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A SIMPLE AND CONVENIENT METHOD FOR THE DEPROTECTION OF TETRAHYDROPYRANYL ETHER USING IODINE IN METHANOL

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Abstract: A simple and efficient method for the deprotection of tetrahydropyranyl and 4,4'-dimethoxytrityl ethers using iodine in methanol is described.

Protecting groups[1] play a major role in organic synthesis. For a protecting group to be quite useful in synthetic chemistry, it has to be installed easily and removed efficiently without harming other functionality. Often, in complex natural product synthesis more than one protecting group has to be introduced and the removal of a selected protecting group is necessary. Tetrahydropyranyl (THP) ether in combination with *tert*-butyldimethylsilyl group are frequently used for this purpose because of their ease of formation, their stability to an wide range of reaction conditions and efficient removal. Deprotection of tetrahydropyranyl ethers are accomplished using a variety of reagents such as acetic acid,[2] amberlyst H-15,[3] $(NCSBu_2Sn)_2O$,[4] $PPh_3.Br_2$,[5] pyridinium toluene-p-sulfonate,[6] boric acid,[7] p-toluene sulfonic acid,[8] $(TMSO)_2SO_2$ in methanol.[9] Recently, CAN,[10] and DDQ[11] were introduced as detetrahydropyranylating reagents. In addition,

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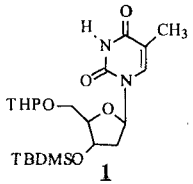
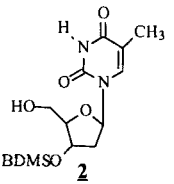
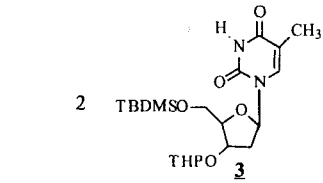
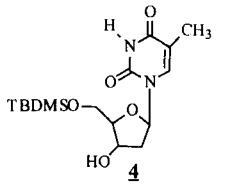
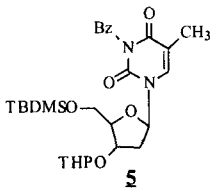
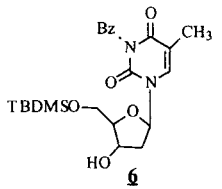
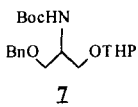
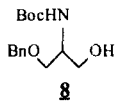
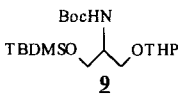
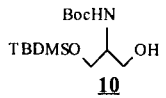
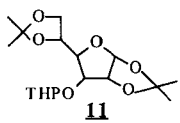
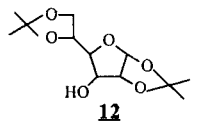
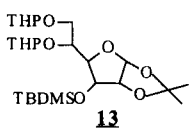
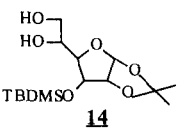
$MgBr_2$[12] and Me_2AlCl[13] have been used to cleave THP ethers in the presence of TBDMS ethers. Herein, we report a new methodology for the selective cleavage of THP ether using iodine in methanol. We further report that 4,4'-dimethoxytrityl (DMT) protecting group is also cleaved with iodine/methanol.[14]

Iodine in methanol is a well-known reagent for the deprotection of cyclic acetals,[15] and has been used for the cleavage of p-methoxybenzyl[16] and *tert*-butyldimethylsilyl[17] ethers. During the course of a synthesis, the removal of *tert*-butyldimethylsiyl group in the presence of tetrahydropyranyl ether was required; it was discovered that iodine in methanol cleaved selectively the tetrahydropyranyl group. Interestingly, the *tert*-butyldimethylsiyl group remained unaffected during that time course. We report that this reaction occurs with iodine in methanol under mild condition and so it is possible to use this methodology to deprotect selectively tetrahydropyranyl ethers in the presence of *tert*-butyldimethylsiyl ethers. Survey of literature revealed that iodine in methanol has not been used for the cleavage of THP ethers.

