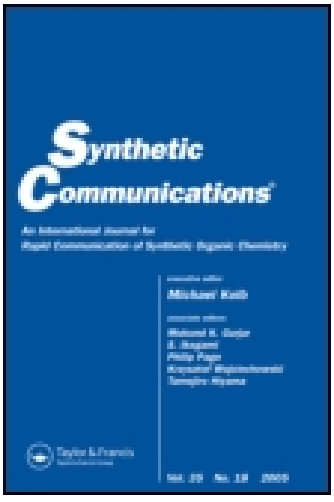

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Novel Synthetic Approach to Multibenzoylated Nucleosides

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Novel Synthetic Approach to Multibenzoylated Nucleosides

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Abstract: An improved and highly efficient synthetic approach to multibenzoylated nucleosides bearing free 5′-hydroxyl groups is described here. By employing *t*-butyldimethylsilyl (TBDMS) rather than the more commonly used dimethoxytrityl (DMTr) as a temporary 5′-OH protecting group of the starting nucleoside, this methodology provides the expected products in nearly quantitative yields, thereby substantially reducing the cost and effort of synthesis.

Keywords: Deprotection, multibenzoylation, nucleoside, protection

INTRODUCTION

Multibenzoylated nucleosides bearing free 5′-hydroxyl groups serve as the key starting materials in the synthesis of small oligonucleotides such as dinucleotides and trinucleotides.[1] For example, the preparations of the dinucleotide pdCpA,[2] which has important utility in synthetic amino acid mutagenesis technology, or the trinucleotides 2-5 A, 2-5 core, and their analogs,[3] which are known for their antiviral and antitumor activity, have started from N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine as a suitably protected nucleoside. More important, N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine and other multibenzoylated nucleosides have wide applications in the synthesis of nucleoside antibiotic angustmycin A analogs,[4] sugar nucleotides,[5] the

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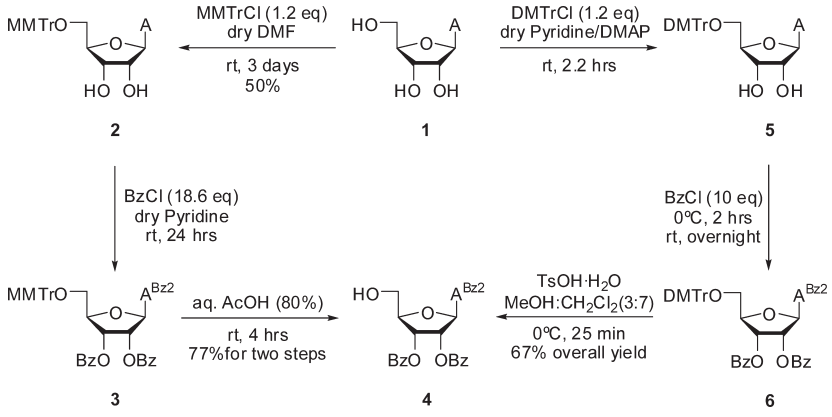


Scheme 1.

5′-terminal cap structure of U1 RNA,[6] diadenosine polyphosphate mimics,[7] and 4′ α-branched 2′-deoxyadenosine.[8]

The synthetic approach to N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine was originally developed by Khorana and coworkers during their seminal investigation of oligonucleotide synthesis 50 years ago and involved the following sequence: (i) direct tritylation of 5′-OH of adenosine **1**, (ii) benzoylation of the trityl derivaties **2**, and (iii) detritylation under acidic conditions.[9] This two-purification, three-step procedure was further simplified by Schultz to a one-purification, three-step methodology.[2a] The improved procedure employed the dimethoxytrityl (DMTr) group, rather than trityl (Tr) or monomethoxytrityl (MMTr) groups, as the temporary protector for the 5′-OH function, resulting in its deprotection under much milder conditions. The tritylation step was also accelerated by adding catalytic amounts of 4-*N*,*N*-dimethylaminopyridine (DMAP). Without any workup or purification of **5**, benzoylation was subsequently executed in one flask. Although the overall yield of **4** is improved from 39% to 67%, both Khorana's and Schultz's protocols use a large excess of benzoyl chloride to secure complete benzoylation. In addition, both methods require the use of predried nucleoside substrate (Scheme 1).

