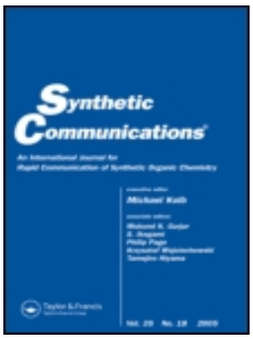

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An Improved Transient Method for the Synthesis of *N*-Benzoylated Nucleosides

Xue-Feng Zhu, Howard J. Williams Jr., and A. Ian Scott*

Center for Biological NMR, Department of Chemistry,
Texas A & M University, College Station,
Texas, USA

ABSTRACT

The Jones' transient method for the synthesis of *N*-benzoylated nucleosides is improved by reducing the amounts of chlorotrimethylsilane (TMSCl) and benzoyl chloride to nearly equivalent quantities. The easy work-up and high yields of products are the major advantages of this approach. Jones' method is further simplified by omitting the addition of ammonium hydroxide. The utility of this modification for the preparation of some useful protected nucleosides is also presented.

*Correspondence: A. Ian Scott, Center for Biological NMR, Department of Chemistry, Texas A & M University, P.O. Box 30012, College Station, TX 77842-3012, USA; E-mail: scott@mail.chem.tamu.edu.

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Key Words: Transient method; *N*-benzoylation; Protection; Nucleosides

Exocyclic amino protection of nucleobases is one of the most important steps in nucleoside chemistry. After protection, the nucleoside can be further transformed into derivatives of biological importance, such as 2′,3′-dideoxycytidine (ddC) and 2′,3′-dideoxyinosine (ddI), which have been used to treat HIV infected patients; or it can be used for making building blocks for oligonucleotide synthesis. Usually an acyl group is introduced to protect the exocyclic amino function. Among numerous acyl groups the benzoyl group is still the most common because of its low price and easy introduction,[1] although a variety of more easily removed protecting groups (phenoxyacetyl (PAC) for A and G, *iso*-butyryl (i-Bu) for C and phthaloyl) have been suggested for oligonucleotide synthesis.[2–4]

In the literature at least three methods are available for *N*-monobenzoylation. The first is the so-called direct selective benzoylation.[5] In principle, this is an atom-economy efficient procedure; in reality, however, it has been successful only with cytosine nucleosides using different benzoylating reagents, since with other nucleosides concomitant *O*-benzoylation invariably accompanies *N*-benzoylation. The second is the perbenzoylation/selective debenzoylation strategy, developed by Khorana, where the nucleoside is first perbenzoylated and subsequently *O*-debenzoylated selectively upon alkaline treatment, to give the desired *N*-benzoylated nucleoside in moderate to good yield.[6] This reliable two-step procedure enjoyed considerable success until 1982 when the third method of transient protection was developed by Jones and co-workers as well as by Sung and Narang.[7] This strategy, now known as the Jones method, can be considered a modification of the Khorana method in which all of the hydroxyl groups of the nucleoside are first protected by trimethylsilyl (TMS) ether. After *N*-benzoylation, they can be cleaved "in situ" upon treatment with ammonium hydroxide. This one-flask procedure takes full advantage of the high lability of TMS ether and therefore avoids the isolation of peracylated intermediate, which is required in the Khorana method. Presently, this is the most widely used method for the protection of the exocyclic amine group of nucleosides.[8]

However, the main problem of the procedure is that a large excess of TMSCl (ca. 2.5–4eq./OH group) and 3–6 fold excess of benzoyl chloride are used in order to secure a good yield of *N*-benzoylated nucleoside. As a result, the work-up is complicated and problematic, especially in large scale synthesis, since removal of impurities such as benzoic acid is

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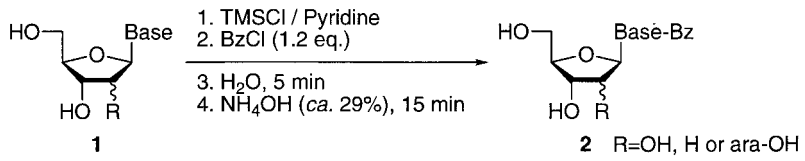
necessary. Both silylation and benzoylation are very clean reactions, so we decided to re-examine this useful *N*-benzoylation method by reducing the amounts of TMSCl and benzoyl chloride (Sch. 1). The results are shown in Table 1. For example, when 1.1 eq. of TMSCl is used for each OH group together with 1.2 eq. of benzoyl chloride, adenosine (**1a**) can be transformed into N^6-benzoyladenosine (**2a**) in 96% yield, which is superior to that reported in the literature,[7c] where large excess of reagents are used. Another direct benefit of this modification is that the work-up can be further simplified (see experimental). This improved approach has proven to be general and highly efficient and can be used to prepare mono-benzoylated ribonucleosides, ara-ribonucleosides and 2′-deoxy ribonucleosides in high yield (Table 1).