In order to demonstrate the generality of this methodology, we have synthesized a variety of tetrahydropyranyl ethers using standard procedures and studied their cleavage with iodine in methanol. The results are summarized in Table 1. Treatment of substrate (entry 1) with one equivalent of iodine in methanol at room temperature for 3 hr followed by quenching the reaction with $Na_2S_2O_3$ and usual work-up afforded the product in 90% yield. When the deprotection was tried at 75°C, the cleavage time was reduced to 0.5 hr with excellent selectivity. Reaction of substrates having secondary THP ethers and primary TBDMS protecting groups (entry 2 & 3) with iodine under similar conditions removed the THP group selectively in 8 hr and 6 hr respectively. Moreover, the selectivity was achieved in the presence of benzyl and isopropylidene protecting groups. In less hindered linear substrates (entry 4 & 5), the THP ethers were cleaved less than 3 hr. We then studied the rate of cleavage of THP ethers with different amounts of iodine in methanol at room temperature. Accordingly, stirring of substrate (entry 5) with one equivalent of iodine, the THP group was removed in 3 hr. But, exposure of the same substrate (entry 5) to

Table 1. Deprotection of Tetrahydropyranyl Ethers by Iodine in Methanol

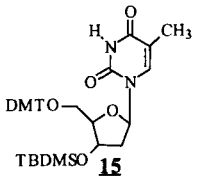
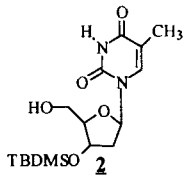
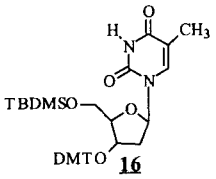
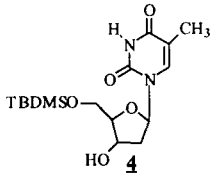
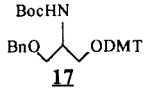
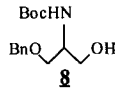
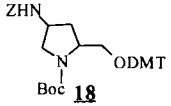
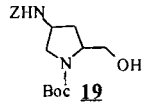
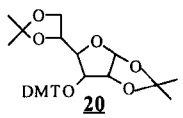
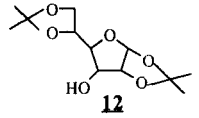
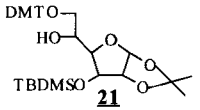
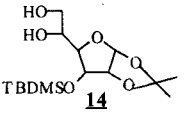
Entry	Substrate	Product	t/h	Yield(%)
1	 **1**	 **2**	3	90
2	 **3**	 **4**	8	85
3	 **5**	 **6**	6	92
4	 **7**	 **8**	2	97
5	 **9**	 **10**	3	87
6	 **11**	 **12**	1	90
7	 **13**	 **14**	1.5	93

Bz = Benzoyl, Bn = Benzyl and Boc = *tert*-Butyloxycarbonyl.

catalytic amount (10 mg) of iodine gave the detetrahydropyranylated product in 6 hr. On the other hand, three equivalent of iodine cleaved the THP group of entry 5 (Table 1) in 1 hr. However, it is advisable to use stochiometric amount of iodine for the deprotection reactions. Further, the selectivity was obtained in entries 6 and 7 too. In these two entries, THP ethers were deprotected selectively in the presence of TBDMS and isopropylidene groups. The versatility of the method was also noticed in the selective cleavage of secondary THP ether over secondary TBDMS ether (entry 7). Furthermore, we have seen that the secondary THP ether can be selectively cleaved in the presence of isopropylidene groups (entry 6). Indeed, most of the deprotection reactions were carried out in methanol at room temperature and found to be an excellent solvent. The cleavage studies were also tried in solvents like THF, CH_3CN and CH_2Cl_2. The deprotection of THP ether proceeds slowly in THF and CH_3CN, and is very sluggish in CH_2Cl_2. Preliminary investigation suggests that methanol is the best choice for deprotection of THP ethers.

