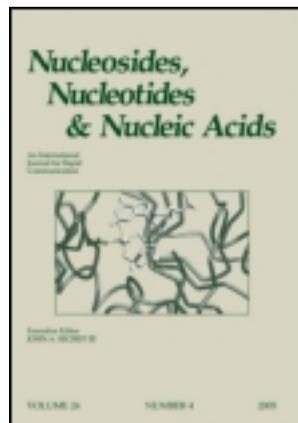


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### Chemoselective Deprotection of Triethylsilyl Ethers

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## CHEMOSELECTIVE DEPROTECTION OF TRIETHYLSILYL ETHERS

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□ *An efficient and selective method was developed for the deprotection of triethylsilyl (TES) ethers using formic acid in methanol (5–10%) or in methylene chloride 2–5% with excellent yields. TES ethers are selectively deprotected to the corresponding alcohols in high yields using formic acid in methanol under mild reaction conditions. Other hydroxyl protecting groups like *t*-butyldimethylsilyl (TBDMS) remain unaffected.*

**Keywords** Chemoselective; dinucleosides; spore photoproduct; S-adenosylmethionine; spore photoproduct lyase

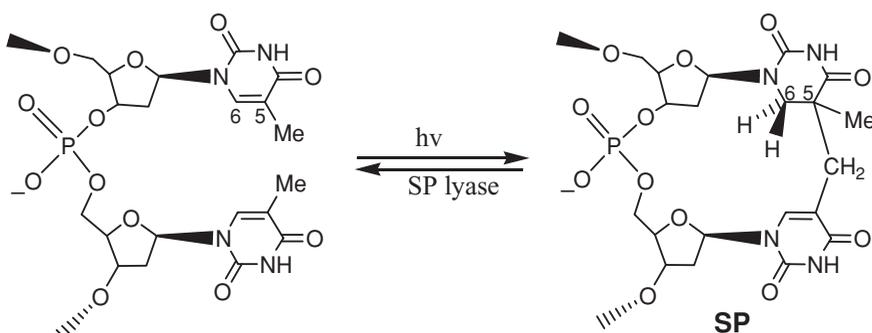
### INTRODUCTION

Selective and efficient protection and deprotection plays a central role in the completion of multistep syntheses of organic molecules. For example, trityl,<sup>[1]</sup> triethylsilyl,<sup>[2]</sup> and *tert*-butyldimethylsilyl<sup>[3]</sup> ethers are normally used for selective protection of primary/secondary alcohols, particularly in carbohydrate and nucleoside/nucleotide chemistry. However, despite the ubiquity of these protecting groups in organic synthesis, only a few methods exist for selectively deprotecting them.<sup>[4]</sup> The selective deprotection of triethylsilyl (TES) ethers in the presence of *tert*-butyldimethylsilyl (TBDMS) can be carried out using 10% Pd/C in methanol or 95% ethanol,<sup>[5]</sup> mesoporous silica MCM-41/MeOH,<sup>[6]</sup> IBX in dimethyl sulfoxide (DMSO),<sup>[7]</sup> and 1-chloroethyl chloroformate in methanol.<sup>[8]</sup> These methods work well in many cases, however all require expensive reagents or catalysts. Our interest in synthesizing 5,6-dihydro-5-( $\alpha$ -thymynyl)-thymine has led us to develop a

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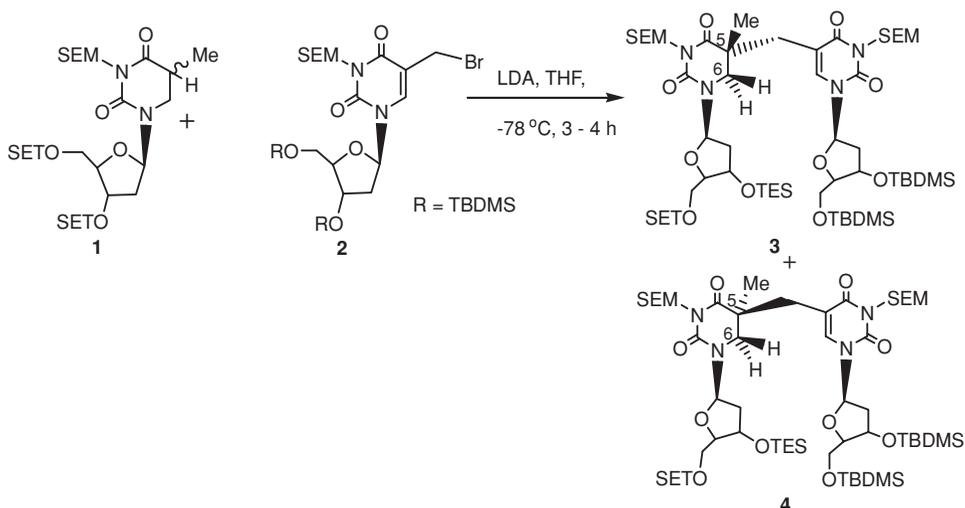
**SCHEME 1** Formation and Repair of SP.

new method for the chemoselective deprotection of triethylsilyl ethers that is both efficient and economical.

5,6-Dihydro-5-( $\alpha$ -thyminyI)-thymine, or spore photoproduct (SP), is a methylene-bridged thymine dimer formed in spore DNA on ultraviolet (UV) irradiation (Scheme 1).<sup>[9,10]</sup> SP is the primary DNA photoproduct of UV irradiation of bacterial spores, and the extreme UV resistance of bacterial spores is due in part to the efficient repair of SP on spore germination. The repair of SP is catalyzed by the enzyme spore photoproduct lyase (SPL), which utilizes an iron-sulfur cluster and *S*-adenosylmethionine (AdoMet) to generate a putative 5'-deoxyadenosyl radical intermediate, which abstracts a hydrogen atom from C-6 of SP to initiate a radical-mediated  $\beta$ -scission.<sup>[11–14]</sup> Developing an understanding of the DNA repair mechanism of SPL has been hindered due to the unavailability of the pure spore photoproduct; in fact, most enzymatic studies in the literature involve the use of UV-irradiated DNA—an inherently impure substance containing numerous different types of damage—as a substrate. Currently, only limited synthetic routes are available in the literature for the generation of pure spore photoproduct with a phosphodiester linkage.<sup>[15]</sup> Our ongoing efforts to understand the SPL mechanism have led us to develop efficient methods for the synthesis of SP.