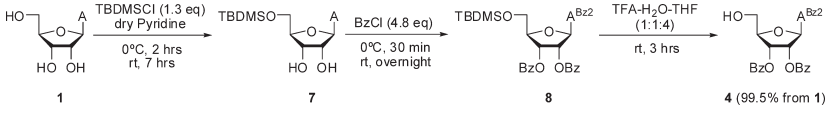
RESULTS AND DISCUSSION

In connection with our work on the synthesis of oligonucleotides, we have developed a one-pot, three-component procedure for preparation of dinucleotides.[2b] This efficient approach requires a multibenzoylated nucleoside such as **4** as one of the key components. Initially, we synthesized **4** by repeating Schultz's protocol with the following modifications: (i) directly using commercially available adenosine, thus omitting the tedious and time-consuming

pretreatment process; (ii) utilizing a slight excess of benzoyl chloride for benzoylation, thereby further simplifying the workup; (iii) performing the detritylation with 2% trifluoroacetic acid (TFA) in dichloromethane at rt. Unfortunately, this method proved not to be routinely reproducible in our hands, in spite of numerous attempts to vary the reaction time, reaction temperature, concentration, and equivalents of DMTrCl, DMAP, and benzoyl chloride. Even addition of 4-Å molecular sieves as drying agents to the mixture of pyridine and adenosine before tritylation did not improve the yield, which varied from 46% to 80%. Also, N^6,N^6,$O^{2'}$,$O^{3'}$,$O^{5'}$-pentabenzoyladenosine was isolated as a main by-product, suggesting that the tritylation step was incomplete. This observation is in accordance with the results reported by Khorana, who obtained the pure trityl derivative **2** in only 50% yield. The poor efficiency of this method prompted us to develop a new and efficient procedure for synthesizing N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine **4**.

The trityl family of protecting groups such as MMTr and DMTr have been used extensively in the preparation of nucleosides and nucleotides mainly because of their exceptional selectivity of protection at primary rather than secondary hydroxyl groups and high acid lability.[10] However, the tritylation process suffers from low yields, probably because of the steric bulk of these groups. Another reason for the low efficiency of the reaction is that trityl groups may react with the exocyclic amino group of adenine. It is already well-established that Tr and MMTr are good amino protecting groups in amino acids[10] and that MMTr and DMTr are occasionally used for the protection of the amino group of guanine.[11] Crucial for the success of our novel synthetic strategy leading to **4** is the ability to identify a protecting group that would be installed at the 5′-OH in a very efficient and highly selective way and that would also be sufficiently acid labile to be removed in the final step, where the amino and hydroxyl groups of the product are fully protected by alkaline labile benzoyl groups. Based upon these considerations, we chose the *tert*-butyldimethylsilyl (TBDMS) group to replace the family of trityl groups as a temporary blocking group. Although TBDMS is widely used as a hydroxyl protecting group in nucleoside and nucleotide chemistry, to our knowledge, its use in preparing multibenzoylated nucleosides has never been report. Its use offers several advantages. First of all, as a protecting group, TBDMS (MW 115.28) is superior to DMTr (MW 303.38) in terms of atom economy efficiency. TBDMSCl is also much cheaper than DMTrCl. Second, its size is not as great as DMTr, but it is still bulky enough to provide preference for silylation of the primary hydroxyl function. Excellent selectivity was achieved for 5′-OH when pyridine was used as both solvent and base. Finally, TBDMS can be exclusively cleaved by a "cocktail" method developed by us.[12] Stirring **8** with the reagent TFA-H_2O-THF (1:1:4) at rt for 3 h leads to quantitative liberation of **4** (Scheme 2).

The success of this work encouraged us to consider extending the methodology to the synthesis of a variety of multibenzoylated nucleosides, and the



Scheme 2.

results are summarized in Table 1. As anticipated, in each case the target compound was obtained in excellent yield. Even 2′-deoxyadenosine monohydrate **9** can be used directly to prepare N^6,N^6,$O^{3'}$-tribenzoyl 2′-deoxyadenosine **11** provided that 1 additional equivalent of TBDMSCl was used to consume the water molecule contained in the starting nucleoside.

