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ACID-CATALYSED ISOMERIZATION OF THE TETRAISOPROPYLDISILOXANE-1,3-DIYL GROUP. SIMULTANEOUS PROTECTION OF TWO SECONDARY ALCOHOLIC FUNCTIONS.

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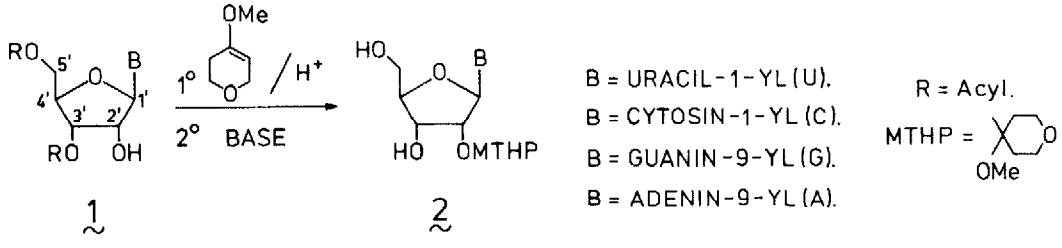
Summary: The reaction of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane with ribonucleosides or sugar derivatives affords products containing one silyl-protected primary and secondary hydroxy function. Treatment of these products with MSA in DMF gives products having two silylated secondary hydroxy functions.

Ribonucleosides which are protected at the 2'-position with the acid labile 4-methoxytetrahydropyran-4-yl group (2'-O-MTHP derivatives, e.g. 2) have proven to be effective building blocks for the synthesis of RNA fragments[1]. Up to now, the most convenient method for the preparation of these key-intermediates is based on the acetalation (see Scheme I) of 3',5'-O-di-acyl ribonucleosides (e.g. 1) with 4-methoxy-5,6-dihydro-2H-pyran[2] (MDHP) followed by the removal of the base labile acyl groups.[2] Unfortunately, the synthesis of starting compound 1



1 2

Scheme I

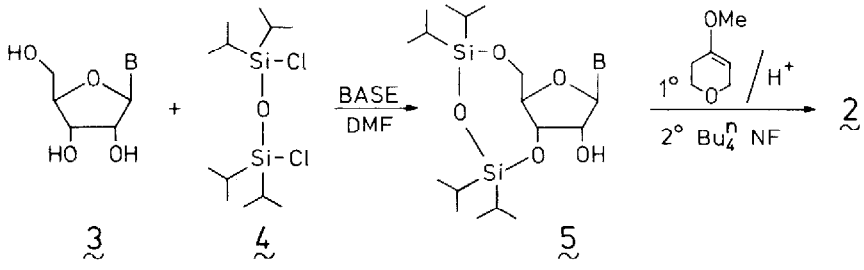
is, despite the fact that a general procedure has been devised[4] for the synthesis of 3',5'-di-acyl derivatives 1 of all four common ribonucleosides, rather laborious and timeconsuming.

Recently, a new methodology has been developed[5] for the synthesis of key-intermediates 2. The new element in this method was based on the use of the bifunctional silylating agent 4 (see Scheme II). Thus reacting together ribonucleoside 3 with 4 gave the 3',5'-di-silyl derivative 5 which could easily be converted into the desired 2'-O-MTHP derivative 2. Because of the easy accessibility of 5 it could therefore be used as an attractive alternative for the 3',5'-di-acyl derivatives 1 in the synthesis of the 2'-O-MTHP derivatives 2. However, for the 3',5'-di-silyl derivatives 5 to function as a replacement of the 3',5'-di-acyl derivatives 1 it had to be established whether 5 was stable under the acidic acetalation conditions.

In this paper we wish to report that the tetraisopropyldisoloxane-1,3-dilyl group migrates under the influence of acid and, furthermore, that this migration reaction promises to be very useful for the simultaneous introduction of two silylated secondary alcoholic functions

of polyhydroxy containing molecules (e.g., sugar moieties).