## RESULTS AND DISCUSSION

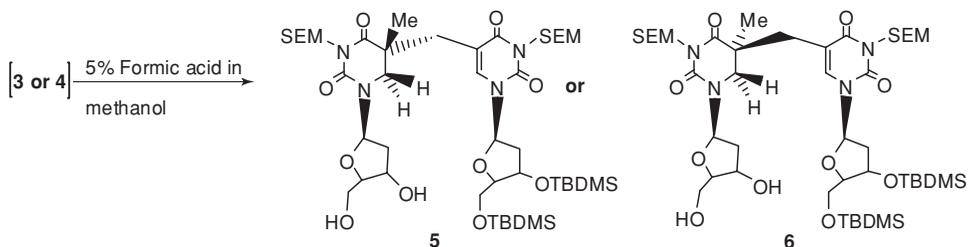
We report here an efficient and cost effective method for making the 5*R* and 5*S*-diastereomers of SP in high yields (Scheme 2) and their subsequent deprotection under mild reaction conditions (Scheme 3). The protected 5*R* and 5*S*-diastereomers (**3** and **4**) were prepared by coupling *N*<sup>2</sup>-trimethylsilylethoxymethyl-3, 5-di-triethylsilyl-5,6-dihydrothymidine **1** and 2-bromomethyl uridine **2** using lithium diisopropyl amide (LDA) as a condensing reagent<sup>[15]</sup> at  $-78^{\circ}\text{C}$ , which afforded 5*R* and 5*S*-diastereomers in a 3:4 ratio (Scheme 2). The 5*R* and 5*S*-diastereomers were easily purified on



**SCHEME 2** Formation of 5*R* and 5*S*-diastereomers.

a silica gel column using a gradient of ethyl acetate and hexanes. The structures of these two closely related compounds were assigned on the basis of  $^1\text{H}$  and  $^{13}\text{C}$  NMR (Table 1) as well as mass spectrometry, and the stereochemical assignments were made on the basis of two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY) and rotational nuclear Overhauser effect spectroscopy (ROESY) data.<sup>[16]</sup> The C-5 methyl carbon of the 5*R* isomer (**3**) was observed at 22.03 ppm, whereas the methyl carbon of the 5*S*-isomer (**4**) was shifted 1.3 ppm to higher field at 20.73 ppm. However, only 0.04 ppm difference was observed in  $^1\text{H}$  NMR of the 5*R* and 5*S*-isomers for the C-5 methyl group (Table 1). Differences in  $^1\text{H}$  (at C-6 and the methylene bridge) and  $^{13}\text{C}$  (at C-5, C-6, and the methylene bridge) chemical shifts for the 5*R* and 5*S* isomers were also observed (Table 1).

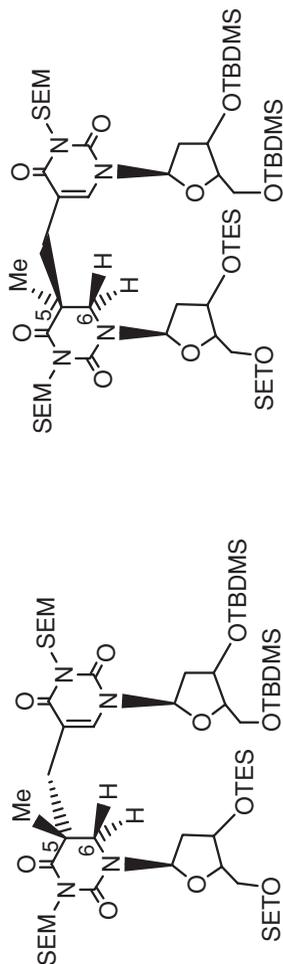
The synthesis of SP from **3** and **4** involves the formation of a phosphodiester linkage between the sugar groups; this requires the selective deprotection of the 3' and 5'-hydroxyls of **3** and **4**. In this case, TES ethers



**SCHEME 3** Selective deprotection of triethylsilyl ether using formic acid:methanol/methylene chloride.

TABLE 1  $^1\text{H}$  and  $^{13}\text{C}$  NMR of **3** and **4**

Compound	Me	$\text{CH}_2$ (base) C-6	$\text{CH}_2$ (bridge)	C-5
<b>3</b> , $^1\text{H}$	1.18	3.03/3.15	2.60/2.68	—
<b>3</b> , $^{13}\text{C}$	22.03	44.25	32.34	42.91
<b>4</b> , $^1\text{H}$	1.14	3.0/3.27	2.49/2.75	—
<b>4</b> , $^{13}\text{C}$	20.73	44.90	32.29	42.24



must be deprotected selectively in the presence of TBDMS ethers. We have developed an efficient method for the deprotection of TES ethers in the presence of TBDMS ethers using 5–10% formic acid. Formic acid has been extensively used in carbohydrate chemistry/nucleoside chemistry as a deprotecting agent for trityl<sup>[17a]</sup> and isopropylidene<sup>[17b–d]</sup> groups, but so far no selective deprotection has been reported for TES versus TBDMS groups using formic acid. The 5*R* and 5*S*-protected thymidine dinucleosides **3** and **4** were prepared and separated in high yields as described above. Reaction of the protected dinucleosides of thymidine (**3** and **4**) separately with 5–10% formic acid:methanol at ambient temperature (Scheme 3), afforded 3',5'-TES deprotected dinucleosides **5** and **6** in 70–85% yields. The 3' and 5' TBDMS groups of the dinucleosides remain unaffected under these reaction conditions (Table 2). The crude reaction mixture after workup showed only the desired product without any undesired side products. Reaction progress was conveniently monitored via thin-layer chromatography (TLC) and <sup>1</sup>H NMR, and the deprotection was generally complete within 2–3 hours.

The deprotection of TES ethers generally proceeded more quickly in protic solvents than in nonprotic solvents. The deprotection reactions in methylene chloride were sluggish, with complete deprotection of TES ethers taking 20–24 hours (Table 2), consequently resulting in lower yields of the desired dinucleosides (50–60%). Under higher concentration of the formic acid in methanol (up to 20%), no deglycosylation or decomposition of the desired product was observed.

Triethylsilyl ethers can be easily deprotected in the presence of *tert*-butyldimethylsilyl ethers using 2% HF in acetonitrile or pyridine.<sup>[18]</sup> Deprotection of TES ethers of the thymidine dinucleosides **3** and **4** with 2–4% HF-pyridine resulted in only ~20–50% of the desired dinucleosides **5** and **6**, along with primary (**7**, **9**) and secondary (**8**, **10**) TBDMS deprotected side products (Scheme 4). The structures of **5**, **6**, and the side products were easily deduced using one- and two-dimensional NMR methods. Higher concentrations of HF:pyridine and longer reaction times produce completely TBDMS/TES-desilylated products. Ultimately, the HF-pyridine method resulted in low yields of the desired thymidine dinucleoside for further synthesis of spore photoproduct.

