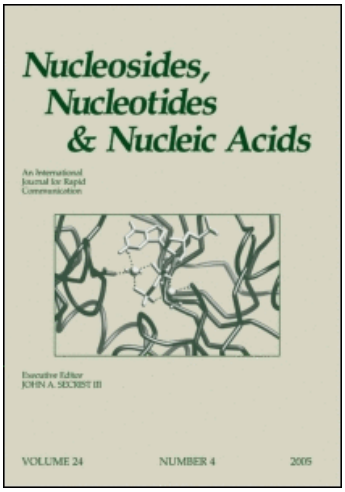

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PROTECTING GROUPS TRANSFER: UNUSUAL METHOD OF REMOVAL OF TR AND TBDMS GROUPS BY TRANSETHERIFICATION

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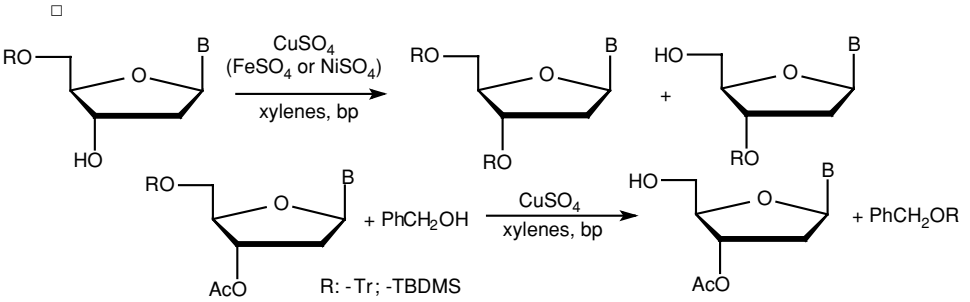

The triphenylmethyl (Tr) group undergoes a transfer (transetherification or disproportionation) between the molecules of 5′-O-Tr-2′-deoxynucleosides in a process mediated by anhydrous sulfates of Cu^{+2}, Fe^{+2}, or Ni^{+2} to yield mixtures of 3′,5′-bis-O-Tr and 3′-O-Tr products. If phenylmethanol is present in a reaction medium, detritylation results with concomitant formation of phenylmethyl triphenylmethyl ether. The behavior of t*-butyldimethylsilyl (TBDMS) group in 5′-O-TBDMS-2′-deoxynucleosides is exactly the same. Such type of transetherifications was not observed before for the* O*-Tr and* O*-TBDMS groups.*

Keywords *t*-Butyldimethylsilyl; deoxynucleoside; deprotection; intermolecular; transetherification; triphenylmethyl

INTRODUCTION

The triphenylmethyl (Ph_3C-, Tr-) group is frequently used to protect primary hydroxyl function due to a strong preference of the tritylating

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agents toward the less hindered positions.[1–5] Detritylation is routinely performed in acidic or reductive medium.[1–5] A recent review summarizes different de-*O*-tritylation procedures up to the year 2005[6] and is amended by seven newest methods: $HClO_4$/silica,[7] CBr_4/MeOH/UV,[8,9] $SbCl_3$,[10] Nafion-H,[11] HCO_2H-diethyl ether (formolysis),[12] $VO(OTf)_2$,[13] and silica sulfuric acid.[14]

The *t*-butyldimethylsilyl (TBDMS) group also gained popularity to protect primary –OH functions.[1–5] Desilylation mediated by fluoride ions coming from tetraalkylammonium fluorides is a routine, even though the ammonium salts can co-migrate with the deprotected product during a chromatography to make purifications difficult. Many alternative deprotection methods are known.[1–5] Selective deprotections of bis-silylated compounds have been reviewed.[15] The following methods of removal of *O*-TBDMS group have been published since the year 2000: $SbCl_3$,[16] 1-chloroethyl chloroformate/MeOH,[17] $CH_3COCH_2P^+(Ph)_3Br^-$,[18] H_2-Pd/C,[19–22] $BiO(ClO_4)$,[23] I_2/microwave,[24] Nafion-H/NaI,[25] KOH/EtOH,[26] $ZrCl_4$,[27] $CsCO_3$,[28] 1,1,3′,3′-tetramethylguanidine,[29] $ZrCl_4/Ac_2O$,[30] AcCl/MeOH,[31] $NaIO_4$,[32] $ZnBr_2$,[33] $Et_3N^+ \rightarrow O^-$,[34] $Ce(OTf)_4$,[35] $CeCl_3$/ CH_3CN/NaI,[36] anh.

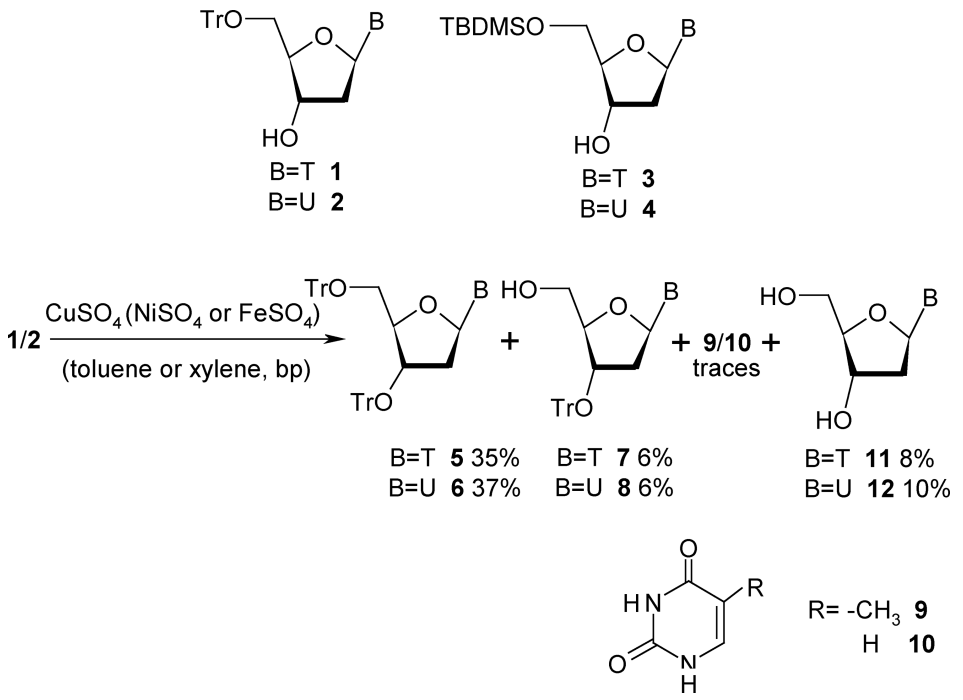
KF/33% HBr/AcOH,[37] Br_2/MeOH,[38] $BiCl_3$/NaI,[39] KF/Al_2O_3,[40] Bu_4N^+ Br_3^-,[41] BCl_3,[42] $InCl_3$,[43] $P(i\text{-}PrNCH_2CH_2)_3N$,[44] CCl_4/MeOH/ultrasounds,[45] $Ce(NH_4)_2(NO_3)_6/SiO_2$,[46] HCO_2H-diethyl ether (formolysis),[12] $TiCl_4$ complex by EtOAc or CH3NO2,[47] $(CH_3)_3$ SiCl-KF·$2H_2O$,[48] polyvinylpolypyrrolidone-Br_2,[49] and $VO(OTf)_2$.[13]

An interesting method of detritylation in a neutral and nonreducing medium in 6-*O*-Tr-glucopyranosides was described by Randazzo and colleagues, and involves a treatment of the substrates with anhydrous sulfates of bivalent cations like Co^{+2}, Cu^{+2}, Fe^{+2}, Ni^{+2} or Zn^{+2} in benzene or toluene at reflux.[50] This process was rationalized in terms of the interaction of the metal cations with the oxygen atom of the –*O*-Tr moiety, which weakens the –*O*–Tr bond and facilitates formation and departure of the trityl cation.