During the selective cleavage of THP ethers in the presence of TBDMS group, we have also observed[18] that iodine in methanol deprotects DMT ethers too. When, 5'-O-(4,4'-dimethoxytrityl)-3'-O-*tert*-butyldimethylsilyl-2'-deoxy-β-D-*erythro*-pentofuranosylthymine (Table 2; entry 1) was treated with one equivalent of iodine/methanol at room temperature, the DMT group was removed in 5 hr and 3'-O-*tert*-butyldimethylsilyl-2'-deoxy-β-D-*erythro*-pentofuranosyl-thymine was isolated in 93% yield. It is pertinent to mention that the removal of 5'-DMT group of entry 1 (Table 2) was carried out with 80% acetic acid[19]; the reaction does not go to completion, and afforded the product in moderate yield. The moderate yield of the product under acidic deprotection condition can be rationalized by the equilibrium of the dimethoxytrityl carbo cation in the reaction medium and thereby makes the detritylation reversible. Recently, a method[20] to scavenge the DMT cation with Et_3SiH in oligonucleotide synthesis was reported. We believe that iodine/methanol method described here is particularly very attractive for the removal of DMT group from the 5'-DMT protected acid sensitive nucleosides and nucleotides. To illustrate the utility of iodine in

Table 2. Deprotection of 4,4'-Dimethoxytrityl Ethers by Iodine in Methanol

Entry	Substrate	Product	t/h	Yield(%)
1	 **15**	 **2**	5	93
2	 **16**	 **4**	2.5[a]	85
3	 **17**	 **8**	0.5	95
4	 **18**	 **19**	1	94
5	 **20**	 **12**	1	88
6	 **21**	 **14**	1	88

[a]The reaction was heated at 75°C. Z = Benzyloxycarbonyl, Bn = Benzyl and Boc = Tert-butyloxycarbonyl.

methanol for the deprotection of DMT group, we prepared different substrates having primary and secondary DMT groups and studied their cleavage. The results are summarized in Table 2. In all cases the deprotection was very efficient and the products obtained in quantitative yields. From the Table 2 it is clear that DMT groups are cleaved selectively in the presence of TBDMS, isopropylidene and benzyl ethers. Remarkably, even if the DMT ether is

secondary and the TBDMS is primary, we did get selectivity (Table 2; entry 2). Furthermore, the DMT group is removed selectively in the presence of TBDMS and isopropylidene groups (entry 6). It was noted that if the reaction time of entry 5 (Table 2) is extended beyond 1 hr, the isopropylidene groups are also gets cleaved.

The significance of iodine/methanol deprotection method is two folds. First, the reagents used in this procedure are inexpensive. Secondly, the reactions were carried out under mild conditions without any special precautions. Furthermore, this simple procedure should be particularly applicable for the selective removal of THP moiety and DMT groups. The paramount importance of the paper is that it describes not only selective deprotection of THP ether in the presence of TBDMS and isopropylidene groups but also offers alternative route for acid sensitive molecules.

The mechanism of the reaction is not very clear. However, it is known that iodine reacts with methanol and produces HI,[21] complexes of type $[IMeOH+][I_3-]$[22] and other products. We believe that the production of HI may be responsible for observed deprotection results. However, iodine/methanol complex catalyzed cleavage can not be ruled out.

In conclusion, we have described a novel methodology for the selective removal of tetrahydropyranyl ether in the presence of a *tert*-butyldimethylsiyl ether and for the deprotection of 4,4'-dimethoxytrityl group. The simplicity of the present method will be attractive and quite useful in organic synthesis.

Experimental

Melting points were taken on a Haake Buchler capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Mercury 300 Hz spectrometer. The chemical shifts are expressed in δ values (ppm) relative to tetramethylsilane as internal standard. Elemental analyses were performed by Quantitative Technologies Inc., White House, NJ. Thin layer chromatography (TLC) was performed on plates of silica gel $60F_{254}$ coated on aluminum sheets (5x10 cm; EM Science) using different

solvents prepared freshly. ICN silica gel 18-32 (60 A) was used for flash column chromatography. All solvents used were reagent grade. Most of the dry solvents were purchased from Fluka and used as such without further purification. Most of the reactions were conducted under argon atmosphere. Evaporations were carried out under reduced pressure with the bath temperature below 35°C.

General Procedure for preparing THP ethers: To a stirred solution of the substrate (1.0 mmol) in dry CH_2Cl_2 (20 ml) was added dihydropyran (10.0 mmol) and pyridinium toluene-4-sulfonate (0.1 mmol) at room temperature under argon atmosphere. The reaction was stirred at room temperature for 12 hr and evaporated to dryness. The residue was dissolved in ethyl acetate (50 ml), washed with 5%$NaHCO_3$ (50 ml), water (50 ml) and brine (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by flash chromatography over silica gel using appropriate solvent. Pure fractions were pooled and concentrated to give pure product.