The formic acid:methanol combination also works well for the selective deprotection of mononucleosides. 3'-*O*-*tert*-Butyldimethylsilyl-5'-*O*-triethylsilylthymidine **13** and 3'-*O*-*tert*-butyldimethylsilyl-5'-*O*-triethylsilyl-adenosine **17** were selectively deprotected in 70–76% yields using 5% formic acid:methanol (Scheme 5). Compound **13** was prepared from thymidine **11** in two steps. In first step, thymidine was selectively protected using 0.9 equivalents of triethylsilyl chloride in 95% yields followed by protection at the 3' hydroxyl with *tert*-butyldimethylsilyl chloride. Compound **17** was

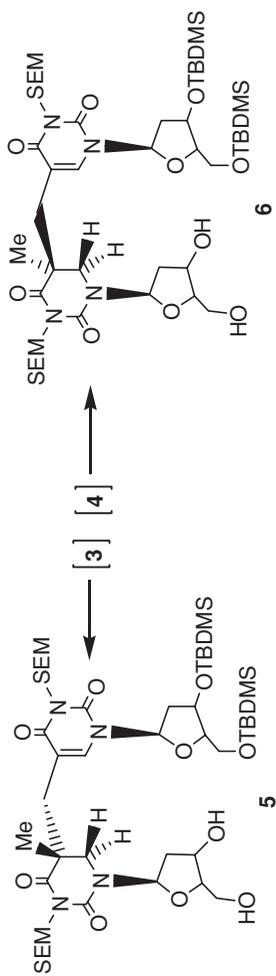
TABLE 2 Deprotection of compounds 3 and 4 using formic acid

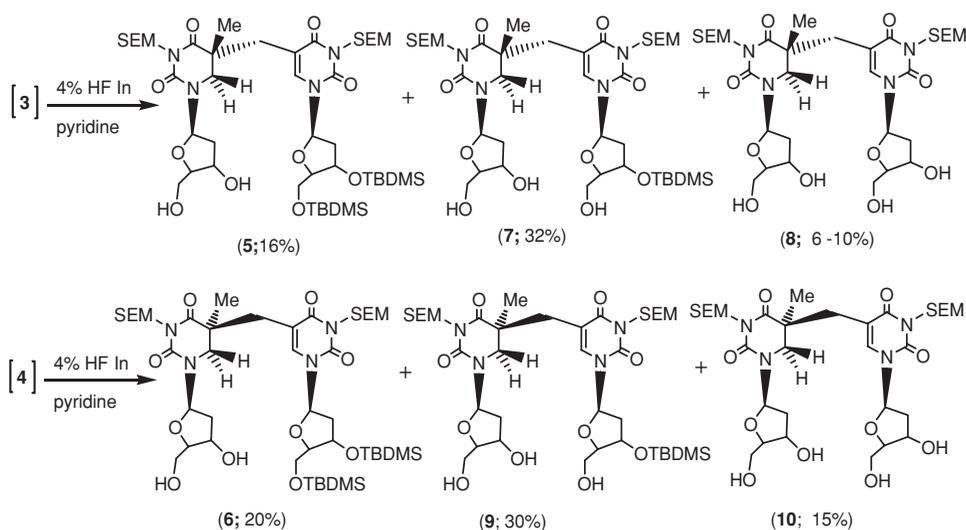
Compound	Time (hours)	Conditions	Compound		Total yields (%)
			5	6	
3	2	a	75	—	75
3	1	b	70	—	70
4	2	a	—	80	80
4	1	b	—	85	85
3	20–24	c	50–60	—	50–60
4	20–24	c	—	50–55	50–55

<sup>a</sup>5% Formic acid:methanol (commercial ACS grade).

<sup>b</sup>10% formic acid:methanol.

<sup>c</sup>5% formic acid:CH<sub>2</sub>Cl<sub>2</sub>.

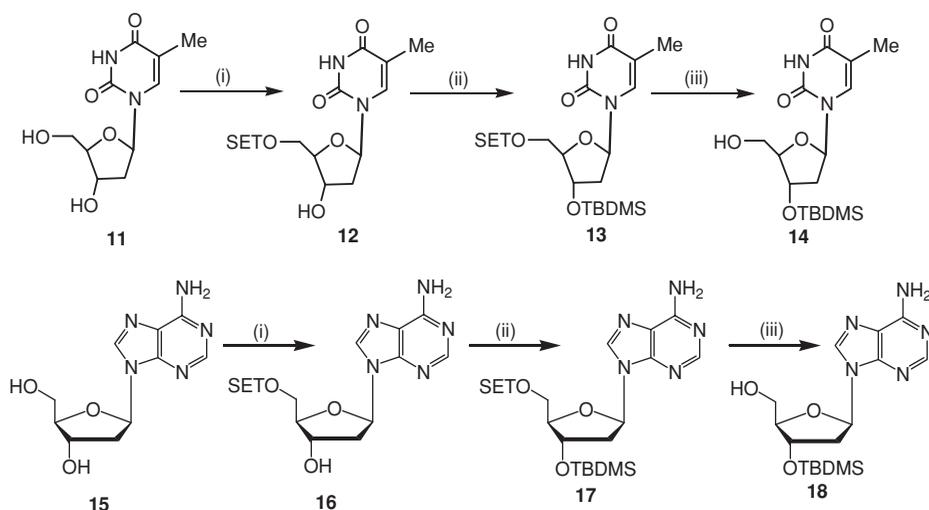




**SCHEME 4** Deprotection 5*R* & 5*S*-diastereomers (**3** and **4**) using 4% HF: pyridine.

also prepared similarly as described for **13**. Deprotection using formic acid in methanol afforded compounds **14** and **18** in excellent yields (Scheme 5).

As control reactions, the 3' and 5' TBDMS-protected thymidine **19**, the fully protected thymidine **20** (*N*<sup>3</sup>-Trimethylsilylethoxymethyl-3', 5'-di-*t*-butyldimethylsilyl thymidine), and the 3' and 5' TES-protected



**Reagents and Conditions:**

(i) TESCl, DMF, Imidazole, 95% (ii) TBDMSCl, DMF, Imidazole, rt., 93% (iii) MeOH:Formic acid, rt, 72-76%.