Unexpected results obtained during application of this procedure to the 5′-*O*-trityl-2′-deoxynucleosides and further to the 5′-*O*-*t*-butyldimethylsilyl-2-deoxynucleosides are the objectives of this communication.

RESULTS AND DISCUSSION

5′-Protected derivatives **1–4** are frequently used as starting materials. Since the publication of Randazzo et al.[50] deals with the triphenylmethylated compounds, we started the experiments with 5-*O*-Tr-thymidine **1**[51] and 5-*O*-Tr-2-deoxyuridine **2**.[52] Treatment of either **1** or **2** with anhydrous $CuSO_4$ in refluxing toluene or xylenes furnished (in the order of decreasing

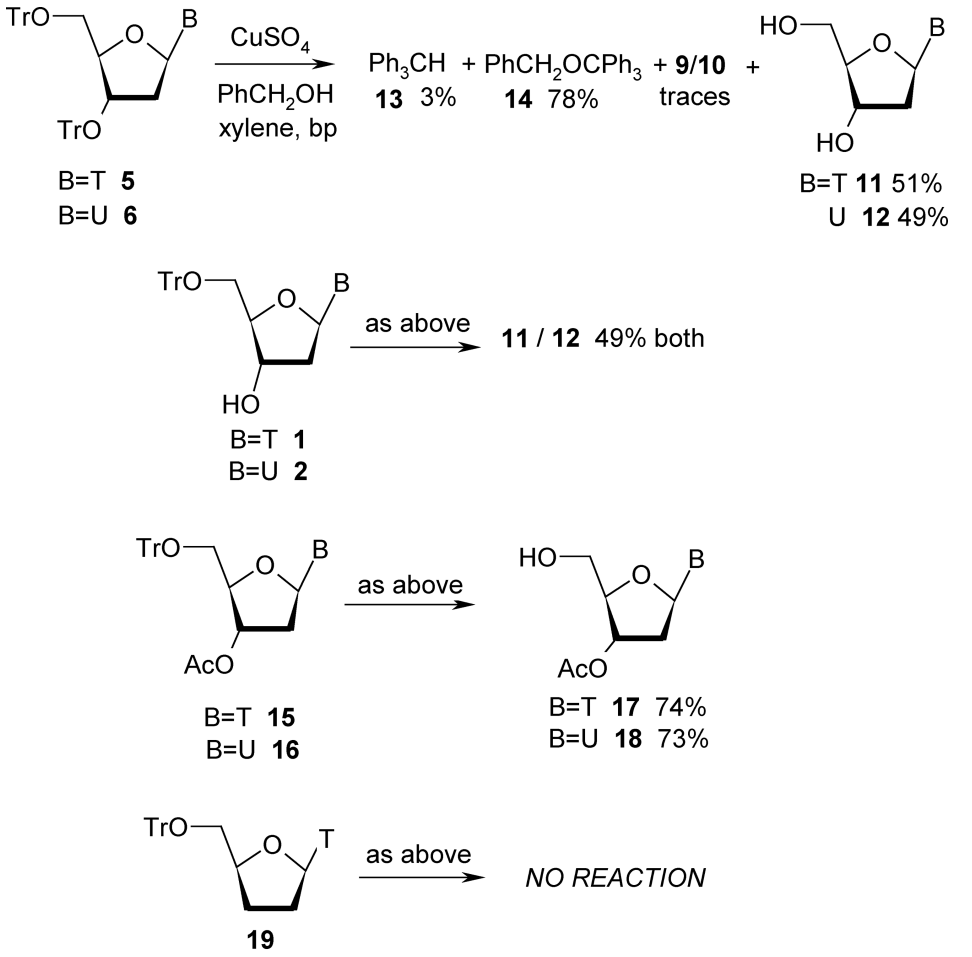


SCHEME 1 Behaviour of 5′ -*O*-Tr substrates during $CuSO_4$ ($FeSO_4$, $NiSO_4$) treatment.

mobility on TLC) 3′,5′-bis-*O*-Tr derivatives **5**[53]/**6**, 3′-*O*-Tr derivatives **7**[54]/**8** and small quantities of thymine **9**/uracil **10** and deprotected nucleosides **11**/**12** (Scheme 1).

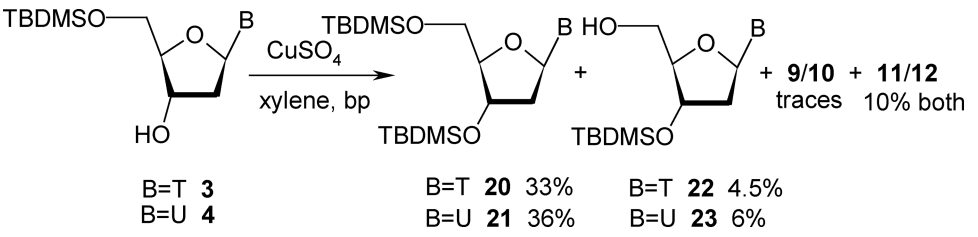
Unreacted compounds **1**/**2** which are slightly more polar than their 3′-*O*- regioisomeric counterparts **7**/**8** could be recovered. The position of the –*O*-Tr group in **7**/**8** is evident from the shape of the signal belonging to the exchangeable proton 5′-OH, which is a triplet (J = 7.4HZ in both **7**/**8**; DMSO-d_6) due to the presence of two vicinal hydrogen atoms. Formation of the unexpected compounds **5**/**6** and **7**/**8** can be rationalized in terms of a capture of the electrophilic triphenylmethyl cation present in **31** (see below) by the –OH group of another molecule. In this way **1**/**2** are converted to **5**/**6** liberating **11**/**12** with two –OH groups, which can react with Ph_3C^+ to regenerate **1**/**2** or to furnish 3′-*O* -protected products **7**/**8**. Likewise **5**/**6** can lose a trityl group to form **1**/**2** or **7**/**8**. The sulfates of Fe^{+2} and Ni^{+2} gave similar results, however $CuSO_4$ furnished the cleanest reactions and was used in the following work.