Scheme 1.

Table 1. *N*-Benzoylation of ribo-, arabino-, 2′-deoxy-ribo nucleosides.

Entry	Substrate	TMSCl (eq.)	Silylation time (h)	Benzoylation time (h)	Yield (%)
1	adenosine	3.3	0.5	2	96
2	cytidine	3.6	0.5	4	95
3	guanosine	3.6	0.5	2	99
4	ara-adenosine	3.6	1.0	2	95
5	ara-cytidine	3.6	1.0	4	98
6	ara-cytidine monohydrochloride	3.6	1.0	4	93
7	2′-deoxycytidine monohydrochloride	2.4	0.5	4	96
8	2′-deoxycytidine monohydrate	2.4	0.5	4	81
		3.6	0.5	4	98
		4.8	0.5	4	95
9	2′-deoxyadenosine monohydrate	3.6	0.5	2	91
10	2′-deoxyguanosine monohydrate	3.6	1.5	6	98

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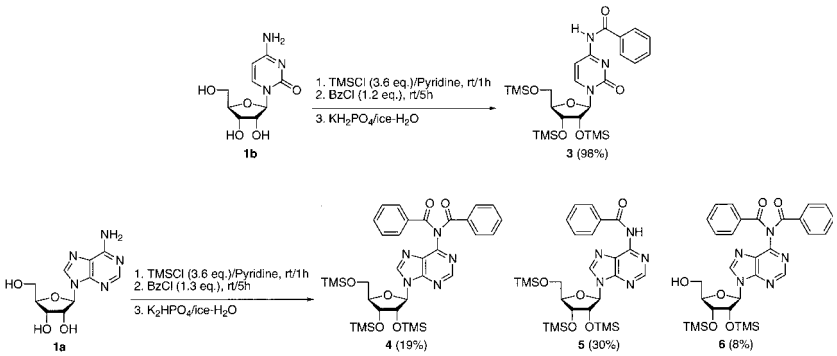
In the literature, all of the nucleoside substrates are pre-dried by co-evaporation with dry pyridine at least twice. However, our study reveals that this tedious step can be avoided. Thus using commercially available nucleosides without purification we find that even nucleoside monohydrates (Entries 8–10) can be used without any pre-treatment. However, in the latter cases, one additional equivalent of TMSCl is added to consume the water molecule associated with the nucleoside substrate.

We also tried to isolate the fully TMS protected nucleoside in order to prove the existence of this presumed intermediate and to study the stability of its TMS groups under different conditions. After cytidine was silylated and benzoylated, the reaction mixture was treated with monobasic potassium phosphate, and the expected intermediate **3** was isolated in high yield. In case of adenosine, more than one intermediate was isolated even when the reaction mixture was treated with dibasic potassium phosphate. Three of these isolated intermediates are shown in Sch. 2.

It turns out that TMS protected cytidine is quite stable. For example, under relatively neutral conditions (pyridine-H_2O [4:1]), it requires about two days to remove the TMS groups; while under basic condition (pyridine-H_2O-NH_4OH (ca. 29%) (4:1:2)), it takes about 1 h to cleave them. It is surprising that the TMS group is very unstable and easily cleaved under mild acidic condition (THF-TFA-H_2O (4:1:1)) in less than 1 min. A similar result was obtained with the adenosine intermediate **4**. Once again this shows that the TMS groups of nucleoside **4** can be easily removed under acidic conditions (Sch. 3).

During silylation and benzoylation, hydrogen chloride is formed and captured by reaction solvent pyridine to form a salt. When water is added



Scheme 2.