**SCHEME 5** Selective deprotection of protected thymidine and adenosine.

dihydrothymidine **21** were stirred in 5–10% formic acid in methanol for 3–5 hours. NMR spectra of the reaction mixtures for **19** and **20** reveals that the TBDMS groups remain intact (Scheme 6). Even at higher concentrations of formic acid:methanol and over longer reaction periods, no deprotection of TBDMS was observed. In contrast, the TES-protected dihydrothymidine 3', 5'-*O*-di-triethylsilyl-5, 6-dihydrothymidine (**21**), is deprotected in high yields under the same reaction conditions (Scheme 6).

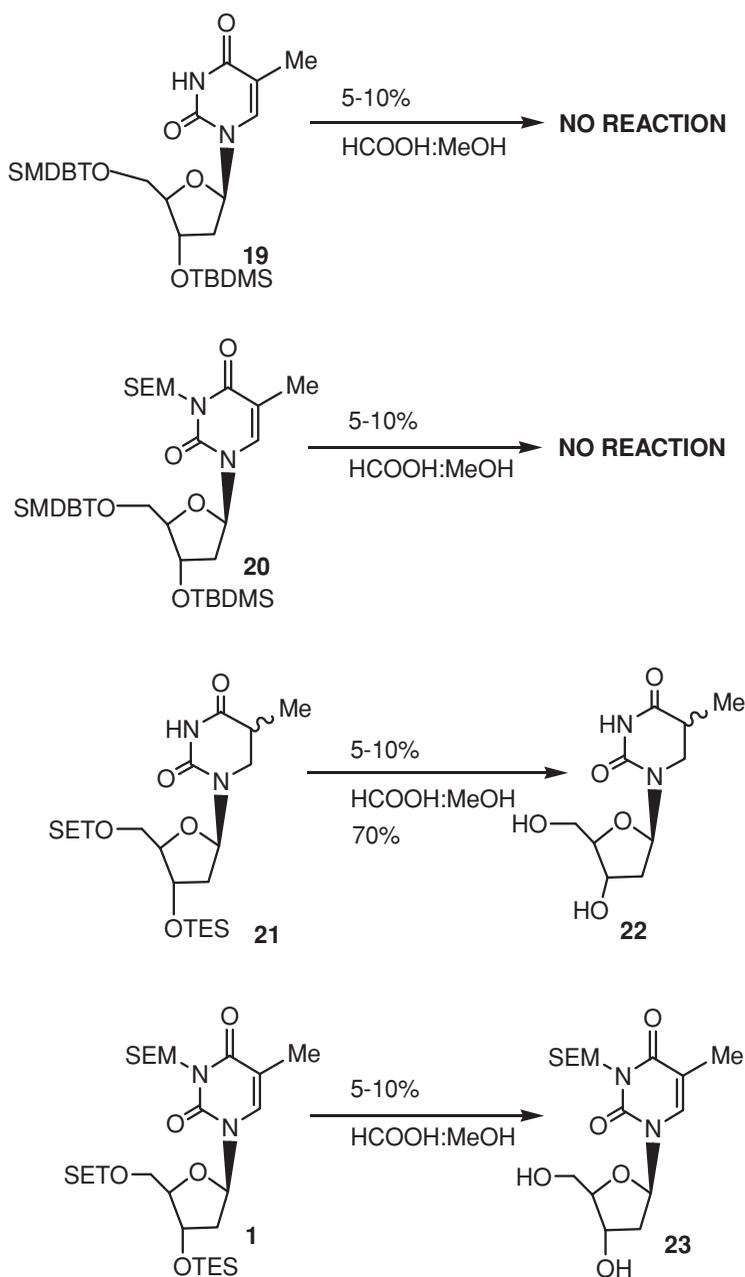
## EXPERIMENTAL

All reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Dichloromethane and pyridine were distilled from calcium hydride. Tetrahydrofuran (THF) was distilled on sodium/benzophenone prior to use. Purification of reaction products was carried out by flash chromatography using silica gel (230–400 mesh). All reagents were commercially available and used without further purification. All reactions were monitored by TLC using silica gel 60, F-254. Column chromatography was conducted using flash silica gel.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker DPX-300, Bruker DRX-500, or on Bruker DRX-600 (Bruker, Billerica, MA, USA). NMR spectra were recorded on solutions in deuterated chloroform ( $\text{CDCl}_3$ ), with residual chloroform ( $\delta$  7.27 ppm for  $^1\text{H}$  NMR and  $\delta$  77.0 ppm for  $^{13}\text{C}$  NMR) or deuterated dimethyl sulfoxide ( $\text{DMSO-}d_6$ ), with residual methyl sulfoxide ( $\delta$  2.50 ppm for  $^1\text{H}$  NMR and  $\delta$  35.0 ppm for  $^{13}\text{C}$  NMR) taken as the standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The multiplicities of the  $^{13}\text{C}$  NMR signals were determined by heteronuclear multiple quantum coherence (HMQC) and distortionless enhancement by polarization transfer (DEPT) techniques. Mass spectra (high resolution fast atom bombardment [FAB] or electrospray transmission [ESI]) were recorded on a Q-Tof and 70-VSEs spectrometer at Noyes Laboratory, University of Illinois Urbana-Champaign.

### General Procedures

#### *Formic acid: Methanol Procedure for the Deprotection of TES Ethers*

A solution of protected thymidine dinucleoside **3** or **4** (0.700 g, 0.58 mmol) in methanol (10 mL) was stirred at 5–10°C for 5 minutes followed by dropwise addition of a solution of 10% formic acid in methanol (10 mL). After complete addition of the formic acid solution, the cooling bath was removed and the reaction mixture was vigorously stirred for 1–2 hours at room temperature; TLC (ethyl acetate:hexanes 1:1) was used to monitor the progress of the reaction. Upon complete desilylation of



**SCHEME 6** Deprotection of protected thymidine/5,6-dihydrothymidine.

TES groups to produce the dihydroxy dinucleoside, the reaction mixture was neutralized with 10% sodium bicarbonate solution (~20 mL) and the solvent was removed on a rotary evaporator under reduced pressure. The residue was dissolved in methylene chloride and washed with saturated

sodium bicarbonate solution. The methylene chloride layer was dried over anhydrous sodium sulfate, concentrated, and the residue was purified on a silica gel column (flash chromatography) using a mixture of ethyl acetate:hexanes (50:50), resulting in the desired product as a white fluffy solid with 75–85% yield.