In order to suppress the unwanted intermolecular transfer (transetherification, disproportionation) of the triphenylmethyl group and to promote deprotections, we added $PhCH_2OH$ as a nucleophile to trap the triphenylmethyl cation (Scheme 2). Treatment of the bis-protected compounds **5**/**6** with $CuSO_4$ and $PhCH_2OH$ in boiling xylenes furnished (in the order



SCHEME 2 Behaviour of 5′ -*O*-Tr substrates during $CuSO_4$-$PhCH_2OH$ treatment.

of increasing polarity on TLC): a small amount of triphenylmethane **13**, phenylmethyl triphenylmethyl ether **14**[55], traces of free bases T/U **9**/**10** and deprotected nucleosides **11**/**12** isolated in ca. 50% yield. These medium yields are probably a consequence of adsorption of **11**/**12** on $CuSO_4$. As expected, triphenylmethyl cation was indeed captured by $PhCH_2OH$ to form ether **14**. A mechanism of formation of triphenylmethane **13** will be discussed later. The same process was applied to **1**/**2** and furnished **11**/**12** in similar yields. 3′-*O*-Acetyl-5′-*O*-triphenylmethyl derivatives **15**[51]/**16**[52] gave **17**[51]/**18**[52] in ca. 75% yield under the same conditions. The procedure failed however for the 3′-deoxy-5′-*O*-triphenylmethylthymidine **19** (see below). This may suggest that a 3′-oxygenated functionality should be present in a molecule of a substrate to chelate a Cu^{+2} cation.

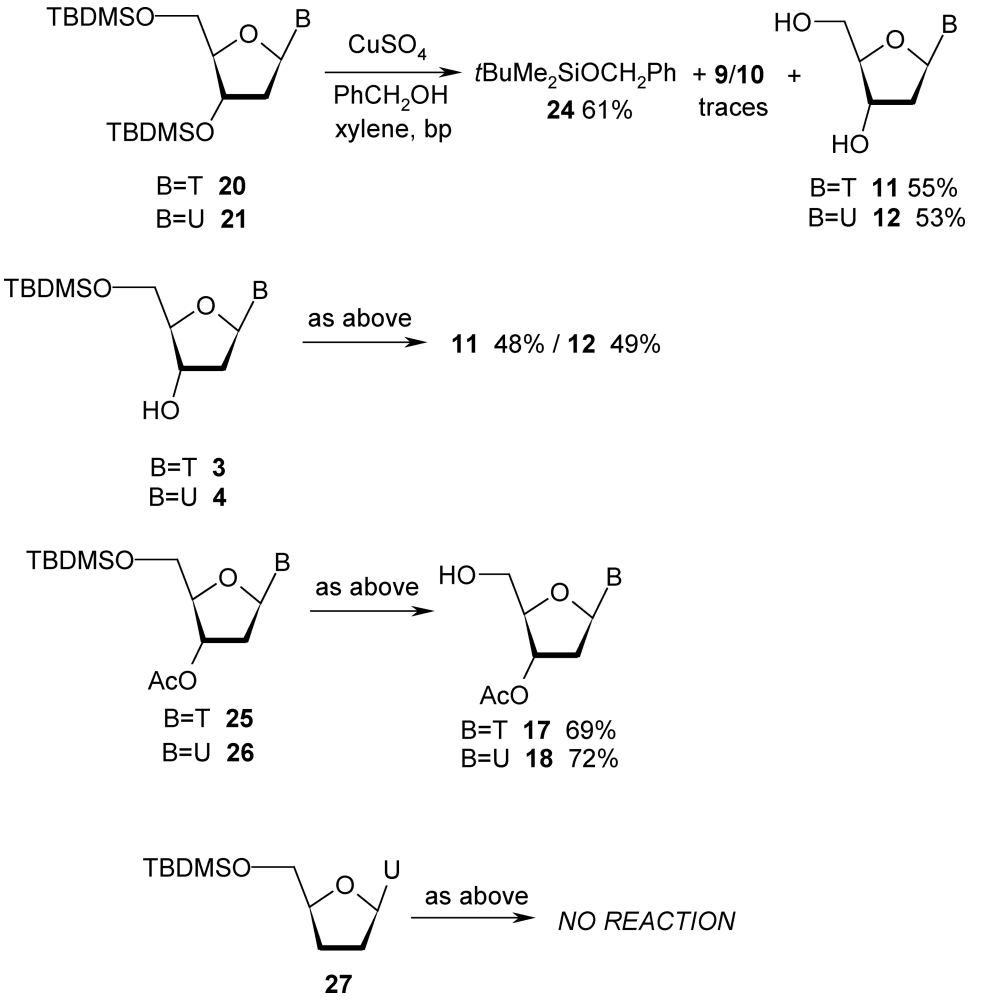


SCHEME 3 Behaviour of 5′ -*O*-TBDMS substrates during $CuSO_4$ treatment.

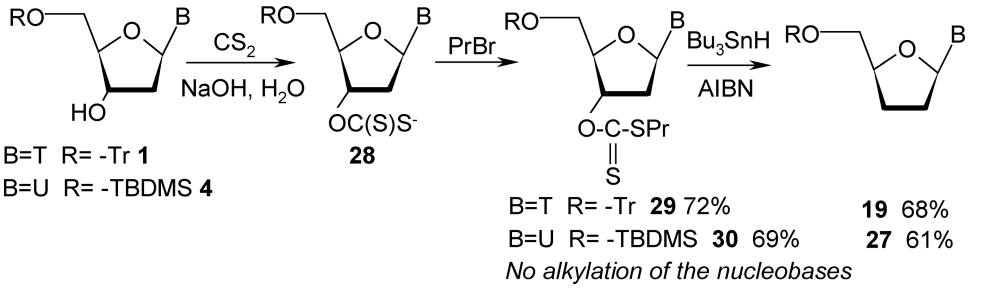
t-Butyldimethylsilyl group, which is another commonly used protection behaved in the same way: either an intermolecular transfer (transetherification, disproportionation; Scheme 3) or a deprotection (Scheme 4) took place as a function of the conditions applied. *t*-Butyldimethylsilyl phenylmethyl ether **24** could be isolated if $PhCH_2OH$ was used. As in the case of **19**, 5′-*O*-*t*-butyldimethylsilyl-2′,3′-dideoxyuridine **27** did not react under these conditions.