5'-O-Tetrahydropyranyl-3'-O-(*tert*-butyldimethylsilyl)thymidine (1): The titled compound **1** was prepared from **2**.[23] Hexane → EtOAc was used for flash chromatography. Yield: 92%, foam. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H, 2C*H*$_3$), 0.86 (s, 9H, *tert*-butyl), 1.44-1.82 (m, 6H), 1.90 (2s, 3H, C*H*$_3$), 2.04 (m, 1H), 2.26 (m, 1H), 3.54 (m, 1H), 3.80-4.04 (m, 3H), 4.42 (2m, 1H), 4.62 (2bs, 1H), 6.34 (2t, 1H), 7.48 (2s, 1H), 8.82 (bs, 1H). Anal. Calcd. for $C_{21}H_{36}N_2O_6Si$: C, 57.24; H, 8.24; N, 6.36. Found: C, 57.31; H, 8.20; N, 6.40.

5'-O-(*tert*-Butyldimethylsilyl)-3'-O-(tetrahydropyranyl)thymidine (3): The titled compound **3** was prepared from **4**.[24] Chloroform → EtOAc was used for flash chromatography. Yield: 91%, foam. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6H, 2C*H*$_3$), 0.82 (s, 9H, *tert*-butyl), 1.40-1.78 (m, 6H), 1.82 (s, 3H, C*H*$_3$), 2.00 (m, 1H), 2.30 (m, 1H), 3.42 (m, 1H), 3.60-3.82 (m, 3H), 4.0 (m, 1H), 4.30 (m, 1H), 4.58 (m, 1H), 6.21 (m, 1H), 7.40 (d, 1H), 8.56 (s, 1H). Anal. Calcd. for $C_{21}H_{36}N_2O_6Si$: C, 57.24; H, 8.24; N, 6.36. Found: C, 57.20; H, 8.34; N, 6.19.

5'-O-(*tert*-Butyldimethylsilyl)-3'-O-(tetrahydropyranyl)-(N_3-benzoyl)thymidine (5): To a stirred solution of **3** (1.1 g, 2.5 mmol) in dry pyridine (30 ml) was added benzoyl chloride (0.42 g, 3.0 mmol) and triethylamine (0.51 g, 5.0 mmol).

The reaction mixture was allowed to stir at room temperature under argon atmosphere for 12 hr and evaporated to dryness. The residue was partitioned between EtOAc (50 ml) and 5%$NaHCO_3$ (50 ml), and extracted in EtOAc. The organic extract was washed with water (50 ml) and brine (50 ml), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel using hexanes → EtOAc as the eluent. Pure fractions were pooled and concentrated to give **5** as foam. Yield: 1.26 g (93%). ^{1}H NMR ($CDCl_3$): δ 0.14 (s, 6H, 2C*H*$_3$), 0.94 (s, 9H, *tert*-butyl), 1.44-1.80 (m, 6H), 1.94 (s, 3H, C*H*$_3$), 2.14 (m, 1H), 2.50 (m, 1H), 3.52 (m, 1H), 3.78-3.88 (m, 2H), 3.94 (d, 1H), 4.08 & 4.22 (2s, 1H), 4.40 & 4.44 (2d, 1H), 4.70 (m, 1H), 6.32 (m, 1H), 7.46 (t, 2H), 7.62 (t, 2H), 8.92 (d, 2H). Anal. Calcd. for $C_{28}H_{40}N_2O_7Si$: C, 61.91; H, 7.40; N, 5.14. Found: C, 61.91; H, 7.59; N, 5.23.

1-O-Benzyl-2-[(*tert*-butyloxycarbonyl)amino]-3-O-(tetrahydropyranyl)-L-propan-1,3-diol (7): The titled compound **7** was prepared from **8**.[25] Hexanes → EtOAc was used for flash chromatography. Yield: 88%, oil. ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 9H, *t*-Boc), 1.46-1.82 (m, 6H), 3.44-3.64 (m, 4H), 3.76-3.88 (m, 2H), 3.94 (bd, 1H), 4.46-4.62 (m, 3H), 4.92-5.06 (bd, 1H), 7.22-7.40 (m, 5H, Ph-*H*). Anal. Calcd. for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.79; H, 8.69; N, 4.01.