#### **HF: Pyridine Procedure for the Deprotection of TES Ethers**

A cold solution of 4% HF:pyridine (10 mL) was slowly added to a mixture of 5*R* or 5*S*- dinucleoside **3** or **4** (0.50 g, 0.41 mmol) in pyridine (5 mL) at 0–5°C while stirring. The reaction mixture was stirred at ambient temperature for 1–2 hours. The reaction progress was monitored using TLC. After completion of the reaction, the solution was cooled and the reaction mixture was neutralized with saturated sodium bicarbonate solution. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in a mixture of methylene chloride and water (1:1, 100 mL). The organic layer was thoroughly washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate; finally, the solvent was removed under reduced pressure. The respective residues were loaded onto a silica gel column and the column was eluted with a 10–50% ethyl acetate:hexanes gradient to afford the desired dinucleosides.

**Compound 3.** Yield: 30%; viscous oil;  $R_f$ : 0.6;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  –0.05 (s, 9H,  $\text{CH}_3$ ), –0.03 (s, 9H,  $3\text{CH}_3$ ), 0.06 (s, 3H,  $\text{CH}_3$ ), 0.07 (s, 3H,  $\text{CH}_3$ ), 0.08 (s, 3H,  $\text{CH}_3$ ), 0.086 (s, 3H,  $\text{CH}_3$ ), 0.5–0.64 (m, 12H,  $\text{CH}_2$ ), 0.87 (s, 9H,  $\text{CH}_3$ ), 0.89 (s, 9H,  $\text{CH}_3$ ), 0.89–0.91 (m, 22 H,  $6\text{CH}_3$  TES &  $\text{CH}_2$  SEM), 1.18 (s, 3H, Me), 1.88–1.96 (m, 3H,  $\text{CH}_2$ , 2'), 2.18–2.2 (m, 1H, CH, 2'), 2.60 (d,  $J = 14$  Hz, 1H,  $\text{CH}_2$ , bridge), 2.6 (d,  $J = 14$  Hz, 1H,  $\text{CH}_2$ , bridge), 3.03 (d,  $J = 13.5$  Hz, 1H,  $\text{CH}_2$ , base), 3.15 (d,  $J = 13.5$  Hz, 1H,  $\text{CH}_2$ , base), 3.52 (t, 2H,  $\text{CH}_2$ , SEM), 3.56 (dd, 2H,  $\text{CH}_2$ , 5'), 3.61 (dd,  $J = 8$  Hz, 2H,  $\text{CH}_2$ , SEM), 3.7 (dd,  $J = 5.5$  Hz, 2H,  $\text{CH}_2$ , 5'), 3.7–3.79 (m, 1H, CH, 4'), 3.8 (m, 1H, 4'), 4.2–4.2 (m, 1H, 3'), 4.4 (m, 1H, 3'), 5.1 (s, 2H,  $\text{NCH}_2$ , SEM), 5.3 (s, 2H,  $\text{NCH}_2$ , SEM), 6.2–6.3 (m, 2H, 1'), 7.4 (s, 1H, base);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  –5.4 ( $\text{CH}_3$ ), –5.3 ( $\text{CH}_3$ ), –4.8 ( $\text{CH}_3$ ), –4.6 ( $\text{CH}_3$ ), –1.4 ( $\text{CH}_3$ ), –1.4 ( $\text{CH}_3$ ), 4.2 ( $\text{CH}_2$ ), 4.6 ( $\text{CH}_2$ ), 6.7 ( $\text{CH}_3$ ), 6.77 ( $\text{CH}_3$ ), 17.9 (Cquat), 18.1 ( $\text{CH}_2$ ), 18.3 (Cquat), 22.0 ( $\text{CH}_3$  C5), 25.7 (Me, TBDMS), 25.9 (Me, TBDMS), 32.3 ( $\text{CH}_2$  bridge), 36.8 ( $\text{CH}_2$ ), 40.2 ( $\text{CH}_2$ ), 42.9, 44.2 ( $\text{CH}_2$ -base), 62.8 ( $\text{CH}_2$ ), 63.0 ( $\text{CH}_2$ ), 66.6 ( $\text{CH}_2$ ), 67.4 ( $\text{CH}_2$ ), 69.9 ( $\text{CH}_2$ , SEM), 70.3 ( $\text{CH}_2$ , SEM), 71.9 (C 3'), 72.0 (C 3'), 84.3 (C 4'), 85.3 (C, 1'), 86.2 (C 1'), 87.4 (C 4'), 108.5 (Cquat), 139.1 (CH), 150.6 (Cquat), 152.2 (Cquat), 163.4 (Cquat), 173.6 (Cquat); HRMS:  $m/z$ : 1201.7001 (calcd. for  $\text{C}_{56}\text{H}_{113}\text{N}_4\text{O}_{12}\text{Si}_6$ ; 1201.6971) (M + H); MS: (TOF, MS, ESI)  $m/z$  1223, 1203, 1202, 1201, 1200, 1173, 1087, 859, 858, 857, 829, 801, 629, 628, 599.

**Compound 4.** Yield: 40%; viscous oil;  $R_f$ : 0.5;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  –0.48 (s, 9H,  $\text{CH}_3$ ), –0.03 (s, 9H,  $3\text{CH}_3$ ), 0.056 (s, 3H,  $\text{CH}_3$ ), 0.06 (s, 3H,  $\text{CH}_3$ ),