Both **19** and **27** were prepared using a slightly modified protocol of Barton[56,57] as shown in the Scheme 5. Methyl iodide routinely used to obtain the intermediate xanthates is known to methylate the nucleobases.[58,59] This unwanted side reaction was completely suppressed by using propyl bromide to capture the intermediate anions **28**. The xanthates **29**/**30** were then treated with tri-*n*-butyltin hydride and α,α'-azo-bis-*iso*butyronitrile to give the deoxygenated products **19**/**27**. The compound **19** was previously obtained via a deoxygenation of its 3′-*O*-phenoxythiocarbonyl predecessor.[60]

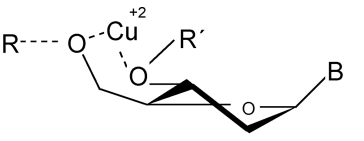
The processes shown in the Schemes 1 through 4 can be rationalized as follows. Chelation of the metal cation by the 3′ and 5′ oxygen functionalities furnished the intermediates **31** in their northern conformation. The inertness of the 3′-deoxygenated compounds **19** and **27** strongly indicates a critical role of the 3′oxygen atom and also seems to exclude an alternative mode of chelation *via* the 5′-O and the endocyclic oxygen atom. The latter possibility was claimed to take place by Matteucci and Caruthers during their work on $ZnBr_2$ removal of dimethoxytritylated 2′-deoxynycleosides.[61] If R = -Tr this chelation evidently weakened the 5′*O* – Tr bond as suggested in the literature 50 and permitted a departure of the triphenylmethyl cation which attacked any nearby nucleophilic site (either an –OH group of another molecule of a nucleoside or a molecule of $PhCH_2OH$). It is also known that a Ph_3C^+ moiety is a selective oxidant of secondary alcohols (in a form of their triphenylmethyl, *t*-butyl or trimethylsilyl ethers) *via* a hydride abstraction.[62,63] This property can be used to explain formation of triphenylmethane **13** and free nucleobases **9**/**10** (Scheme 6). Thus, abstraction of a hydrogen anion from the position 3′ furnished **13** and a cation **32**, which underwent a fragmentation to yield the ketonucleosides **33**, and



SCHEME 4 Behaviour of 5′ -*O*-TBDMS substrates during $CuSO_4$-$PhCH_2OH$ treatment.



SCHEME 5 3′ Deoxygenation of **1**/**4** using a Barton-type procedure.



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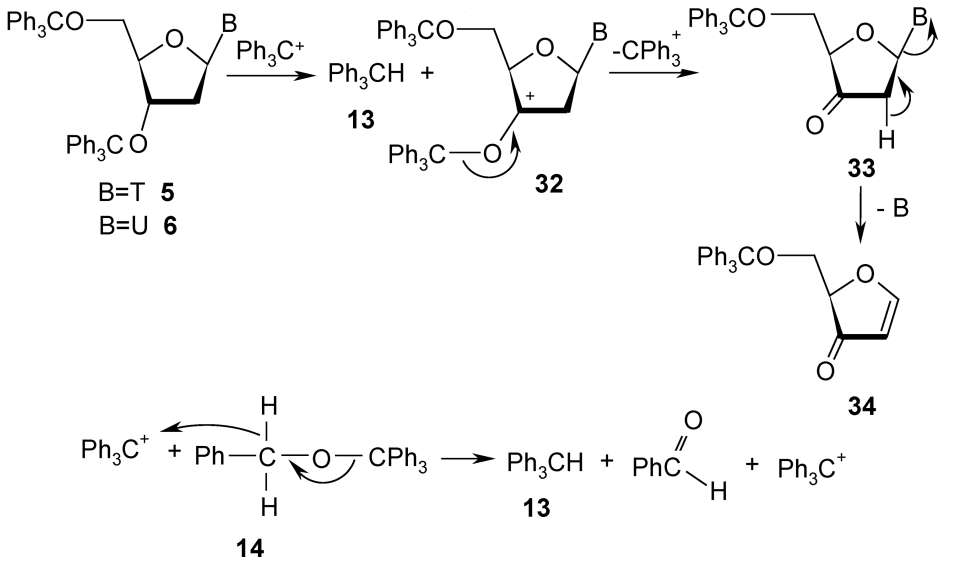

SCHEME 6 Possible mechanism of formation of Ph_3CH and thymine/uracil.

regenerated Ph_3C^+. The ketonucleosides **33** are known to be unstable[64–66] and suffer a fragmentation to release the nucleobases and furan **34**.[64] An independent source of triphenylmethane **13** could be a chain reaction[67] which involved Ph_3C^+ and alkyl triphenyl ethers, particularly **14**, as shown in the Scheme 6. Since the behavior of *t*-butyldimethylsilyl nucleoside derivatives used in this work is the same as their triphenylmethyl counterparts, one can surmise that cationic *t*-butyldimethylsilyl species were transiently formed during the reactions described above. One needs to point out that the inertness of the 5′-O-TBDMS-2′,3′-dideoxyuridine **27** toward Cu^{+2} cation demonstrates some limitations of the desilylation procedure devised by Dalla Cort (Lewis acid, e.g., Cu^{+2}, CH_3CN, rt).[68]

One has to distinguish the intermolecular transfers of a TBDMS group presented here from its intramolecular migration,[69,70] which can be a nuisance during a work related to nucleosides and carbohydrates. Also, an example of a triphenylmethyl ether isomerization similar to this presented here, but promoted by protic acid was noticed during a total synthesis of a racemic fungal secondary metabolite brefeldin A.[71] Finally, chelation of

two hydroxyl groups by Cu^{+2} suggested in this work as a necessary event, is known to take place in a basic medium in carbohydrates and permits to achieve some selective alkylations.[70]

In summary, a new method of removal of both *O*-Tr and *O*-TBDMS groups in 2′-deoxynucleosides under neutral and nonreducing conditions was devised. Practical significance of some of the deprotections using $CuSO_4/PhCH_2OH$ presented here (e.g., **1–6**, **20**, **21**) doesn't seem to be broad due to medium yields (∼50%) probably resulting from irreversible adsorption on $CuSO_4$, however a rare process of transetherification was clearly demonstrated. Deprotections of the 3′-*O*-acetylated substrates **15**,**16**, **25** and **26** proceeded in higher yields (69–74%) which were not optimized and there is a scope for improvements. Application of this procedure to 2′-deoxypurine nucleosides and to carbohydrates will be published in due course.

EXPERIMENTAL

General Methods

Column chromatography was performed on a silica gel G 70–230 mesh, and TLC chromatography on aluminum plates precoated with silica gel 60 F_{254}, both from Merck (Darmstadt, Germany). 10% H_2SO_4 in MeOH was used to char the TLC chromatograms. "Xylenes" refers to a mixture of isomers. This solvent was dried by azeotropic distillation. $CuSO_4$ was dried at ca. 130° during 4 hours. The NMR spectra were recorded on a Varian 200MHz or 300MHz instruments in DMSO-d_6 solutions unless otherwise stated. Exact mass measurements of samples judged to be at least 95% pure by ^{1}H NMR were performed on a Jeol SX 102A spectrometer using an FAB mode in NaOAc-thioglycerol matrices or using a CI mode and CH_4 as a reagent gas.