1-O-(*tert*-Butyldimethylsilyl)-2-[(*tert*-butyloxycarbonyl)amino]-3-O-(tetrahydropyranyl)-L-propan-1,3-diol (9): Reaction of N-(*tert*-butyloxycarbonyl)-3-O-tetrahydropyranyl-L-serinol with *tert*-butyldimethylsilyl chloride in dry pyridine in the presence of TEA provided the titled compound as an oil. Hexanes → EtOAc was used for flash chromatography. Yield: 100%. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H, 2C*H*$_3$), 0.88 (s, 9H, *tert*-butyl), 1.44 (s, 9H, *t*-Boc), 1.46-1.84 (m, 6H), 3.38-3.90 (m, 7H, 3C*H*$_2$ & C*H*), 4.60 (2m, 1H), 4.80-5.00 (2bd, 1H). Anal. Calcd. for $C_{19}H_{39}NO_5Si$: C, 58.57; H, 10.09; N, 3.59. Found: C, 58.59; H, 10.19; N, 3.71.

3-O-Tetrahydropyranyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (11): The titled compound **11** was prepared from 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**12**). Hexanes → EtOAc was used for flash chromatography. Yield:

93%, foam. ^{1}H NMR ($CDCl_3$): δ 1.32-1.86 (m, 18H, 3CH_2 & 4CH_3), 3.34 (m, 1H), 3.90-4.14 (m, 5H), 4.38 (m, 1H), 4.40-4.70 (m, 2H), 5.76 (m, 1H). Anal. Calcd. for $C_{17}H_{28}O_7$: C, 59.28; H, 8.19. Found: C, 59.41; H, 8.49.

5,6-Di-O-tetrahydropyranyl-3-O-(*tert*-butyldimethylsilyl)-1,2-O-isopropylidene-α-D-allofuranose (13): 1,2:5,6-Di-O-isopropylidene-α-D-allofuranose **(12)** was reacted with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole at room temperature which on work-up gave 3-(*tert*-butyldimethylsilyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose. This intermediate on exposure to 80% acetic acid for 36 hr followed by work-up provided **14** after column chromatography. The compound **14** on treatment with dihydropyran as described in the general procedure afforded the titled compound. Hexanes → EtOAc was used for the flash chromatography. Yield: 80%, foam. ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 6H, 2CH_3), 0.92 (s, 9H, *tert*-butyl), 1.34 & 1.5.2 (2s, 6H, isopropylidene-CH_3), 1.42-1.84 (m, 12H, 6CH_2), 3.42-3.60 (m, 2H), 3.80-4.24 (m, 7H), 4.40 (m, 1H), 4.60-5.02 (m, 2H), 5.72 (m, 1H). Anal. Calcd. for $C_{25}H_{46}O_8Si$: C, 59.73; H, 9.22. Found: C, 59.79; H, 9.47.

General Procedure for preparing DMT ethers: To a stirred solution of the substrate (1.0 mmol) and TEA (1.5 mmol) in dry CH_2Cl_2 (20 ml) was added DMTCl (1.0 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for 12 hr and evaporated to dryness. The residue was dissolved in ethyl acetate (50 ml), washed with 5%$NaHCO_3$ (50 ml), water (50 ml) and brine (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel using appropriate solvent. Pure fractions were pooled and concentrated to give pure product.

5'-O-(4,4'-Dimethoxytrityl)-3'-O-(*tert*-butyldimethylsilyl)thymidine (15): The titled compound **15**[23] was prepared from Thymidine. Choloform → EtOAc was used for flash chromatography. Yield: 90%, foam. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H, 2CH_3), 0.86 (s, 9H, *tert*-butyl), 1.52 (s, 3H, CH_3), 2.20-2.40 (m, 2H, *H*-2'), 3.30 (dd, 1H, *H*-5'), 3.48 (dd, 1H, *H*-5'), 3.82 (s, 6H, 2xOCH_3), 4.00 (d, 1H, *H*-4'), 4.58 (m, 1H, *H*-3'), 6.40 (t, 1H, *H*-1'), 6.87 (d, 4H, Ph-*H*), 7.24-7.44 (m, 9H,

Ph-*H*), 7.68 (s, 1H, C_6-*H*), 8.42 (s, 1H, N*H*). Anal. Calcd. for $C_{37}H_{46}N_2O_7Si$: C, 67.45; H, 7.03; N, 4.25. Found: C, 67.61; H, 6.99; N, 4.31.