During the synthesis of the 2'-O-MTHP derivative of guanosine (2, B=G), which consisted



3 4 5 2

Scheme II

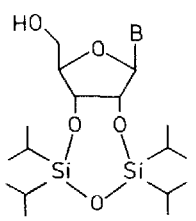
of treating a solution of 5 (B=G) in dry DMF with 4-methoxy-5,6-dihydro-2H-pyran (MDHP) in the presence of dry mesitylenesulphonic acid (MSA) followed by fluoride-ion treatment, we obtained, besides product 2, an unexpected side-product. This product showed to be identical in every aspect - ^{1}H-, ^{13}C-NMR spectroscopy, T.L.C. analysis - with synthetically prepared 5'-O-MTHP-guanosine. The formation of this unexpected side-product can be explained by assuming that the silyl-bond between the primary oxygen in the 3',5'-di-silyl derivative 5 is disrupted by acid. The intermediate silyl-cation thus obtained forms a new bond with oxygen at the 2'-position to afford the 2',3'-disilyl derivative 6 (B=G). The latter is converted, after reaction with MDHP followed by fluoride treatment, into 5'-O-MTHP-guanosine. Indeed, treatment of 5 (3 mmole, B=G) with dry MSA (1.5 mmole) in dry DMF at 20° C for 10 hr gave, after work-up and purification by short column chromatography, a crystalline product which was in every aspect - ^{1}H, ^{13}C-NMR spectroscopy, T.L.C. analysis - identical with 6 (B=G) obtained by treating 5'-O-acetyl-guanosine with 4 followed by removal of the acetyl group. In the same way, the 3',5'-di-silyl derivatives 5 (B=U,C,A) could be converted into the isomeric 2',3'-di-silyl derivatives 6 (B=U,C,A). The yield of the isolated crystalline products 6a,b,c,d[6] was rather poor (30%) but could be increased to 50% by using pyridine-HCl instead of MSA.

It has to be emphasized that the acid-catalysed isomerization of the 3',5'-di-silyl-derivates 5 into the 2',3'-derivatives 6 proceeds only in the solvent DMF. Other solvents such as dioxan, acetonitrile, tetrahydrofuran or chloroform are not effective. The latter is in accordance with the observation that compounds 5 are not affected by p-toluenesulphonic acid (0.3 M) in dioxane.[5] It was for this reason that Markiewicz[5] was successfull in preparing 2 (B=U) starting from 5 (B=U).

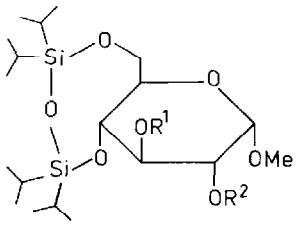
At this stage, we were anxious to find out if the reaction sequence established by ribonucleosides, i.e., (a) the simultaneous protection of one primary and one secondary hydroxy group by using reagent 4 and (b) the acid-catalysed isomerisation of the silylated compound thus obtained in the solvent DMF, could also be applied for the protection of sugar moieties. To establish this, we used methyl α-D-glucopyranoside as a model compound in our further studies.

Treatment of methyl α-D-glucopyranoside 9a (20 mmoles) with reagent 4 (30 mmoles) in dry pyridine at 20° C for 1 hr gave, after work-up and purification by short column chromato-

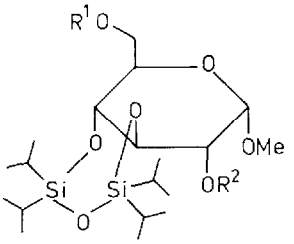
graphy, crystalline 7a[6] in 60% yield. The identity of 7a was established unambiguously by ^{1}H, ^{13}C-NMR spectroscopy and mass spectrometry as well as by chemical means. Thus, short



6 B=U; C; A; G.



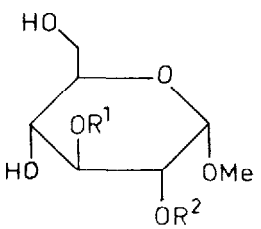
7 a: $R^1=R^2=H$.
b: $R^1=H$; $R^2=Ac$.
c: $R^1=R^2=Ac$.



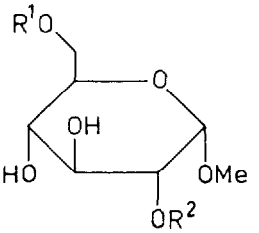
8 a: $R^1=R^2=H$.
b: $R^1=Ac$; $R^2=H$.
c: $R^1=R^2=Ac$.
d: $R^1=Piv$; $R^2=H$.
e: $R^1=Piv$; $R^2=MTHP$.

treatment of 7a with Ac_2O in pyridine gave 7b[7], while prolonged treatment afforded 7c[7]. Furthermore, removal of the silyl groups from 7a,b,c with tetrabutylammonium fluoride (Bu^n_4NF) in dry THF containing pyridinium-HCl salt[8], gave solely 9a,b,c[7], respectively.