3′,5′-Bis-*O*-triphenylmethylthymidine 5 and 3′-*O*-triphenylmethylthymidine 7

A mixture of 5′-*O*-triphenylmethylthymidine **1**[51] (1.30 g, 2.7 mmol) in xylenes (30 ml) and $CuSO_4$ (2.5 g, 15.7 mmol), was stirred at reflux during 4 hours with exclusion of moisture (argon blanket or a $CaCl_2$ guard tube). To get a sample for TLC examination, few drops of the reaction slurry were evaporated in a conical flask in a stream of air, and the same volume of MeOH was added to solubilize the organic products. TLC of this solution showed the presence of **5**, **7**, unreacted substrate **1**, thymine **9** and thymidine **11** in this order of decreasing mobility. In $CHCl_3$- MeOH 10:0.4 the R_fs are as follow: **5**, 0.81; **7**, 0.47; **1**, 0.28; in $CHCl_3$-MeOH 10:1 **9**, 0.30 and **11**, 013. Silica gel was added to a reaction mixture and the solvent was evaporated. The residue was applied on a top of a chromatography column prepared

in $CHCl_3$. Gradient elution using 0 →15% MeOH in $CHCl_3$ gave **5** (0.68 g, 35%), **7** (0.078 g, 6%) and **11**(0.052 g, 8%).

5: foam; lit.[53] m.p.122–124°; ^1H (200 MHz): 11.33(s,1H, exchangeable, NH); 7.37–7.00 (16H, aromatic, 6); 6.21(dd, J = 5.9Hz, 8.5Hz, 1H, 1); 4.22(bs, 1H, 3′); 3.88(bs, 1H, 4′); 3.05(d, J = 9.1Hz, 1H, 5′); 2.89(dd, J = 3.6Hz, 9.2Hz, 5″); 1.91–1.61(unresolved, 2H, 2′,2″); 1.42(s, 3H, 5Me).

^{13}C (50MHz): 163.69; 150.50; 144.03; 143.48; 135.39; 128.52; 128.24; 127.48; 127.34; 109.83; 87.38; 86.75; 84.33; 75.03; 63.99; 11.87.

HRMS (FAB): calc. for ($C_{48}H_{42}N_2O_5$+ Na): 749.2991; found: 749.2985.

7: foam; lit.[54] m.p.125–130° (benzene-petroleum); ^1H (200 MHz): 11.24(s, 1H, exchangeable, NH); 7.59–7.21(16H, aromatic, 6); 6.19(dd, J = 5.3HZ, 8.6HZ, 1H, 1′); 4.92(t, J = 4.7Hz, exchangeable, 1H, 5′OH); 4.27(d, J = 5.5Hz, 1H, 3′); 3.76(broad s, 1H, 4′); 3.41–3.23(superimposed on the signal of residual H_2O, 5′); 3.19–3.06(m, 1H, 5″); 1.70(s superimposed on the unresolved signal, 3H, 2, 5Me); 1.52(dd, J = 5.8HZ, 13.1Hz, 1H, 2″).

^{13}C (50 MHz): 163.72; 150.58; 144.25; 135.86; 128.61; 128.22; 127.71; 127.44; 109.71; 87.38; 86.30; 83.99; 75.26; 61.50; 12.35.

HRMS (FAB): calc. for ($C_{29}H_{28}N_2O_5$ + Na): 507.1896; found: 507.1880.

2′-Deoxy- 3′,5′-bis-*O*-triphenylmethyluridine 6 and 2′-deoxy-3′-*O*-triphenylmethyluridine 8

Using the same procedure and the chromatography conditions as described above, 2′-deoxy-5′-O-triphenylmenthyluridine **2**[52] (1.27 g, 2.7 mmol) and $CuSO_4$ (1.3 g, 8.1 mmol) in xylenes (15 ml) furnished **6** (0.71, 37%), **8** (0.076 g, 6%) and **12**(0.062 g, 10%).

6: foam; ^1H (200 MHz): 11.39(s, exchangeable, 1H, NH); 7.48(d, J = 8.3HZ, 1H, 6); 7.44–7.00(15H, aromatic); 6.16(t, J = 6.7HZ, 1H, 1′); 5.42(d, J = 8.1HZ, 1H, 5); 4.17(bs, 1H, 3′(4′)); 3.93(bs, 1H, 4′(3′); 3.17–2.92(unresolved, 2H, 5′,5″); 1.78–1.62(unresolved, 2H, 2′,2″).

HRMS (FAB): calc. for ($C_{47}H_{40}N_2O_5$+Na): 735.2835; found: 735.2841.

8: foam; ^1H (200 MHz): 11.29(s, 1H, exchangeable, NH); 7.75(d, 1H, J = 8.2HZ, 6); 7.44–7.23(15H, aromatic); 6.19(t, 1H, J = 7.1HZ, 1); 5.57(d, J = 8.2HZ, 1H, 5); 4.92(t, J = 4.7HZ, 1H, exchangeable, 5′OH); 4.27(bs, 1H, 3′); 3.67(s, 1H, 4′); 3.26(d, J = 11.8HZ, 1H, 5′); 3.07(d, J = 11.8HZ, 1H, 5″).

HRMS (FAB): calc. for ($C_{28}H_{26}N_2O_5$ +Na): 493.1739; found: 493.1743.

3′,5′-Bis-*O*-*t*-butyldimethylsilylthymidine 20 and 3′-*O*-*t*-butyldimethylsilylthymidine 22

Using the same procedure as described above 5′-*O*-*t*-butyldimethysilylthymidine **3**[71] (1.6 g, 4.5 mmol) and $CuSO_4$ (1.7 g, 10.6 mmol) in xylenes (15 ml) furnished **20**[71] (0.70 g, 33%), **22**[71] (0.072 g,

4.5%) and **11**(0.109 g, 10%) after chromatography using a gradient (0→15%) of MeOH in CH_2Cl_2.

20: m.p. 140–142° (CH_2Cl_2); lit.[71] m.p. 144–145° (hexane); ^1H (200MHz): 11.28(s, 1H, exchangeable, NH); 7.36(d, J = 1.4HZ, 1H, 6′); 6.09(t, J = 7.1HZ, 1H, 1′); 4.29(quintette, J = 2.5HZ, 1H, 3′); 3.72–3.64(unresolved, 3H, 4,5′,5″); 2.13(ddd, J = 6.3HZ, 7.8HZ, 13.5HZ, 1H, 2′); 1.99(ddd, J = 3.0HZ, 5.4HZ, 13.0HZ, 1H, 2″); 1.71(s, 3H, 5Me); 0.81(s, 18H, 2x*t*Bu); 0.06(s, 12H, 4xMe).

22: m.p. 80–83° (CH_2Cl_2-MeOH); lit.[71] 83–84° (EtOH-H_2O); ^1H (200MHz): 11.23(s, 1H, exchangeable, NH); 7.58(d, J = 1.0HZ, 1H, 6′); 6.07(dd, J = 6.0HZ, 7.8Hz, 1H, 1′); 5.01(t, J = 5.2HZ, 1H, exchangeable, 5′OH); 4.33(quintette, J = 2.8HZ, 1H, 3′); 3.67(apparent q, J = 3HZ, 1H, 4′); 3.51–3.44(unresolved, 2H, 5′,5″); 2.10(ddd, J = 6.3HZ, 7.7HZ, 14.0HZ, 1H, 2′); 1.94(ddd, J = 3.2HZ, 6.2HZ, 13.0HZ, 1H, 2″); 1.69(s, 3H, 5Me); 0.85(s, 9H, -*t*Bu); 0.06(s, 6H, 2xMe).