5'-O-(*tert*-Butyldimethylsilyl)-3'-O-(4,4'-dimethoxytrityl)thymidine (16): To a stirred solution of **4**[24] (1.0 g, 2.8 mmol) in dry pyridine (50 ml) under argon atmosphere was added silver trifluoromethane sulfonate (2.56 g, 10 mmol). The reaction mixture was stirred for 30 min and treated with 4,4'-dimethoxytrityl chloride (3.38 g, 10 mmol). The reaction mixture was allowed to stir at 50°C for 12 hr and evaporated to dryness. The residue was partitioned between EtOAc (100 ml) and sat. $NaHCO_3$ (50 ml), and extracted in EtOAc. The organic extract was washed with water (50 ml) and brine (50 ml), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel using hexanes → EtOAc as the eluent. Pure fractions were pooled and concentrated to give 1.2 g (65%) of a foamy material. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H, 2C*H*$_3$), 0.85 (s, 9H, *tert*-butyl), 1.56-1.80 (m, 2H, *H*-2'), 1.90 (s, 3H, C*H*$_3$), 3.32 (d, 1H, *H*-5'), 3.72 (d, 1H, *H*-5'), 3.84 (s, 6H, 2xOC*H*$_3$), 4.04 (s, 1H, *H*-4'), 4.32 (d, 1H, *H*-3'), 6.44 (m, 1H, *H*-1'), 6.88 (d, 4H, Ph-*H*), 7.24-7.60 (m, 10H, C_6-*H* & Ph-*H*), 8.68 (s, 1H, N*H*). Anal. Calcd. for $C_{37}H_{46}N_2O_7Si$: C, 67.45; H, 7.04; N, 4.25. Found: C, 67.67; H, 7.22; N, 4.29.

1-O-Benzyl-2-[(*tert*-butyloxycarbonyl)amino]-3-O-(4, 4'-dimethoxytrityl)-L-propan-1,3-diol (17): The titled compound **17** was prepared from **8**.[25] Hexanes → EtOAc was used for flash chromatography. Yield: 79%, oil. ^{1}H NMR ($CDCl_3$): δ 1.44 (d, 9H, *t*-Boc), 3.16 & 3.32 (2m, 1H), 3.60-3.84 (m, 12H, 3C*H*$_2$, 2xOC*H*$_3$), 4.00-4.18 (m, 1H), 4.52 (d, 2H, PhC*H*$_2$), 4.84 & 5.20 (2m, 1H), 6.80-6.84 (m, 4H, Ph-*H*), 7.18-7.42 (m, 14H, Ph-*H*). Anal. Calcd. for $C_{36}H_{41}NO_6$: C, 74.07; H, 7.08; N, 2.39. Found: C, 74.09; H, 7.21; N, 2.43.

4-[(Benzyloxycarbonyl)amino]-1-(*tert*-butyloxycarbonyl)-2-[(4, 4'-dimethoxytrityl)oxymethyl]pyrrolidine (18): The titled compound **18** was prepared from **19**.[26] Yield: 90%, foam. ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H, t-Boc), 2.02 (m, 1H), 2.26 (m, 1H), 3.20 (m, 2H), 3.38 (m, 1H), 3.62 (m, 1H), 3.78 (s, 6H, 2xOC*H*$_3$), 4.02 (m, 1H), 4.40 (m, 1H), 4.80 (m, 1H), 5.12 (s, 2H, C*H*$_2$Ph), 6.80 (d, 4H, Ph-

H), 7.20-7.42 (m, 14H, Ph-*H*). Anal. Calcd. for $C_{39}H_{44}N_2O_7$: C, 71.76; H, 6.79; N, 4.29. Found: C, 71.79; H, 7.01; N, 4.33.