In conclusion, the synthetic methodology developed here is not only simpler in execution and workup than those previously reported, but also the overall yields of expected products are significantly increased. On the other hand, the overall costs are markedly reduced by directly using commercially available nucleosides, employing the less expensive TBDMSCl as protecting reagent and avoiding the use of a large excess of benzoyl chloride. Therefore, the current approach represents an important and useful improvement in this field.

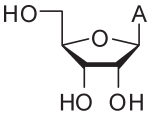
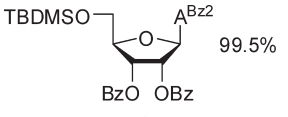
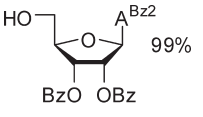
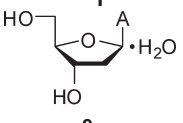
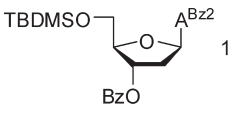
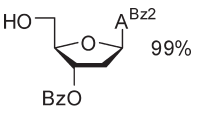
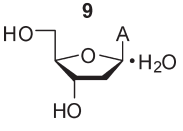
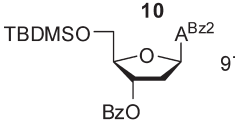
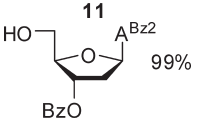
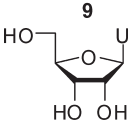
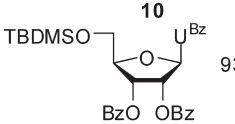
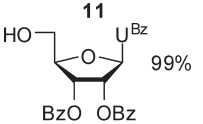
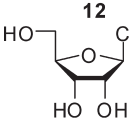
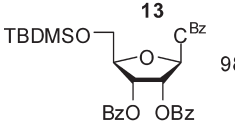
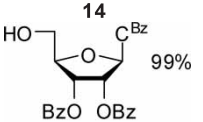
EXPERIMENTAL

All reactions were performed using commercially available solvents and reagents without inert gas protection. As new compounds, intermediates **8**, **10**, **13**, and **16** were isolated and characterized by high-resolution NMR spectroscopy and +FAB mass spectrometry. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded in $CDCl_3$ on a Bruker ARX-500 spectrometer. Coupling constants are expressed in hertz. The chemical shifts and coupling constants in ABX patterns of the 5′ protons in compounds **8** and **13** were calculated using the PCPMR program developed by M. Saunders (Yale University) and K. E. Gilbert and J. J. Gajewski (Indiana University) in 1980. +FAB mass spectra were obtained on a VG analytical 70s high-resolution double-focussing magnetic-sector mass spectrometer.

N^6,N^6,$O^{2'}$,$O^{3'}$-Tetrabenzoyladenosine (4)

To a precooled mixture of adenosine (99%) **1** (540 mg, 2.0 mmol) and pyridine (10 mL), TBDMSCL (99%) (396 mg, 2.6 mmol) was added in one portion at 0 °C. After stirring for 2 h at 0 °C, and the reaction mixture was allowed to warm to rt and was further stirred for 7 h. Then the resulting mixture was cooled to 0 °C, and benzoyl chloride (99%) (1.12 mL, 9.6 mmol) was added dropwise via a syringe during 30 min. The ice bath was then removed, and the reaction mixture was stirred at rt overnight (about 8 h). The resulting mixture

