane under exclusion of moisture. Hydrogen bromide was vigorously generated. The reaction was followed by ir as above. Then the solvent was evaporated down under reduced pressure /1 mm/ and the resulted liquid, $TIPDSiBr_2$, was used without further purification.

General procedure for syntheses of the TIPDSi protected nucleosides /IIIa-e, R=H and V/.

A. $TIPDSiCl_2$ /1.388 g, 4.4 mmole, 1.1 eqval/ was added to solution /or suspension/ of nucleoside /4 mmoles, 1 eqval/ and imidazole /1.20 g, 17.6 mmole, 4.4 eqval/ in anh. DMF /6 ml/. Undissolved substrate /in the case of poor soluble nucleosides/ went

into the solution during the reaction. The reaction was followed by TLC analysis /see Table 2./ and was completed in 0.5 - 8 hr. The reaction was quenched by addition of water /30 ml/ and the resulted precipitate /the heavy oil in the case of IIIa, R=H/ was separated, washed with water and dissolved in $CHCl_3$. This solution was dried, concentrated and pure IIIa-e, R=H or V was isolated in 70 - 80% yield after a short column chromatography /see Table 3/.

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The same procedure was applied when $TIPDSiBr_2$ was used as the silylation reagent.

B. $TIPDSiCl_2$ /348 mg, 1.1 mmole, 1.1 eqval/ was added to the solution of IIa /244 mg, 1 mmole, 1 eqval/ in anh. pyridine /3 ml/. The reaction went to completion in ca. 2 hr. Water /20 ml/ was added to quench the reaction and separate the oil of crude IIIa /R=H/. The further work up procedure was analogous as in A.

2',3'-O-/Tetraisopropyldisiloxane-1,3-diyl/uridine /VI/.

V /100 mg, 0.131 mmole/ was dissolved in ca. 0.1 M TsOH in dioxan /1.5 ml/. The reaction was quenched by addition of saturated aq $NaHCO_3$ /2 ml/ after 3 hr. The mixture was extracted with $CHCl_3$ /2x5 ml/. Combined organic layers were dried, concentrated and pure VI /50 mg, 0.102 mmole, 78%/ was isolated after the short column chromatography and crystallization from MeOH. See Tables 1, 2 and 3.

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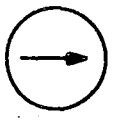

General procedure for acetylation of the TIPDSi nucleoside derivatives.

Acetic anhydride /0.5 ml/ was added to the solution of the TIPDSi nucleoside derivative /ca. 50 mg/ in anh. pyridine /1 ml/. The reactions were followed by TLC analysis and went to completion in 1 - 8 hr at room temp. MeOH was added to quench the reaction. After ca. 10 min. the reaction mixture was concentrated and the residue was coevaporated with toluene several times to give a foam of the acetyl derivative. Pmr spectra of these compounds were taken /see Table 1./.

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Tri-n-butylammonium fluoride /TBAHF/.

Hydrofluoric acid /40%, 0.25 g/ was added to the solution of tri-n-butylamine /0.927 g, 5 mmoles/ in anh. EtOH /10 ml/ /final pH ca. 7/. The solution was concentrated and then successively

Table 2. TLC analysis, mp, ms and UV data for the TIPDSi nucleoside derivatives /IIIa-e and VI/

compound R=H	R_F [a]	mp °C	ms /m/e/	UV λ /nm/ max	UV λ /nm/ min
IIIa	0.54	--	M^+- i-Pr 443.16774 /calc. 443.16119/	263	230
VI	0.42	180subl 202-203	M^+- i-Pr 443.16331 /calc. 443.16119/	263	231
IIIb	0.24	165-167	M^+ 485.23834 /calc. 485.23775/ M^+- i-Pr 442.18385 /calc. 442.18298/	274	253
IIIc	0.63	100-101	M^+ 589.26405 /calc. 589.26396/ M^+- i-Pr 546.21001 /calc. 546.20919/	261, 305	233, 285
IIId	0.22	284-286	--	255	225
IIIe	0.42	--	M^+ 509.24885 /calc. 509.24898/ M^+- i-Pr 466.19423 /calc. 466.19421/	261	231

[a] In $CHCl_3$-MeOH /9 : 1, by vol./.

coevaporated with anh.: EtOH /2x15 ml/, toluene /2x15 ml/ and THF /10 ml/. The resulted oil was dissolved in anh. THF /5 ml/ to give ca. 1 M solution of TBAHF. This reagent did not change its deblocking properties for silyl groups within a week.