3-O-(4, 4'-Dimethoxytrityl)-1, 2 : 5, 6-di-O-isopropylidene-α-D-allofuranose (20): The titled compound **20** was prepared from **12**. Hexanes → EtOAc was used for flash chromatography. Yield: 84%, foam. ^{1}H NMR ($CDCl_3$): δ 1.20, 1.29, 1.41 & 1.61 (4s, 12H, isopropylidene-CH_3), 3.28 (t, 1H), 3.42-3.60 (m, 3H), 3.80 (m, 7H, C*H* & 2xOCH_3), 4.30 (dd, 1H), 5.44 (d, 1H), 6.82 (d, 4H, Ph-*H*), 7.20-7.60 (m, 9H, Ph-*H*).Anal. Calcd. for $C_{33}H_{38}O_8$: C, 70.44; H, 6.81. Found: C, 70.59; H, 6.89.

6-O-(4, 4'-Dimethoxytrityl)-5-hydroxy-3-(*tert*-butyldimethylsilyl)-1, 2-O-isopropylidene-α-D-allofuranose (21): The titled compound **21** was prepared from **14**. Hexanes → EtOAc was used for the flash chromatography. Yield: 93%, foam. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 3H), 0.16 (s, 3H), 0..92 (s, 9H, *tert*-butyl), 1.40 & 1.60 (2s, 6H, isopropylidene-CH_3), 2.66 (bs, 1H), 3.08-3.46 (m, 2H), 3.84 (s, 6H, 2xOCH_3), 3.98 (m, 1H), 4.22 (m, 2H), 4.48 & 4.54 (2t, 1H), 5.78 & 5.82 (2d, 1H), 6.92 (d, 4H, Ph-*H*), 7.20-7.60 (m, 9H, Ph-*H*). Anal. Calcd. for $C_{36}H_{48}O_8Si$: C, 67.89; H, 7.59. Found: C, 67.93; H, 7.61.

General Procedure for Deprotection reactions: To a stirred solution of the THP/DMT protected ether (0.25 mmol) in methanol (10 ml) was added iodine (45 mg, 0.25 mmol). The reaction mixture was stirred at room temperature until TLC indicates that no starting material remained. The reaction was quenched with sodium thiosulfate solution (1N) and evaporated to dryness. The residue was extracted with EtOAc (50 ml). The organic extract was dried and evaporated. The crude material was crystallized in a suitable solvent or purified by flash chromatography. The products that obtained were identified in comparison with authentic samples known in the literature as well as by TLC, ^{1}HNMR and analysis.

3'-O-(tert-Butyldimethylsilyl)thymidine (2): Chloroform → EtOAc was used for flash chromatography. Mp 116-119°C (ether-hexanes); lit[24] mp 83-85°C . ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 6H, 2CH_3), 0.88 (s, 9H, *tert*-butyl), 1.91 (s, 3H, CH_3),

2.22 (m, 1H, *H*-2'), 2.38 (m, 1H, *H*-2'), 2.62 (m, 1H), 3.76 (m, 1H), 3.92 (m, 2H), 4.26 (m, 1H, *H*-3'), 6.13 (t, 1H, *H*-1'), 7.36 (s, 1H, C_6-*H*), 8.76 (bs, 1H, N*H*). Anal. Calcd. for $C_{16}H_{28}N_2O_5Si$: C, 53.91; H, 7.92; N, 7.86. Found: C, 53.96; H, 7.99; N, 7.91.

5'-O-(*tert*-Butyldimethylsilyl)thymidine (4): Chloroform → acetone was used for flash chromatography. Mp 192-195°C (CH_2Cl_2/hexanes); lit[24] mp 198-99°C . ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 6H, 2C*H*$_3$), 0.92 (s, 9H, *tert*-butyl), 1.91 (s, 3H, C*H*$_3$), 2.10 (m, 1H, *H*-2'), 2.34 (m, 1H, *H*-2'), 2.76 (m, 1H, O*H*), 3.86 (m, 2H, *H*-5'), 4.05 (m, 1H, *H*-4'), 4.45 (m, 1H, *H*-3'), 6.38 (q, 1H, *H*-1'), 7.52 (s, 1H, C_6-*H*), 9.07 (bs, 1H, N*H*). Anal. Calcd. for $C_{16}H_{28}N_2O_5Si$: C, 53.91; H 7.92; N, 7.86. Found: C, 54.12; H, 8.01; N, 7.79.