0.07 (s, 6H, 2CH<sub>3</sub>), 0.5–0.6 (m, 12H, CH<sub>2</sub>), 0.8 (s, 9H, CH<sub>3</sub>, TBDMS), 0.87 (s, 9H, CH<sub>3</sub> TBDMS), 0.9–0.9 (m, 4 H, 2 CH<sub>2</sub>), 0.9 (s, 9H, TES), 0.9 (s, 9H, TES), 1.1 (s, 3H, Me), 1.9–2.01 (m, 3H, CH<sub>2</sub>, 2'), 2.2 (dd, J = 7.5 Hz, 1H, CH, 2'), 2.4 (d, J = 14 Hz, 1H, CH<sub>2</sub>, bridge), 2.7 (d, J = 14 Hz, 1H, CH<sub>2</sub>, bridge), 3.0 (d, J = 13.5 Hz, 1H, CH<sub>2</sub>, base), 3.2 (d, J = 13.5 Hz, 1H, CH<sub>2</sub>, base), 3.5 (t, J = 8 Hz, 2H, CH<sub>2</sub>, SEM), 3.5 (dd, 2H, CH<sub>2</sub>, 5'), 3.6 (t, J = 8.5 Hz, 2H, CH<sub>2</sub>), 3.7 (dd, 2H, CH<sub>2</sub>, 5'), 3.8 (bt, 1H, 4'), 3.91 (bt 1H, 4'), 4.2 (bt, 1H, 3'), 4.3 (bt, 1H, 3'), 5.1 (d, J = 9.5 Hz, 1H, CH<sub>2</sub>, SEM), 5.1 (d, 1H, CH<sub>2</sub>, SEM), 5.3 (s, 2H, CH<sub>2</sub>, SEM), 6.2 (t, J = 6 Hz, 1H, 1'), 6.3 (t, 1H, 1'), 7.4 (s, 1H, base); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ -5.4 (CH<sub>3</sub>), -5.3 (CH<sub>3</sub>), -4.8 (CH<sub>3</sub>), -4.69 (CH<sub>3</sub>), -1.4 (CH<sub>3</sub>), 4.2 (CH<sub>2</sub>), 4.6 (CH<sub>2</sub>), 6.7 (CH<sub>3</sub>), 6.7 (CH<sub>3</sub>), 17.9 (Cquat), 18.0, 18.1, 18.3, 20.7 (CH<sub>3</sub>), 25.7 (Me), 25.8 (Me), 32.2 (CH<sub>2</sub>), 37.0 (CH<sub>2</sub>), 40.7 (CH<sub>2</sub>), 42.2 (Cquat), 44.9 (CH<sub>2</sub>-base), 63.2 (CH<sub>2</sub>), 63.3 (CH<sub>2</sub>), 66.6 (CH<sub>2</sub>), 67.3 (CH<sub>2</sub>), 69.9 (CH<sub>2</sub>), 70.0 (CH<sub>2</sub>), 70.2, 72.1, 72.6, 72.73, 84.95, 86.22, 86.72, 87.97, 108.44 (Cquat), 137.9 (CH), 150.5 (Cquat), 152.5 (Cquat), 163.3 (Cquat), 173.5 (Cquat); HRMS: *m/z*: 1201.7021 (calcd. for C<sub>56</sub>H<sub>113</sub>N<sub>4</sub>O<sub>12</sub>Si<sub>6</sub>; 1201.6971) (M + H); MS: (TOF, MS, ESI) *m/z* 1223, 1203, 1202, 1201, 1200, 1173, 1087, 859, 858, 857, 829, 801, 629, 628, 599.

**Compound 5.** Yield: 75%; R<sub>f</sub>: 0.4; white fluffy solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ -0.011 (s, 9H, CH<sub>3</sub>, SEM), -0.01 (s, 9H, 3CH<sub>3</sub>, SEM), 0.09 (s, 6H, CH<sub>3</sub>, TBDMS), 0.1 (s, 6H, CH<sub>3</sub>), 0.8 (s, 9H, CH<sub>3</sub>), 0.8 (s, 9H, CH<sub>3</sub>), 0.9–0.9 (m, 4H, 2CH<sub>2</sub>), 1.1 (s, 3H, Me), 1.9–2.0 (m, 1H, CH<sub>2</sub>, 2'), 2.0–2.1 (m, 1H, CH, 2'), 2.2–2.27 (m, 2H, CH, 2'), 2.33 (m, 1H, OH), 2.72–2.81 (m, 2H, CH<sub>2</sub>, bridge), 3.09 (bt, 1H, OH), 3.19 (d, J = 13 Hz, 1H, CH<sub>2</sub>, base), 3.51 (d, J = 13 Hz, 1H, CH<sub>2</sub>, base), 3.58 (t, J = 8.5 Hz, 4H, CH<sub>2</sub>, SEM), 3.68–3.78 (m, 4H, 5'), 3.8 (q, 1H, 4') 3.9 (q, 1H, 4'), 4.41 (m, 1H, 3'), 4.4 (m, 1H, 3'), 5.1 (d, J = 9.5 Hz, 1H, CH<sub>2</sub>, SEM), 5.2–5.2 (m, 2H, CH<sub>2</sub>, SEM), 5.4 (d, 1H, CH<sub>2</sub>, SEM), 6.2 (t, J = 7 Hz, 1H, 1'), 6.3 (t, J = 6 Hz, 1H, 1'), 7.5 (s, 1H, base); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ -5.4 (CH<sub>3</sub>), -5.3 (CH<sub>3</sub>), -4.8 (CH<sub>3</sub>), -4.7 (CH<sub>3</sub>), -1.5 (CH<sub>3</sub>), -1.4 (CH<sub>3</sub>), 17.87 (Cquat), 17.9 (CH<sub>2</sub>), 18.1 (CH<sub>2</sub>), 18.3 (Cquat), 20.8 (CH<sub>3</sub>), 25.65 (Me), 25.8 (Me), 31.8 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 40.6 (CH<sub>2</sub>), 42.1 (Cquat), 44.9 (CH<sub>2</sub>-base), 62.4 (CH<sub>2</sub>), 63.0 (CH<sub>2</sub>), 66.6 (CH<sub>2</sub>), 67.7 (CH<sub>2</sub>), 69.8 (CH<sub>2</sub>), 70.1 (CH<sub>2</sub>), 72.1 (CH), 72.2 (CH), 85.5 (CH), 85.6 (CH), 86.1 (CH), 87.8 (CH), 108.5 (Cquat), 139.0 (CH), 150.5 (Cquat), 152.2 (Cquat), 163.5 (Cquat), 174.2 (Cquat); HRMS: *m/z*: 973.5267 (calcd. for C<sub>44</sub>H<sub>85</sub>N<sub>4</sub>O<sub>12</sub>Si<sub>4</sub>; 973.5241) (M + H); MS: (TOF, MS, ESI) *m/z* 995 [M + Na], 973, 947, 946, 945, 917, 829, 801, 729; Anal. Calcd. for C<sub>44</sub>H<sub>84</sub>N<sub>4</sub>O<sub>12</sub>Si<sub>4</sub>: C, 54.29; H, 8.70; N, 5.76; Found: C, 54.19, H, 8.74, N, 5.67.