2′-Deoxy-3′,5′-bis-*O*-*t*-butyldimethylsilyluridine 21 and 2′-deoxy-3′-*O*-*t*-butyldimethylsilyluridine 23

Using the same procedure and the chromatography conditions as described above, 2′-deoxy-5′-*O*-*t*-butyldimethylsilyluridine **2**[72,73] (1.19g, 3.5mmol) and $CuSO_4$ (1.4 g, 8.7 mmol) in xylenes (12 ml) furnished **21** (0.57 g, 36%), **23** (0.071 g, 6%) and **12**(0.08 g, 10%).

21: foam; ^1H (200MHz): 11.28(s,1H, exchangeable, NH); 7.64(d, J = 8.2HZ, 1H, 6′); 6.06(t, J = 6.4HZ, 1H, 1′); 5.52(d, J = 8.0HZ, 1H, 5′); 4.30(q, J = 4HZ, 1H, 4′); 3.76–3.57(m, 3H, 4′,5′,5″); 2.16(dd, J = 6.1HZ, 12.8HZ, 1H, 2′); 2.02(dd, J = 5.7HZ, 12.8HZ, 1H, 2″); 0.90(s, 18H, 2x*t*Bu); *ca* 0(s, 6H, 2xMe).

HRMS (FAB): calc. for ($C_{21}H_{40}N_2O_5Si_2$ + Na): 479.2373; found: 479.2372.

23: foam; ^1H (200MHz): 11.33(bs, 1H, exchangeable, NH); 7.81(d, J = 8.1Hz, 1H, 6′); 6.13(t, J = 6.7Hz, 1H, 1′); 5.63(dd, J = 2.0Hz, 8.1Hz, 1H, 5′); 5.08(t, J = 5.2Hz, 1H, exchangeable, 5OH); 4.39(quintette, J = 2.8Hz, 2.9Hz, 5.4Hz, 1H, 3′); 3.75(q, J = 3.3Hz, 1H, 4′); 3.59–3.47(m, 2H, 5′,5″); 2.26–2.00(m, 2H, 2′,2″); 0.86(s, 9H, -*t*Bu); 0.07(s, 6H, 2xMe).

^{13}C (50MHz): 163.67; 150.78; 140.98; 102.27; 87.84; 84.44; 72.46; 61.16; 26.07; 18.09; −4.44; −4.51. The signal of the C2′ is hidden under the signal of the solvent.

HRMS (FAB): calc. for ($C_{15}H_{26}N_2O_5Si$ + Na): 365.1509; found: 365.1516.

Triphenylmethane 13, Phenylmethyl Triphenylmethyl Ether 14 and Thymidine 11

3′,5′-Bis-*O*-triphenylmethylthymidine **5**[53] (0.98 g, 1.35 mmol), CuSO4, (1.8 g, 11.3 mmol), and $PhCH_2OH$ (1.5 ml, 14.5 mmol) in xylenes

(15 ml) were stirred at reflux during 5 hours under exclusion of moisture. TLC (hexane) showed a presence of triphenylmethane **13** (R_f 0.36) and phenylmethyl triphenylmetyl ether **14** (R_f 0.15). TLC run twice in CH_2Cl_2-MeOH 10:1 showed a small amount of thymine **9** (R_f 0.37) and the main product thymidine **11** (R_f 0.18). No traces of 2-deoxyribose were noticed. The reaction mixture was filtered through a sintered glass and the solids were washed with MeOH. Silica gel was added to the filtrate and the solvents were evaporated. The residue was applied on a top of a chromatography column prepared in hexane. Elution with hexane gave **13** (0.011 g, 3%). Elution with hexane-EtOAc 99:1 gave **14** (0.74 g, 78%). Elution with a gradient of MeOH in CH_2Cl_2 (0→20%) furnished **11** (0.17 g, 51%).

Under the same conditions 5′-*O*-triphenylmethylthymidine **1**[51] (1.0 g, 2.1 mmol), CuSO4, (1.8g, 11.3 mmol) and $PhCH_2OH$ (1.3ml, 12.6 mmol) in xylenes (15ml) furnished **11** (0.24g, 49%).

13: ^1H (200MHz, $CDCl_3$): 7.35–7.03(15H, aromatic); 5.55(s, 1H, −CH).

^{13}C (50MHz, $CDCl_3$): 143.84; 129.41; 128.25; 126.24; 56.78.

14: m.p. 102–104° (hexane); lit.[55] m.p. 95° (EtOH); 1H (200MHz, $CDCl_3$): 7.55–7.21(15H, aromatic); 4.18(s, 2H, -CH_2Ph).

^{13}C (50MHz, $CDCl_3$): 144.40; 139.39; 128.98; 128.51; 128.11; 127.33; 127.27; 127.18; 87.17; 65.88.

11: 11.28(s, exchangeable, 1H, NH); 7.69(s, 1H, 6′); 6.16(t, 1H, J = 6.6Hz and 7.0Hz, 1H, 1′); 5.23(d, J = 4.0Hz, exchangeable, 1H, 3OH); 5.05(t, J = 4.8Hz, exchangeable, 1H, 5′OH); 4.28–4.18 and 3.80–3.70(both unresolved, 1H each, 3′,4′); 3.68–3.46(apparent AB, 2H, 5′,5″); 2.18–1.96(unresolved, 2H, 2′,2″); 1.76(s, 3H, Me).

Deprotections of 2′-Deoxy-3′,5′-bis-*O*-triphenylmethyluridine 6 and 2′-Deoxy-5′-*O*-triphenylmethyluridine 2 Using $CuSO_4/PhCH_2OH$

The same procedure as applied above, but using 2′-deoxy-3′,5′-bis-*O*-triphenylmethyluridine **6** (1.11 g, 1.5 mmol), $CuSO_4$ (1.5 g, 9.4 mmol), and $PhCH_2OH$ (1.5 ml, 14.5 mmol) in xylenes (15 ml) furnished 2′-deoxyuridine **12** (0.16 g, 46%). 2′-Deoxy-5′-*O*-triphenylmethyluridine **2** (0.49 g, 1.0 mmol), CuSO4, (0.58 g, 3.6 mmol), and $PhCH_2OH$ (0.5 ml, 4.8 mmol) in xylenes (15 ml) furnished **12** (0.12 g, 49%). **12**: 11.29(bs, exchangeable, 1H, NH); 7.85(d, J = 8.2Hz, 1H, 6); 6.15(t, J = 6.8Hz, 6.6Hz, 1H, 1′); 5.63(d, J = 8.0Hz, 1H, 5′); 5.25(d, exchangeable, J = 2.6Hz, 1H, 3′OH); 5.02(bs, exchangeable, half-width = 10.3Hz, 1H, 5′OH); 4.29–4.16 and 3.84–3.72 (both unresolved, 1H each, 3′,4′); 3.65–3.44(unresolved, 2H, 5′,5″); 2.18–1.96(unresolved, 2H, 2′,2″).