5'-O-(*tert*-Butyldimethylsilyl)-(N_3-benzoyl)thymidine (6): Chloroform → EtOAc was used for flash chromatography. Foam. ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 6H, 2C*H*$_3$), 0.94 (s, 9H, *tert*-butyl), 1.94 (s, 3H, C*H*$_3$), 2.04 (m, 1H, *H*-2'), 2.26 (m, 1H, *H*-2'), 2.84 (bs, 1H, O*H*), 3.78 (d, 1H, *H*-5'), 3.88 (d, 1H, *H*-5'), 3.96(s, 1H, *H*-4'), 4.28 (bs, 1H, *H*-3'), 6.30 (t, 1H, *H*-1'), 7.48 (t, 2H, Ph-*H*), 7.64 (m, 2H, Ph-*H*), 7.90 (d, 2H, Ph-*H*). Anal. Calcd. for $C_{23}H_{32}N_2O_6Si$: C, 59.97; H, 7.00; N, 6.08. Found: C, 60.01; H, 7.05; N, 6.28.

1-O-Benzyl-2-[(*tert*-butyloxycarbonyl)amino]-L-propan-1,3-diol (8): Hexanes → EtOAc was used for flash chromatography. Oil. ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H, *t*-Boc), 3.35 (m, 2H, C*H*$_2$), 3.44 (m, 2H, C*H*$_2$), 3.64 (m, 1H), 4.46 (s, 2H, C*H*$_2$Ph), 4.65 (t, 1H), 6.56 (d, 1H, N*H*), 7.38 (m, 5H, Ph-*H*). Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.23; H, 8.20; N, 5.11.

1-O-(*tert*-Butyldimethylsilyl)-2-[(*tert*-butyloxycarbonyl)amino]-L-propan-1,3-diol (10): Hexanes → EtOAc was used for flash chromatography. Oil. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H, 2C*H*$_3$), 0.88 (s, 9H, *tert*-butyl), 1.44 (s, 9H, *t*-Boc), 3.32-3.90 (m, 5H, 2C*H*$_2$ & C*H*), 4.54(m, 1H), 5.20 (d, 1H, N*H*). Anal. Calcd. for $C_{14}H_{31}NO_4Si$: C, 55.04; H, 10.23; N, 4.59. Found: C, 55.24; H, 10.49; N, 4.71.

1,2:5,6-Di-O-isopropylidene-α-D-allofuranose (12): Hexanes → EtOAc was used for flash chromatography. Mp 72-75°C. ^{1}H NMR ($CDCl_3$): δ 1.38 & 1.40 (2s, 6H, isopropylidene-C*H*$_3$), 1.44 & 1.56 (2s, 6H, isopropylidene-C*H*$_3$), 2.54(d,

1H, O*H*), 3.82 (m, 1H), 4.00-4.10 (m, 3H), 4.32 (q, 1H), 4.62 (t, 1H), 5.82 (d, 1H).

1,2-O-Isopropylidene-3-O-(*tert*-butyldimethylsilyl)-α-D-allofuranose (14): Chloroform → EtOAc was used for flash chromatography. Foam. ^{1}H NMR ($CDCl_3$): δ 0.12 (d, 6H, 2CH_3), 0.88 (s, 9H, *tert*-butyl), 1.28 & 1.52 (2s, 6H, isopropylidene-CH_3), 2.74 (bs, 2H), 3.60-3.70 (m, 2H), 3.94 (m, 1H), 4.00 (m, 1H), 4.08 (m, 1H), 4.42 (t, 1H), 5.72 (d, 1H). Anal. Calcd. for $C_{15}H_{30}O_6Si$: C, 53.86; H, 9.04. Found: C, 53.91; H, 9.23.

4-[(Benzyloxycarbonyl)amino]-1-(*tert*-butyloxycarbonyl)-2-hydroxymethyl-pyrrolidine (19): Chloroform → EtOAc was used for flash chromatography. Foam. ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H, t-Boc), 1.80-2.2 (m, 3H), 3.34 (d, 1H), 3.52-3.62 (m, 4H), 4.04 (bs, 1H), 4.20 (bs, 1H), 4.60 (bs, 1H), 5.08 (s, 2H), 5.10-5.22 (m, 2H), 7.32 (m, 5H, Ph). Anal. Calcd. for $C_{18}H_{26}N_2O_5$: C, 61.69; H, 7.48; N, 7.99. Found: C, 61.71; H, 7.21; N, 8.13.

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