**Compound 6.** The 5S-di-TBDMS dinucleoside was prepared in a similar manner as described for compound (5). Purification was carried out using a mixture of ethyl acetate:hexanes (50:50%) as eluent. Yield: 80%; R<sub>f</sub>: 0.2; white fluffy solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ -0.01 (s, 9H, 3CH<sub>3</sub> SEM), -0.02 (s, 3CH<sub>3</sub>, 9H, 3CH<sub>3</sub>, SEM), 0.08 (s, 6H, CH<sub>3</sub>, TBDMS), 0.0 (s, 3H, CH<sub>3</sub>), 0.13 (s, 3H, CH<sub>3</sub>), 0.8 (s, 9H, CH<sub>3</sub>), 0.9 (s, 9H, CH<sub>3</sub>), 0.9–0.9 (m, 4H, 2CH<sub>2</sub>),

1.2 (s, 3H, Me), 1.8 (bs, 1H, OH), 1.9–2.0 (m, 1H, CH<sub>2</sub>, 2'), 2.08–2.1 (m, 1H, CH, 2'), 2.2–2.2 (m, 1H, CH, 2'), 2.2–2.3 (m, 1H, CH, 2'), 2.4 (bs, 1H, OH), 2.6 (d, J = 14.5 Hz, 1H, CH<sub>2</sub>, bridge), 2.8 (d, J = 14.5 Hz, 1H, CH<sub>2</sub>, bridge), 3.2 (q, 2H, CH<sub>2</sub>, base), 3.5 (t, J = 8 Hz, 4H, CH<sub>2</sub>, SEM), 3.6 (dd, 4H, CH<sub>2</sub>, 5'), 3.7 (m, 2H, 5'), 3.8 (bt, 2H, 4), 3.9 (bt, 1H, 4'), 4.3 (bt, 1H, 3'), 4.5 (bt, 1H, 3'), 5.1 (d, J = 10 Hz, 1H, CH<sub>2</sub>, SEM), 5.2 (d, 1H, CH<sub>2</sub>, SEM), 5.3–5.3 (m, 2H, CH<sub>2</sub>, SEM), 6.2 (t, J = 7 Hz, 1H, 1'), 6.3 (t, 1H, 1'), 7.6 (s, 1H, base); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ -5.5 (CH<sub>3</sub>), -5.3 (CH<sub>3</sub>), -4.8 (CH<sub>3</sub>), -4.7 (CH<sub>3</sub>), -1.47 (CH<sub>3</sub>), -1.43 (CH<sub>3</sub>), 17.93 (Cquat), 18.01 (CH<sub>3</sub>), 18.0 (CH<sub>3</sub>), 18.3 (Cquat), 21.7 (CH<sub>3</sub>), 25.7 (CH<sub>3</sub>), 25.9 (CH<sub>3</sub>), 32.0 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>), 41.1 (CH<sub>2</sub>), 42.4 (Cquat), 45.0 (CH<sub>2</sub>-base), 62.5 (CH<sub>2</sub>), 63.3 (CH<sub>2</sub>), 66.7 (CH<sub>2</sub>), 67.7 (CH<sub>2</sub>), 70.0 (CH<sub>2</sub>), 70.3 (CH<sub>2</sub>), 71.8 (CH), 72.8 (CH), 85.3 (CH), 86.1 (CH), 86.4 (CH), 88.2 (CH), 108.4 (Cquat), 138.9 (CH), 150.3 (Cquat), 152.9 (Cquat), 164.0 (Cquat), 173.5 (Cquat); HRMS: *m/z*: 973.5215 (calcd. for C<sub>44</sub> H<sub>85</sub> N<sub>4</sub> O<sub>12</sub> Si<sub>4</sub>; 973.5241) (M + H); MS: (TOF, MS, ESI) *m/z* 996, 973, 973, 947, 946, 945, 917, 829, 801, 729.

**Compound 7.** Mono TBDMS dinucleoside was isolated from the deprotection reaction of **3** using 4% HF:Pyridine. Yield: 32%; white solid; R<sub>f</sub>: 0.7; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ -0.0 (s, 9H, SiCH<sub>3</sub>), -0.0 (s, 9H, SiCH<sub>3</sub>), -0.06 (s, 9H, CH<sub>3</sub>, TBDMS), 0.8 (s, 6H, SiCH<sub>3</sub>, TBDMS), 0.8–0.9 (m, 4H, CH<sub>2</sub>), 1.1 (s, 3H, Me, C5), 2.0–2.0 (m, 1H, CH<sub>2</sub>, 2'), 2.1–2.2 (m, 2H, CH, 2'), 2.3–2.3 (m, 1H, CH, 2), 2.6 (d, J = 14.5 Hz, 1H, CH<sub>2</sub>, bridge), 2.7 (d, J = 14.5 Hz, 1H, CH<sub>2</sub>, bridge), 3.1 (d, J = 13 Hz, 1H, CH<sub>2</sub>, base), 3.4 (d, J = 13 Hz, 1H, CH<sub>2</sub>, base), 3.5 (t, J = 8 Hz, 2H, CH<sub>2</sub>, SEM), 3.6 (t, J = 9 Hz, 2H, CH<sub>2</sub>, SEM), 3.6–3.7 (m, 3H, CH<sub>2</sub>, 5'), 3.8 (bt, 1H, 4'), 3.9 (d, J = 11 Hz, 1H, 5'), 4.0 (bt, 1H, CH, 4'), 4.4 (bt, 1H, 3'), 4.4 (bt, 1H, 3'), 5.1–5.1 (m, 2H, CH<sub>2</sub>, SEM), 5.2 (d, J = 10 Hz, 1H, CH<sub>2</sub>, SEM), 5.3 (d, J = 9.5 Hz, 1H, CH<sub>2</sub>, SEM), 6.1–6.1 (m, 2H, 1), 7.8 (s, 1H, base); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ -4.9 (CH<sub>3</sub>), -4.7 (CH<sub>3</sub>), -1.5 (CH<sub>3</sub>), 17.9 (CH<sub>2</sub>), 18.05 (CH<sub>2</sub>), 21.45 (CH<sub>3</sub>), 25.6 (CH<sub>3</sub>), 31.7 (CH<sub>2</sub>), 37.1 (CH<sub>2</sub>), 41.8 (CH<sub>2</sub>), 42.4, 45.15 (CH<sub>2</sub>-base), 61.8 (CH<sub>2</sub>), 62.5 (CH<sub>2</sub>), 66.9 (CH<sub>2</sub>), 67.6 (CH<sub>2</sub>), 69.8 (CH<sub>2</sub>), 70.1 (CH<sub>2</sub>), 71.7 (CH), 72.37 (CH), 85.63 (CH), 86.02 (CH), 87.52 (CH), 88.5 (CH), 107.5 (Cquat), 139.98 (CH), 150.4 (Cquat), 152.1 (Cquat), 163.9 (Cquat), 174.5 (Cquat); HRMS: *m/z*: 859.4369 (calcd. for C<sub>38</sub> H<sub>71</sub> N<sub>4</sub> O<sub>12</sub> Si<sub>3</sub>; 859.4376) (M + H); MS: (TOF, MS, ESI) *m/z* 882, 881, 831, 803, 715, 687, 615, 597, 543.