Table 1. Preparation of multibenzoylated nucleosides

Substrate	TBDMSCl (eq.)	BzCl (eq.)	Intermediate yield (silylation & benzylation)	Product yield (desilylation)
 **1**	1.30	4.8	 99.5% **8**	 99% **4**
 **9**	1.25	3.6	 12% **10**	 99% **11**
 **9**	2.35	3.6	 97% **10**	 99% **11**
 **12**	1.25	3.6	 93% **13**	 99% **14**
 **15**	1.30	3.2	 98% **16**	 99% **17**

was diluted with 100 mL of CH_2Cl_2 and washed with brine (40 mL), and the aqueous layer was further extracted with CH_2Cl_2 (2 × 40 mL). The combined extracts were dried over Na_2SO_4 and evaporated at reduced pressure. The dried residue was then dissolved in THF (36 mL), and aqueous TFA (18 mL, TFA–H_2O = 1:1) was slowly added. After stirring for 3 h at rt, the reaction mixture was cautiously neutralized with equimolar amounts of aqueous $NaHCO_3$ (9.72 g in 100 mL H_2O) at 0 °C and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The residue was subjected to flash chromatography on silica gel (Eluent: hexane–EtOAc = 4:1 to 1:1 then CH_2Cl_2 – CH_3OH = 100:5) to provide the pure product **4** as a white solid (1.36 g, 99.5%). In a large-scale synthesis, purification of the desired product can be achieved by simply stirring crude **4** with warm benzene, followed by cooling and filtration, thus avoiding a chromatographic step. Following a similar procedure, compounds **11**, **14**, and **17** were obtained as white solids.

$O^{5'}$-*tert*-Butyldimethylsilyl-N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine (8)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.50 (s, 1H), 7.99 (dd, J = 8.2, 0.9 Hz, 2H), 7.89 (dd, J = 8.2, 1.0 Hz, 2H), 7.84 (dd, J = 8.2, 0.9 Hz, 4H), 7.56 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.8 Hz, 2H), 7.35–7.31 (m, 6H), 6.67 (d, J = 7.0 Hz, 1H, 1′-H), 6.06 (dd, J = 7.0, 5.4 Hz, 1H, 2′-H), 5.90 (dd, J = 5.4, 2.2 Hz, 1H, 3′-H), 4.55 (ddd, J = 2.2, 2.2, 2.2 Hz, 1H, 4′-H), 4.05 (dd, J = 14, 2.2 Hz, 1H, 5′-H), 4.03 (dd, J = 14, 2.2 Hz, 1H, 5′-H), 0.96 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (2C), 165.5 (1C), 164.9 (1C), 153.2 (1C), 152.4 (1C), 151.9 (1C), 142.8 (1C), 134.0 (2C), 133.7 (1C), 133.6 (1C), 132.9 (2C), 129.8 (2C), 129.7 (2C), 129.5 (4C), 128.9 (1C), 128.7 (4C), 128.5 (2C), 128.4 (1C), 128.3 (2C), 127.6 (1C), 85.4 (1C), 84.8 (1C), 74.7 (1C), 72.5 (1C), 63.3 (1C), 26.0 (3C), 18.5 (1C), −5.3 (1C), −5.4 (1C); HRMS $[M + Na]^+$ found: 820.2770; $C_{44}H_{43}O_8N_5SiNa$ requires m/z 820.2779.

$O^{5'}$-*tert*-Butyldimethylsilyl-N^6,N^6,$O^{3'}$-tribenzoyl-2′-deoxyadenosine (10)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.43 (s, 1H), 8.06 (dd, J = 8.3, 1.1 Hz, 2H), 7.85 (dd, J = 8.3, 1.1 Hz, 4H), 7.60 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 4H), 7.34 (t, J = 7.8 Hz, 4H), 6.64 (dd, J = 8.3, 6.1 Hz, 1H, 1′-H), 5.66 (dd, J = 3.6, 1.4 Hz, 1H, 3′-H), 4.38 (ddd, J = 2.7, 2.7, 1.4 Hz, 4′-H), 4.01 (dd, J = 11.2, 2.7 Hz, 1H, 5′-H), 3.95 (dd, J = 11.2, 2.7 Hz, 1H, 5′-H), 2.86–2.77 (m, 2H, 2′-H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (2C), 166.0 (1C), 152.8 (1C), 152.2 (1C),

151.8 (1C), 142.9 (1C), 134.1 (2C), 133.6 (1C), 132.9 (2C), 129.7 (2C), 129.5 (4C), 129.3 (1C), 128.7 (4C), 128.6 (2C), 127.7 (1C), 86.0 (1C), 84.5 (1C), 75.9 (1C), 63.6 (1C), 39.1 (1C), 26.0 (3C), 18.4 (1C), −5.3 (1C), −5.5 (1C); HRMS $[M + Na]^+$ found: 700.2597; $C_{37}H_{39}O_6N_5SiNa$ requires m/z 700.2567.