t-Butyldimethylsilyl phenylmethyl ether 24 and thymidine 11

3′,5′-*O*-*t*-butyldimethylsilylthymidine **20**[72] (1.32g, 2.81 mmol) was stirred with $CuSO_4$ (1.51 g, 9.50 mmol) and $PhCH_2OH$ (1.8 ml, 17.4 mmol) in xylenes (15 ml) at reflux. TLC (a sample was prepared in the same way as described before for detritylation of **5**, **6**, **1**, and **2**) showed a spot of *t*-butyldimethylsilyl phenylmethyl ether **24** (R_f 0.29 in hexane-EtOAc 20:0.1); thymine **9** and thymidine **11** were visible after running a plate in CH_2Cl_2-MeOH 10:1; R_fs were 0.29 and 0.12, respectively. Workup as for detritylation of **5**,**6**,**1** and **2**, and chromatography (the column was prepared in hexane) furnished **24** (0.76g, 61%, elution with hexane-EtOAc 20–0.1). Subsequent elution with a gradient of MeOH in CH_2Cl_2 (0→20%) furnished thymidine **11** (0.37 g, 55%).

24: oil; ^{1}H (200MHz): 7.30(5H, aromatic); 4.70(s, 2H, -CH_2Ph); 0.90(s, 9H, -*t*Bu); 0.06(s, 6H, 2xMe).

^{13}C: 141.20; 128.16; 126.88; 125.97; 64.24; 25.73; 17.92; −5.43.

HRMS: molecular ion was not visible in a CI mode.

Under the same conditions 5′-*O*-*t*-butyldimethylsilylthymidine **3**[72] (0.6 3 g, 1.70 mmol), $CuSO_4$ (0.9 g, 5.6 mmol), and $PhCH_2OH$ (0.8 ml, 7.7 mmol) in xylenes (15 ml) furnished thymidine **11** (0.21 g, 48%). The ether **24** was not isolated.

Likewise 3′,5′-*O*-bis-*t*-butyldimethylsilyl-2′-deoxyuridine **21** (1.46 g, 3.2 mmol), $CuSO_4$ (1.7 g, 10.6 mmol), and $PhCH_2OH$ (1.8 ml, 17.4 mmol) in xylenes (15 ml) furnished **24** (0.92 g, 65%) and 2′-deoxyuridine **12** (0.39 g, 53%) after chromatography in the same system as above. Under the same conditions **4**[73,74] (0.54g, 1.7 mmol) was deprotected using $CuSO_4$ (0.8 g, 5.0 mmol) and $PhCH_2OH$ (0.7 ml, 6.7 mmol) in xylenes (15 ml) to yield **12** (0.18 g, 49%).

3′-*O*-Acetylthymidine 17

A. 3′-*O*-Acetyl-5′-*O*-triphenylmethylthymidine[51][**15** (0.69 g, 1.3 mmol), $CuSO_4$ (1.1 g, 6.9 mmol), and $PhCH_2OH$ (1.0 ml, 9.6 mmol) in xylenes (15 ml) were stirred at reflux during 2 hours. TLC showed that a new more polar compound was formed. The reaction mixture was filtered through a sintered glass and the solids were washed with MeOH. Silica gel was added and xylenes and methanol were evaporated. The residue was applied on a top of a chromatography column prepared in CH_2Cl_2. Elution using a 0→10% gradient of MeOH in CH_2Cl_2 furnished **17** (0.28 g, 74%). The ether **14** was not isolated.

B. 3′-*O*-Acetyl-5′-*O*-*t*-butyldimethylsilylthymidine **25**[75] (1.2 g, 3.3 mmol), $CuSO_4$ (2.1 g, 13.2 mmol), and $PhCH_2OH$ (1.8 ml, 17.4 mmol) in xylenes (15 ml) furnished **17** (0.59 g, 69%) using the same procedure as described above.

17: m.p. 175–177° (CH_2Cl_2-MeOH); lit.[51] 176° (acetone); ^1H (300MHz): 11.37(s, 1H, exchangeable, NH); 7.75(d, J = 1.2Hz, 1H, 6′); 6.19(t, J = 7.4Hz, 1H, 1′); 5.37(t, J = 5.3Hz, 1H, exchangeable, 5′OH); 5.24–5.21(unresolved, 1H, 3′); 4.03–3.98(unresolved, 1H, 4′); 3.80–3.62(partially superimposed on the residual H_2O signal, 5′,5″); 2.35–2.21(unresolved, 2H, 2′,2″); 2.08(s, 3H, OAc); 1.80(s, 3H, 5Me).

3′-*O*-Acetyl-2′-deoxyuridine 18

A. 3′-*O*-Acetyl-2′-deoxy-5′-*O*-triphenylmethyluridine **16**[52] (0.71 g, 1.39 mmol), $CuSO_4$ (0.9 g, 5.6 mmol), and $PhCH_2OH$ (1.0 ml, 9.6 mmol) in xylenes (15 ml) were stirred at reflux during 2 hours. TLC showed that a substrate was no longer present. Workup as described for **17** and chromatography in the same system furnished **18**[52] (0.27 g, 73%). The ether **14** was not isolated.

B.3′-*O*-Acetyl-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine **26** (1.4 g, 3.6 mmol), $CuSO_4$ (2.2 g, 13.8 mmol), and $PhCH_2OH$ (1.8 ml, 17.4 mmol) in xylenes (15 ml) furnished **18** (0.71 g, 72%) using the same procedure as described above. The ether **24** was not isolated.

18: m.p. 173–174° (CH_2Cl_2-MeOH); lit.[52] m.p. 188° (EtOH-acetone-cyclohexane); ^1H (300MHz): 11.40(bs, 1H, exchangeable), NH); 7.90(d,1H, J = 8.1Hz, 6); 6.17(t, 1H, J = 7.2Hz, 1′); 5.70(d, 1H, J = 8.1Hz, 5); 5.34(t, J = 4.6Hz, 1H, exchangeable, 5′OH); 5.25–5.19(m, 1H, 3′); 4.02(apparent q, J = 2.7Hz, 1H, 4′); 3.63(apparent t, J = 3.8Hz, 2H, 5′,5″); 2.32–2.22(m, 2H, 2′,2″); 2.07(s, 3H, -OAc).