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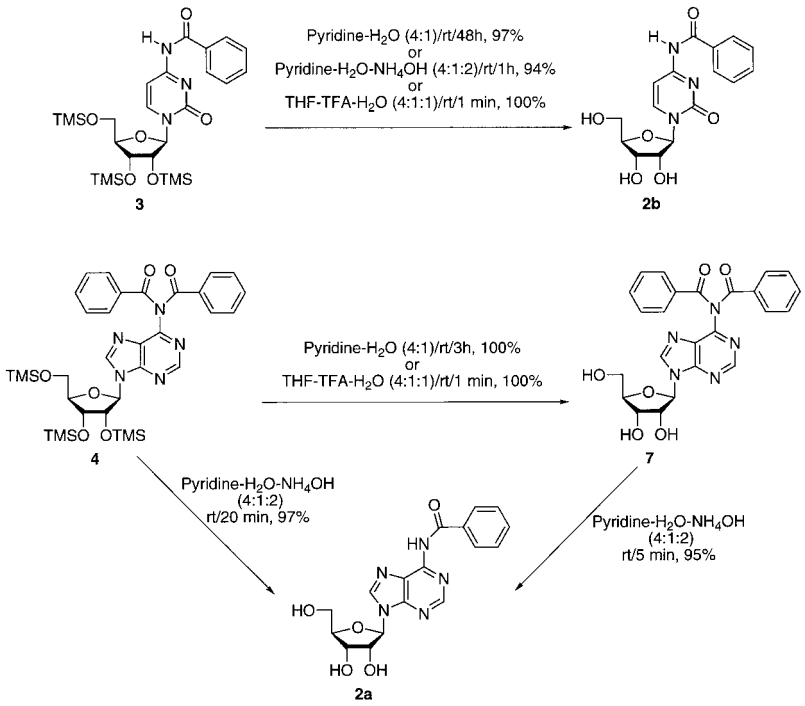

Scheme 3.

at the end of the reaction, this salt can be hydrolyzed to release species **8** that is believed to be acidic enough to cleave the nucleoside's TMS groups. Based on this analysis, our improved approach was further simplified by adding only H_2O and omitting the addition of ammonium hydroxide during work-up. After stirring for 30 min, *N*-benzoylated nucleosides are obtained in high yields (Sch. 4). In the case of adenosine, N^6, N^6-dibenzoylated nucleoside **7** was isolated from the reaction mixture when excess benzoyl chloride (2.4 eq.) is used. As expected, **7** can be smoothly transformed into *N*-benzoyladenosine (**2a**) upon treatment with aqueous ammonium hydroxide (Sch. 3).

The utility of this simplified procedure was further exemplified in the synthesis of some other useful protected nucleosides. For example, in nucleoside chemistry, not only do exocyclic amino groups need to be protected, but in some cases, even the imide group of uridine and thymidine have to be masked.[9] However, benzoylation of imides cannot be achieved using the conventional Jones' method, because the benzoyl group of the imide is very unstable when treated with ammonium

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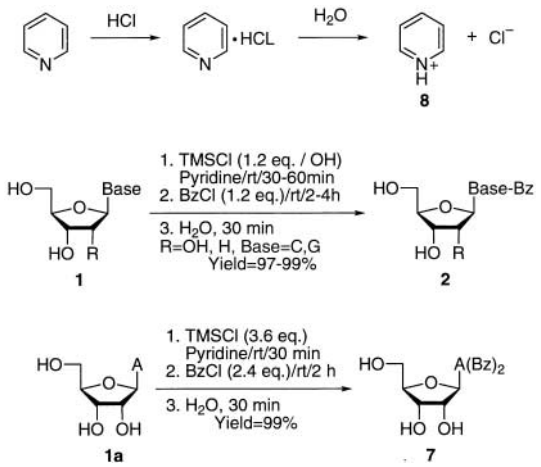

Scheme 4.

hydroxide. Fortunately, using our simplified procedure, benzoylated thymidine (**9a**) and uridine (**9b**) are obtained in good yield. The same approach has been used to prepare nucleoside **10**, a key intermediate in the synthesis of 2′-*O*-methyl uridine, an important naturally occurring nucleoside.[10] Using our simplified trasient method as a key step, nucleoside **10** is obtained in an efficient one-pot procedure. Starting from **10**, 2′-*O*-methyl uridine can easily be synthesized by literature procedures (Sch. 5).[11]

EXPERIMENTAL

All reactions were performed using commercially available nucleoside substrates, solvents and reagents without inert gas protection. As new compounds, intermediates **3**, **4**, **5**, **6** and nucleoside **7** were characterized by high-resolution NMR spectroscopy and ESI Mass spectrometry. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded in $CDCl_3$ on a Bruker ARX-500 spectrometer. ESI mass spectra were obtained on a PE SCIEX API QSTAR PULSAR mass spectrometer.