General procedure for 3'-end cleavage of the TIPDSi group of III /R=H/.

NaOH.

III /R=H/ /1 mmole/ was dissolved in dioxan /8 ml/ and 1 M NaOH aq /2 ml/ was added. The reaction mixture was stirred at room temperature. The reaction was followed by TLC analysis and was comp-

leted within 1 - 3 hr. The solution was neutralized with acetic acid, partitioned between $CHCl_3$ /30 ml/ and water /30 ml/ and the aqueous layer was extracted with $CHCl_3$ /2x25 ml/. Combined $CHCl_3$ extracts were dried and concentrated to give a foam of pure VII in 90 - 95% yield. See Table 1.

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TBAHF.

To the solution of IIIa /R=H/ /0.487 g, 1 mmole/ in anh. THF /1 ml/ freshly prepared 1 M TBAHF in THF /1.0 ml, 1 eqval/ was added. After 30 min. a TLC analysis has shown the presence of ca. 60% of VIIa /R=H, X=F/ and ca. 40% of IIa. The solution was diluted with pyridine-MeOH-water /3:2:2, by vol., 25 ml/ and was passed through a Dowex 50Wx2 /pyridinium form/ column /1.5 cm x 5 cm/. The effluent was concentrated, purified with the short column chromatography and precipitated with water to give VIIa /R=R'=H, X=F/ /0.304 g, 60%/: R_F 0.30 /$CHCl_3$-MeOH, 9:1, by vol /; pmr - see Table 1.

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VIIa /R=R'=H, X=F/ was quantitatively hydrolyzed into VIIa /R=R'=H, X=OH/ /R_F 0.30 $\longrightarrow$ 0.24 /$CHCl_3$-MeOH, 9:1, by vol.// when kept overnight in aqueous pyridine. This sample was identical /R_F, pmr and acetyl derivative/ with VIIa /R=R'=H, X=OH/ obtained in the reaction of 3'-end cleavage with NaOH /above/.

Partial cleavage of the TIPDSi group of IIIa /R=H/ under acidic conditions.

IIIa /R=H/ /0.264 g, 0.54 mmole/ was dissolved in 0.2 M HCl in dioxan-water /4:1, by vol., 2 ml/. After 2.5 hr the reaction was quenched with $NaHCO_3$ aq and the products were partitioned between $CHCl_3$ and water. The organic layer was dried and concentrated to the oil /0.237 g/ which was then separated by the short column chromatography. The minor product was isolated /36 mg, 15%/ and identified as VIIa /R=R'=H, X=OH/ /R_F, pmr/. Pmr spectrum /Table 1./ of the main fraction /0.168 g, 71%/ showed that this was a mixture of two compounds in the ratio 5 : 3. This fraction was converted by acetylation into a mixture of two derivatives separable by the short column chromatography: VIIIa and IXa /R=R'=Ac, X=OH/: 72 mg, mp 101-103° and 42 mg, mp 89-91°, 37% and 22% respectively. /See Table 1./

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5'-End cleavage of the TIPDSi group of IIIa /R=Ac/ under acidic conditions.

IIIa /R=Ac/ /0.264 g, 0.5 mmole/ was dissolved in 0.2 M HCl in dioxan-water /4:1, by vol., 2.5 ml/. The reaction was quenched with NH_4HCO_3aq after ca. 6 hr. The solution was concentrated and the residue was partitioned between $CHCl_3$ and water. The $CHCl_3$ solution was dried, concentrated and a crude product was purified by the short column chromatography. The obtained foam was crystallized /0.232 g, 85%/, mp 132-134°; R_F 0.47 /$CHCl_3$-MeOH, 9:1, by vol./; pmr - see Table 1.

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2'-O-Methoxytetrahydropyranyluridine /Xa, R=mthp/.