3′-*O*-Acetyl-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine 26

Conventional acetylation of **4** in a mixture of Ac_2O-Py 2:1 followed by extraction (CH_2Cl_2 /H_2O) furnished **26** (69%) after crystallization from EtOAc-hexane. M.p. 144–145°. ^1H (300MHz): 11.44(bs, 1H, exchangeable, NH); 7.77(d, J = 8.4Hz, 1H, 5′); 6.15(dd, J = 6.0Hz, 8.1Hz, 1H, 1′); 5.65(d, J = 8.1Hz, 1H, 5′); 5.21–5.15(m, 1H, 3′); 4.09(apparent q, J = 2.5Hz, 1H, 4′); 2.38(ddd, J = 1.8Hz, 6.0Hz, 14.0Hz, 1H, 2′); 2.23(ddd, J = 6.3Hz, 8.0Hz, 14.1Hz, 1H, 2″); 2.07(s, 3H, -OAc); 0.88(s, 9H, -*t*Bu); 0.08(s, 6H, 2xMe). The signals of the H5′,5″ protons were superimposed on the residual H_2O signal at 3.95–3.80 ppm.

HRMS (FAB): calc. for ($C_{17}H_{28}N_2O_6Si$ + Na): 407.1614; found: 407.1611.

3′-*O*-[(Propylthio)thiocarbonyl]-5′-*O*-triphenylmethylthymidine 29

To a cold (ice bath) and stirred solution of 5′-*O*-triphenylmethylthymidine **1** (0.9 g, 1.8 mmol) in DMSO (5 ml) under

a blanket of argon was added CS_2 (2 ml) and 5N NaOH (1 ml). The mixture turned red. After 0.5 hours propyl bromide (2.8 ml, 32 mmol) was added via a syringe. The solution turned yellow. The ice bath was removed and stirring was continued for 1 hour. The reaction mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was evaporated and the yellow residue was applied on a top of a chromatography column prepared in CH_2Cl_2. Elution using a gradient of MeOH in CH_2Cl_2 (0→5%) furnished a yellowish syrup of **29** (0.80 g, 72%). ^{1}H (200MHz, MeOH-d_4): 7.59(d, J = 1Hz, 1H, 6′); 7.37–7.12(15H, aromatic); 6.27(t, J = 7.2Hz, 1H, 1′); 6.20–6.12(unresolved, 1H, 3′); 4.28–4.08(unresolved, 1H, 4′); 3.51(dd, J = 2.8Hz, 10.6Hz, 1H, 5′); 3.30(dd, J = 2.4Hz, 10.2Hz, 1H, 5″); 3.03(t, J = 7.2Hz, 2H, -SCH_2-); 2.53(dd, J = 7.0Hz, 7.4Hz, 2H, 2′,2″); 1.61(hextette, J = 7.2Hz, 2H,-**CH_2**CH_3); 1.32(d, J = 1Hz, 3H, 5Me); 0.91(t, J = 7.4Hz, 3H, -CH_2**CH_3**).

^{13}C (50MHz): 215.93; 166.13; 152.20; 144.73; 137.09; 129.87; 129.10; 128.59; 112.09; 88.99; 86.04; 85.21; 84.76; 65.11; 38.98; 38.66; 22.95; 13.71; 12.13.

HRMS: molecular ion was invisible in a CI mode.

5′-*O*-*t*-butyldimethylsilyl-2′-deoxy-3′-*O*-[(propylthio)thiocarbonyl]uridine 30

Compound **4** (0.51 g, 1.5 mmol) was converted to a its propyl xanthate using DMSO (5 ml), CS_2 (1.6 ml), 5N NaOH (0.8 ml), and propyl bromide (2.3 ml, 25 mmol) as described for **29**. Workup and chromatography (0→5% gradient of MeOH in CH_2Cl_2) furnished **30** (0.47 g, 69%) as a yellow syrup. ^{1}H (200MHz, MeOH-d_4): 7.96(d, J = 8.0Hz, 1H, 6′); 6.35(dd, J = 5.6Hz, 8.4Hz, 1H, 1′); 6.03(d, J = 5.6Hz, 1H, 3′); 5.71(d, J = 8.0Hz, 1H, 5′); 4.35(bs, 1H, 4′); 4.06(dd, J = 2.2Hz, 11.6Hz, 1H, 5′); 3.96(dd, J = 2.2Hz, 11.4Hz, 1H, 5″); 3.16(t, J = 7.2Hz, 2H, -SCH_2-); 2.67(dd, J = 5.6Hz, 14.0Hz, 1H, 2′); 2.34(ddd, J = 6.2Hz, 8.4Hz, 14.4Hz, 1H, 2″); 1.75(hextette, J = 7.3Hz, 2H, -**CH_2**CH_3); 1.05(t, J = 7.2Hz, 3H, -CH_2**CH_3**); 0.96(s, 9H, *t*Bu); 0.17(s, 6H, 2xMe). HRMS: molecular ion was invisible in a CI mode.

3′-Deoxy-5′-*O*-triphenylmethylthymidine 19

To a boiling solution of **29** (0.58 g, 1 mmol) in toluene (15 ml) was added dropwise a solution of Bu_3SnH (97%, 0.53 ml, 1.9 mmol) and AIBN (0.03 g, 0.19 mmol) in toluene (10 ml) during 15 minutes. under a blanket of argon. Reflux was maintained for 1 hour. Evaporation of the solvent gave an oil that was applied on a top of a chromatography column prepared in CH_2Cl_2. Elution using a gradient of MeOH in CH_2Cl_2 (0→5%) furnished **19** (0.31 g, 68%) as a foam; lit.;[60] foam; ^{1}H (300MHz): 11.33(s, 1H, exchangeable, NH); 7.48(s, 1H, 6′); 7.38–7.21(15H, aromatic); 5.98(dd,

J = 3.0Hz, 6.3Hz, 1H, 1′); 4.18–4.06(unresolved, 2H, 4′,5′); 2.36–2.18 and 2.08–1.88(two groups of unresolved signals, 4H, 2′,2″,3′,3″); 1.46(s, 3H, 5Me). The signal of the proton 5″ was hidden under the signal of the residual H_2O at 3.90- 3.50 ppm.

^{13}C (75MHz): 164.38; 150.80; 143.86; 136.22; 128.56; 128.33; 127.55; 109.51; 86.54; 85.34; 79.62; 65.21; 31.47; 25.86; 12.25.

5′-*O*-*t*-Butyldimethylsilyl-2′,3′-dideoxyuridine 27

Compound **30** (0.42 g, 0.91 mmol) in toluene (15 ml) was deoxygenated and purified as described for **29**, using Bu_3SnH (97%, 0.55 ml, 2 mmol) and AIBN (0.03 g, 0.19 mmol) in toluene (15 ml) to furnish **27** (0.29 g, 61%). ^1H (200MHz, $CDCl_3$): 9.09(bs, 1H, exchangeable, NH); 8.08(d, J = 8.0Hz, 1H, 6′); 6.04(dd, J = 2.8Hz, 6.4Hz, 1H, 1′); 5.62(d, J = 8.2Hz, 1H, 5′); 4.20–3.93 and 3.74–3.60(two groups of unresolved signals, 3H, 4,5,5″); 2.48–1.80(two groups of unresolved signals, 4H, 2′,2″,3′,3″); 0.89(s, 9H, -*t*Bu); 0.07(s, 6H, 2xMe).

HRMS (FAB): calc. for ($C_{15}H_{26}N_2O_4Si$ + Na): 349.1554; found: 349.1548.

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