Typical Procedure for *N*-benzoylation of nucleosides: Method 1 (Entry 5 of Table 1). To a mixture of cytosine-1-β-D-arabinofuranoside (99%) **1e** (997 mg, 4.06 mmol) and pyridine (16 mL) was added TMSCl (98%) (1.9 mL, 14.7 mmol) at r.t. After stirring for 1 h, the reaction

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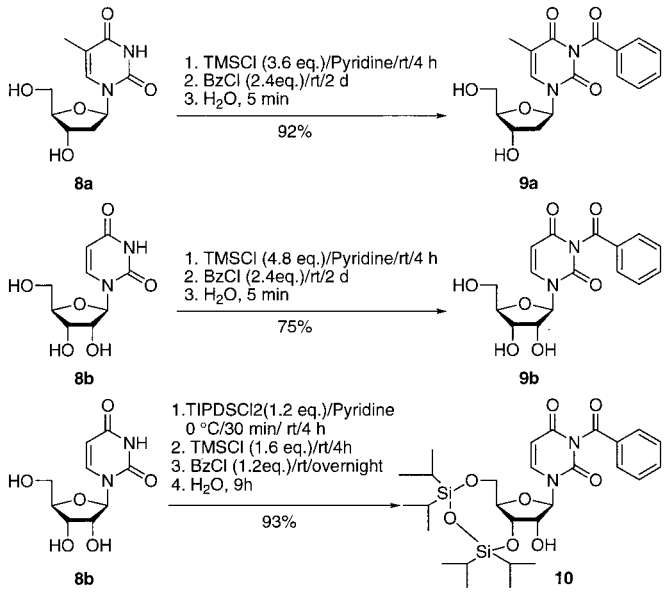

Scheme 5.

mixture was cooled to 0°C, and benzoyl chloride (99%) (0.58 mL, 4.95 mmol) was added dropwise by syringe. The ice-bath was then removed and the reaction mixture stirred at r.t. for 4 h. The reaction was quenched by the addition of water (4 mL); after stirring for 5 min at r.t., concentrated aqueous ammonia (ca. 29%) (8 mL) was added and the mixture was stirred at r.t. for 15 min. The resulting mixture was then evaporated to dryness under reduced pressure. The dried residue was stirred with cold water (20 mL) and filtered. After the solid product was filter-washed with cold water (2 × 5 mL) and ether (2 × 5 mL) and dried, the *N*-benzoylated nucleoside **2e** was obtained (1.388 g, 98%) as a white solid. **Method 2:** After silylation and benzoylation, the reaction was stopped by the addition of water and stirred at r.t. Under these conditions, hydrolysis of TMS groups is complete in 30 min. Following the same work-up described in method 1, *N*-benzoylated nucleoside can be obtained in high yield (Sch. 4).

***O*$^{2'}$,*O*$^{3'}$,*O*$^{5'}$-tris-trimethylsilyl-*N*^{4}-benzoylcytidine (3).** Cytidine (7.5 mmol, suspended in 30 mL of pyridine) was first silylated and benzoylated (Sch. 2), and the reaction mixture cooled to 0°C. To this mixture was added KH_2PO_4 (10 g) and ice-water (48 g). After the mixture was stirred for several minutes, a white precipitate appeared.

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The solid was collected by filtration, washed with cooled water (8×25 mL), and dried under reduced pressure overnight. **3** was obtained as a white solid (4.16 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ8.68 (d, $J = 6.96$ Hz, 1H, 6-H), 8.62 (s, br, 1H, NH), 7.87 (d, $J = 6.70$ Hz, 2H, arom. H), 7.59 (t, $J = 7.40$ Hz, 1H, arom. H), 7.51–7.45 (m, 3H, 2 arom. H+H-5), 5.79 (s, 1H, 1′-H), 4.15 (ddd, $J = 8.32$, 1.96, 1.32 Hz, 1H, 4′-H), 4.11 (d, $J = 4.04$ Hz, 1H, 2′-H), 4.06 (dd, $J = 8.32$, 4.04 Hz, 1H, 3′-H), 4.03 (dd, $J = 11.75$, 1.92 Hz, 1H, 5′-H), 3.71 (dd, $J = 11.75$, 1.36 Hz, 1H, 5′-H), 0.20 (s, 9H), 0.19 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ166.8 (1C), 162.1 (1C), 154.7 (1C), 145.1 (1C), 133.2 (1C), 133.0 (1C), 128.9 (2C), 127.5 (2C), 95.6 (1C), 91.6 (1C), 82.6 (1C), 76.5 (1C), 68.1 (1C), 59.3 (1C), 0.27 (3C), 0.008 (3C), −0.73 (3C); HRMS $[M+H]^+$, Found: 564.2373, $C_{25}H_{42}O_6N_3Si_3$ requires m/z 564.2381.