IIIa /R=H/ /97 mg, 0.2 mmole/ was dissolved in anh. dioxan /1 ml/ containing TsOH· H_2O /0.01 mmole/ and 4-methoxy-5,6-dihydro--2H-pyran /0.25 ml, 1.25 mmole, 6.25 eqval/ was added. After 1 hr the products were neutralized with diluted NH_3 aq. The solution was concentrated, coevaporated with toluene, redissolved in this solvent and filtered to remove $TsONH_4$. The filtrate was concentrated to a gum, dissolved in anh. THF /0.5 ml/ and 1 M TBAF in THF /0.4 ml/ was added. After 30 min. the solution was diluted with pyridine-MeOH-water /3:1:1, by vol., 10 ml/ and passed through a Dowex 50Wx2 /pyridinium form/ column /1 cm x 4 cm/. The effluent was concentrated and the residue was purified by the short column chromatography and crystallization from EtOAc to give colourless crystals of Xa /R=mthp/ /55 mg, 77%/ identical with the authentic sample /mixed mp, R_F and pmr spectrum/.

2'-O-Tosyladenosine /Xe, R=Ts/.

IIIe /R=H/ /100 mg, 0.186 mmole/ was dissolved in anh. pyridine /1 ml/ and TsCl /67 mg, 0.35 mmole/ was added. The reaction mixture was kept overnight in darkness. After TLC analysis has shown that the reaction went to completion the solution was concentrated and the residue was partitioned between $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$ /2x3 ml/. Combined extracts were dried, concentrated and after the short column chromatography IIIe /R=Ts/ was isolated as a gum: /115 mg, 89%/; pmr /$CDCl_3$/ δ 8.20 and 7.84 /2xs, 2x1, H-2 and 8/, 7.8 and 7.2 /4, Ts/, 6.17 /s, 2, 6-NH_2/, 6.04 /s, 1, H-1'/, 5.51 /d, 1, J=5 Hz, H-2'/, 5.15 /q, 1, J=5 and 8 Hz, H-3'/, 4.05 /m, 3, H-4'and 5'/, 2.42 /s, 3, CH_3Ts/, 1.04 /21, 3x i-PrSi/, 0.92 /7, 1x i-PrSi/.

IIIe /R=Ts/ /69 mg, 0.1 mmole/ was dissolved in anh. THF /0.4

ml/ and 1 M TBAF in THF /0.2 ml/ was added. After 15 min. the solution was concentrated and the residue was dissolved in 50% aq EtOH /0.5 ml/ and the resulted crystals of Xe /R=Ts/ /34 mg, 80%/ were collected by filtration: mp 221-223° /lit. 226-228°/;[9] R_F 0.33 /$CHCl_3$-MeOH, 9:1, by vol./; UV /MeOH/ λ_{max} 261.5 nm; pmr /d_6-DMSO/δ 8.15 and 7.98 /2xs, 2x1, H-2 and 8/, 7.4 and 7.2 /4, Ts/, 6.09 /d, 1, J=4 Hz, H-1'/, 6.02 /s, 2, 6-NH_2/, 5.47 /q, 1, H-2'/, 4.37 /m, 1, H-3'/, 2.27 /s, 3, $\underline{CH}_3$Ts/.

Acknowledgement.

The author wishes to thank Prof. M. Wiewiórowski for encouragement and valuable discussions. This work was supported by the Polish Academy of Sciences project MR - I. 12. 1. 7. 11.

Table 3. Analytical data for the TIPDSi derivatives /IIIa-e and VI/

compound R=H	calculated C	calculated H	calculated N	found C	found H	found N
IIIa+	51.82	7.87	5.76	51.69	7.99	6.02
VI	51.82	7.87	5.76	51.94	7.80	5.89
IIIb	51.93	8.09	8.65	52.01	8.13	8.47
IIIc	57.01	7.35	7.12	56.75	7.19	7.28
IIId	50.26	7.48	13.32	49.95	7.47	13.19
IIIe+	51.83	7.71	13.74	51.67	7.81	13.95

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+ Samples obtained as dry foams. Compare Table 2 for ms.