**3'-O-tert-butylidimethylsilyl-thymidine 14:** Yield: 72%; white solid; R<sub>f</sub>: 0.2; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ -0.07 (s, 9H, TBDMS), -0.8 (s, 6H, SiCH<sub>3</sub>, TBDMS), 1.8 (s, 3H, Me, C5), 2.05–2.0 (m, 1H, CH<sub>2</sub>, 2'), 2.3–2.38 (m, 1H, CH, 2'), 3.3 (s, 1H, OH), 3.79 (d, J = 13 Hz, 1H, CH<sub>2</sub>, 5), 3.85 (d, J = 13 Hz, 1H, CH<sub>2</sub>, 5), 4.0 (s, 1H), 4.4 (s, 1H), 6.3 (t, 1H, 1), 7.52 (s, 1H, C6); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ -5.4 (CH<sub>3</sub>), -5.3 (CH<sub>3</sub>), 12.53 (CH<sub>3</sub>), 18.34 (CH<sub>2</sub>), 25.9 (CH<sub>3</sub>), 41.1 (CH<sub>2</sub>), 63.6 (CH<sub>2</sub>), 72.5 (CH), 85.0 (CH), 87.1 (CH), 110.9 (Cquat), 135.5 (CH), 150.6 (Cquat), 164.0 (Cquat); MS: (TOF, MS, ESI) *m/z* 357, 342.

**5'-O-triethylsilyl-adenosine 16:** A solution of adenosine **3** (0.300 g, 1.19 mmol) in DMF (3 mL) was stirred at room temperature for 5 minutes followed by dropwise addition of a solution of triethylsilyl chloride (0.163 g, 1.0 mmol) in DMF (3 mL). After complete addition the reaction mixture was stirred for 8 hours at room temperature. Upon complete triethylsilylation, the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride and washed with saturated sodium bicarbonate solution. The methylene chloride layer was dried over anhydrous sodium sulfate, concentrated, and finally the residue was purified on a silica gel column (flash chromatography) using a mixture of methanol: methylene chloride (10:90), resulting in the desired product as a white fluffy solid with 85% yield. White solid;  $R_f$ : 0.2;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.48 (q, 6H,  $3\text{CH}_2$ ), 0.83 (t,  $J = 7.5$  Hz, 9H,  $3\text{CH}_3$ ), 2.25–2.3 (m, 1H,  $\text{CH}_2$ , 2'), 2.6–2.7 (m, 1H,  $\text{CH}_2$ , 2'), 3.64 (dd,  $J = 4/7$  Hz, 1H, 5), 3.75 (dd,  $J = 4/7$  Hz, 1H,  $\text{CH}_2$ , 5'), 3.9 (d,  $J = 3.5$  Hz, 1H), 4.3 (bt, 1H), 5.3 (d, 1H), 6.3 (t, 1H, 1'), 8.0 (s, 1H), 8.2 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.8 ( $\text{CH}_2$ ), 6.6 ( $\text{CH}_2$ ), 39.0 ( $\text{CH}_2$ ), 62.8 ( $\text{CH}_2$ ), 70.4 (CH), 83.3 (CH), 87.2 (CH), 119.1 (Cquat), 139.5 (CH), 149.14 (Cquat), 152.5 (CH), 156.0 (Cquat).

**3'-O-tert-butyltrimethylsilyl-5'-O-triethylsilyl-adenosine 17:** Viscous oil;  $R_f$ : 0.5;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.05 (s, 6H, TBDMS), 0.59 (q, 6H,  $3\text{CH}_2$ ), 0.87 (s, 9H, TBDMS), 0.94 (t,  $J = 7.5$  Hz, 9H,  $3\text{CH}_3$ ), 2.38–2.4 (m, 1H,  $\text{CH}_2$ , 2'), 2.5–2.6 (m, 1H,  $\text{CH}_2$ , 2'), 3.7 (dd,  $J = 4/7$  Hz, 1H, 5'), 3.8 (dd,  $J = 4/7$  Hz, 1H,  $\text{CH}_2$ , 5'), 3.9 (bt, 1H), 4.5 (bt, 1H), 5.3 (d, 1H), 6.32 (bs, 2H,  $\text{NH}_2$ ), 6.4 (m, 1H, 1), 8.1 (s, 1H), 8.2 (s, 1H).

**3'-O-tert-butyltrimethylsilyl-adenosine 18:** White solid;  $R_f$ : 0.3;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.0 (s, 6H, TBDMS), 0.87 (s, 9H, TBDMS), 2.2–2.3 (m, 1H,  $\text{CH}_2$ , 2'), 2.6–2.6 (m, 1H,  $\text{CH}_2$ , 2'), 3.65 (dd,  $J = 4/7$  Hz, 1H, 5), 3.7 (dd,  $J = 4/7$  Hz, 1H,  $\text{CH}_2$ , 5'), 3.8 (m, 1H), 4.29 (bt, 1H), 5.4 (s, 1H, OH), 6.3 (m, 1H, 1), 6.32 (bs, 2H,  $\text{NH}_2$ ), 8.1 (s, 1H), 8.2 (s, 1H).

**$N^3$ -Trimethylsilylethoxymethyl-thymidine 23:** Yield: 76%; white solid;  $R_f$ : 0.2;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  -0.05 (s, 9H, SEM), -0.09 (t, 2H, SEM), 1.8 (s, 3H, Me, C5'), 2.3 (t, 2H,  $\text{CH}_2$ , 2'), 3.1 (bs, 1H, OH), 3.3 (bs, 1H, OH), 3.6 (t, 2H, SEM), 3.79 (d,  $J = 13$  Hz, 1H,  $\text{CH}_2$ , 5'), 3.85 (d,  $J = 13$  Hz, 1H,  $\text{CH}_2$ , 5'), 3.9 (bt, 1H), 4.51 (bt, 1H), 5.3 (s, 2H, SEM), 6.1 (t, 1H, 1'), 7.4 (s, 1H, C6);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  -1.4 ( $\text{CH}_3$ ), 13.2 ( $\text{CH}_3$ ), 18.1 ( $\text{CH}_2$ ), 40.1 ( $\text{CH}_2$ ), 62.1 ( $\text{CH}_2$ ), 67.7, 70.1, 71.1, 86.9, 110.3 (Cquat), 135.5 (CH), 151.0 (Cquat), 163.0 (Cquat); MS: (TOF, MS, ESI)  $m/z$  373, 372.

## CONCLUSION

In summary, we describe here a simple methodology for the deprotection of TES ethers to the corresponding alcohols with control of chemoselectivity. A published method for deprotection of TES ethers using

HF:pyridine resulted in low yields of the desired dinucleosides. However, we found that TES ethers are selectively deprotected to the corresponding alcohols in high yields using formic acid in methanol under mild reaction conditions. In addition, the protected 5*R* and 5*S*-dinucleosides were easily prepared and purified on a silica gel column.

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