$O^{5'}$-*tert*-Butyldimethylsilyl-N^3,$O^{2'}$,$O^{3'}$-tribenzoyluridine (13)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, $J = 8.3$ Hz, 1H), 7.99 (d, $J = 7.5$ Hz, 2H), 7.91 (dd, $J = 8.3$, 1.0 Hz, 2H), 7.86 (d, $J = 7.5$ Hz, 2H), 7.57 (t, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.39 (t, $J = 7.8$ Hz, 4H), 7.28 (t, $J = 7.8$ Hz, 2H), 6.56 (d, $J = 7.3$ Hz, 1H, 1′-H), 5.90 (d, $J = 8.3$ Hz, 1H), 5.73 (dd, $J = 5.5$, 1.3 Hz, 1H, 3′-H), 5.63 (dd, $J = 7.3$, 5.5 Hz, 1H, 2′-H), 4.46 (ddd, $J = 1.7$, 1.3, 1.3 Hz, 1H, 4′-H), 4.05 (dd, $J = 14$, 1.7 Hz, 1H, 5′-H), 4.02 (dd, $J = 14$, 1.3 Hz, 1H, 5′-H), 1.00 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (1C), 165.5 (1C), 165.4 (1C), 161.7 (1C), 149.5 (1C), 139.3 (1C), 134.9 (1C), 133.7 (1C), 133.6 (1C), 131.4 (1C), 130.5 (2C), 129.9 (2C), 129.7 (2C), 129.0 (2C), 128.9 (1C), 128.6 (2C), 128.4 (2C), 128.3 (1C), 103.2 (1C), 85.9 (1C), 84.5 (1C), 74.4 (1C), 72.9 (1C), 63.5 (1C), 25.9 (3C), 18.4 (1C), −5.4 (1C), −5.5 (1C); HRMS $[M + Na]^+$ found: 693.2277; $C_{36}H_{38}O_9N_2SiNa$ requires m/z 693.2244.

$O^{5'}$-*tert*-Butyldimethylsilyl-N^4,$O^{2'}$,$O^{3'}$-tribenzoylcytidine (16)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H, NH), 8.44 (d, $J = 6.9$ Hz, 1H, 6-H), 7.97–7.96 (m, 2H), 7.95–7.94 (m, 2H), 7.89–7.87 (m, 2H), 7.60–7.52 (m, 3H, 2 arom. H + 6-H), 7.51–7.48 (m, 3H), 7.39–7.33 (m, 4H), 6.76 (d, $J = 6.39$ Hz, 1H, 1′-H), 5.75 (dd, $J = 5.32$, 2.74 Hz, 1H, 3′-H), 5.63 (dd, $J = 6.39$, 5.41 Hz, 1H, 2′-H), 4.49 (ddd, $J = 2.74$, 1.82, 1.67 Hz, 1H, 4′-H), 4.08 (dd, $J = 11.58$, 1.82 Hz, 1H, 5′-H), 4.00 (dd, $J = 11.58$, 1.67 Hz, 1H, 5′-H), 0.99 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5 (1C), 165.4 (1C), 165.1 (1C), 162.3 (1C), 154.7 (1C), 144.4 (1C), 133.5 (1C), 133.4 (1C), 133.1 (1C), 132.9 (1C), 129.9 (2C), 129.7 (2C), 128.9 (2C), 128.8 (1C), 128.6 (1C), 128.4 (2C), 128.3 (2C), 127.5 (2C), 97.4 (1C), 86.8 (1C), 84.2 (1C), 75.4 (1C), 72.1 (1C), 62.9 (1C), 25.9 (3C), 18.3 (1C), −5.5 (1C), −5.6 (1C); HRMS $[M + Na]^+$ found: 692.2437; $C_{36}H_{39}O_8N_3SiNa$ requires m/z 692.2404.

ACKNOWLEDGMENTS

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