Isomerization of 7a ($R^1=R^2=H$) was performed by treating 7a (10 mmoles) with dry MSA



9 a: $R^1=R^2=H$.
b: $R^1=H$; $R^2=Ac$.
c: $R^1=R^2=Ac$.



10 a: $R^1=Ac$; $R^2=H$.
b: $R^1=R^2=Ac$.
c: $R^1=Piv$; $R^2=H$.
d: $R^1=Piv$; $R^2=MTHP$.

(1 mmole) in dry DMF (80 ml) for 6 hr at 20° C. Analysis of the reaction mixture by T.L.C. showed the presence of only one product having a different R_f-value than starting product 7a. Work-up of the reaction mixture and purification by column chromatography gave 8a as a homogeneous oil (yield 60%). The identity of 8a was confirmed by ^{1}H- and ^{13}C-NMR spectroscopy as well as by chemical means. Thus fluoride (Bu^n_4NF) treatment of 8a gave solely 9a[7], short treatment of 8a with Ac_2O gave 8b[7] which after fluoride treatment afforded solely 10a ($R^1=Ac$; $R^2=H$). Prolonged treatment of 8a with Ac_2O gave 8c[7] which, after fluoride treatment, was converted into 10b[7].

The usefulness of the isomerization product 8a was demonstrated in the synthesis of the glucose derivatives 10c and 10d, respectively. Thus, treatment of 8a ($R^1=R^2=H$) with pivaloyl chloride in pyridine gave crystalline 8d[6,7] (yield 84%) which, after treatment with fluoride, afforded 10c[7] as a homogeneous glass (yield 95%). Acetalation of 8d with MDHP in THF, in the presence of MSA, gave the fully-protected glucose derivative 8e (yield, 70%) which, after treatment with fluoride ion, was converted into 10d[9] and isolated as a homogeneous glass (yield; 95%).

In conclusion, the data presented in this paper show that (a) the bifunctional reagent 4

promised to be general applicable for the synthesis of compounds with silylated primary and secondary hydroxy groups, and (b) that subsequent acid-catalysed isomerization of the disilyl-protected products obtained under (a) results in the formation of products having two silylated secondary hydroxy groups.

A full report dealing with the application of the above described methodology in sugar chemistry will be published shortly.

REFERENCES AND NOTES

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5. W.T. Markiewicz, J. Chem. Research (S), 24 (1979); W.T. Markiewicz and M. Wiewiorowski, Nucl. Acids Res., s185 (1978).
6. Satisfactory C,H,Si analytical data were obtained.
7. The identity of the compound(s) was established by ^{1}H- and ^{13}C-NMR spectroscopy.
8. It is well established that removal of silyl ether functions from compounds containing also ester functions e.g. carbohydrates (see F. Franke et al. Aust, J. Chem., 30, 639, 1977, ibid 31, 1285, 1978), nucleic acids (see J.F.M. de Rooij et al. Nucleic Acids Res., 6, 2237, 1979) or glycerides (see G.H. Dodd et al. J.C.S. Chem. Comm., 249, 1975) with dry $Bu^{n}_{4}NF$ in dry THF (E.J. Corey et al. J. Am. Chem. Soc., 94, 6190, 1972) may lead to migration of the ester functions. To overcome this unwanted migration we added dry pyridinium-HCl salt (equimolar amount with respect to the compound to be desilylated) to the solution of $Bu^{n}_{4}NF$ in dry THF (see also G.H. Dodd et al. J.C.S. Perkin I, 2273, 1976, who tryed to prevent migration by adding sulphuric acid).
9. ^{1}H-NMR ($CDCl_3$) data (δ-values in ppm) of 10d and its fully acetylated derivative, respectively: 4.72 (d, J 3.8 Hz, H_1); 4.84 (d, J 3.8 Hz, H_1), 4.96 (t, J 9.0 Hz, H_4), 5.40 (t, J 9.0 Hz, H_3).
^{13}C-NMR ($CDCl_3$) data (δ-values in ppm) of compound 10d: 99.0 (C_1), 72.1 (C_3), 71.3 (C_2), 70.7 (C_5), 69.1 (C_4), 63.7 (C_6), 54.7 (OCH_3); pivaloyl group, 178.7, 38.8 and 27.2; MTHP group, 99.4, 64.7 and 65.0, 34.6 and 34.3, 48.3.

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