TMS protected adenosine intermediates. Adenosine (7.5 mmol, suspended in 30 mL of pyridine) was first silylated and benzoylated (Sch. 2), the reaction was then cooled to 0°C. To this mixture was added K_2HPO_4 (12 g) and ice-water (60 g). The mixture was then diluted with 200 mL CH_2Cl_2 and washed with brine (40 mL). The organic phase was dried over Na_2SO_4 and evaporated at reduced pressure. The residue was subjected to flash chromatography on silica gel (Eluent: EtOAc/Hexane = 1:8 to 1:2) to provide three TMS protected intermediates **4**, **5** and **6** as white solids. $O^{2'}$,$O^{3'}$,$O^{5'}$-*tris*-trimethylsilyl-N^6,N^6-dibenzoyladenosine (**4**) (0.99 g, 19%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.41 (s, 1H), 7.83 (d, $J = 7.37$ Hz, 4H, arom. H), 7.45 (t, $J = 7.43$ Hz, 2H, arom. H), 7.31 (dd, $J = 7.43$, 7.37 Hz, 4H, arom. H), 6.09 (d, $J = 4.80$ Hz, 1H, 1′-H), 4.63 (t, $J = 4.58$ Hz, 1H, 2′-H), 4.26 (t, $J = 4.20$ Hz, 1H, 3′-H), 4.12 (m, 1H, 4′-H), 3.90 (dd, $J = 11.46$, 3.50 Hz, 1H, 5′-H), 3.72 (dd, $J = 11.46$, 2.72 Hz, 1H, 5′-H), 0.14 (s, 18H), −0.054 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (2C), 152.9 (1C), 152.1 (1C), 151.7 (1C), 143.8 (1C), 134.2 (2C), 132.8 (2C), 129.4 (4C), 128.6 (4C), 128.1 (1C), 88.6 (1C), 85.3 (1C), 75.8 (1C), 71.6 (1C), 61.4 (1C), 0.235 (3C), −0.092 (3C), −0.653 (3C); HRMS $[M+H]^+$, Found: 692.2742, $C_{33}H_{46}O_6N_5Si_3$ requires m/z 692.2756. $O^{2'}$,$O^{3'}$,$O^{5'}$-*tris*-trimethylsilyl-N^6-benzoyladenosine (**5**) (1.32 g, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H, NH), 8.79 (s, 1H), 8.43 (s, 1H), 8.00 (dd, $J = 7.19$, 1.34 Hz, 2H, arom. H), 7.58 (td, $J = 7.39$, 1.34 Hz, 1H, arom. H), 7.49 (dd, $J = 7.39$, 7.19 Hz, 2H, arom. H), 6.10 (d, $J = 4.31$ Hz, 1H, 1′-H), 4.62 (t, $J = 4.35$ Hz, 1H, 2′-H), 4.28 (t, $J = 4.48$ Hz, 1H, 3′-H), 4.16–4.13 (m, 1H, 4′-H), 3.94 (dd, $J = 11.44$, 3.31 Hz, 1H, 5′-H), 3.73 (dd, $J = 11.44$, 2.56 Hz, 1H, 5′-H), 0.17 (s, 9H), 0.14 (s, 9H), −0.0012 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (1C), 152.7 (1C), 151.6 (1C), 149.3 (1C),

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141.9 (1C), 133.7 (1C), 132.7 (1C), 128.8 (2C), 127.8 (2C), 123.3 (1C), 88.7 (1C), 84.9 (1C), 75.9 (1C), 71.2 (1C), 61.1 (1C), 0.19 (3C), −0.04 (3C), −0.66 (3C); HRMS $[M+H]^+$, Found: 588.2588, $C_{26}H_{42}O_5N_5Si_3$ requires m/z 588.2493. $O^{2'}$,$O^{3'}$-di-trimethylsilyl-N^6,N^6-dibenzoyladenosine (**6**) (0.37 g, 8%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.11 (s, 1H), 7.83 (d, $J = 7.64$ Hz, 4H, arom. H), 7.47 (t, $J = 7.39$ Hz, 2H, arom. H), 7.33 (dd, $J = 7.64$, 7.39 Hz, 4H, arom. H), 5.86 (d, $J = 7.86$ Hz, 1H, 1′-H), 5.70 (dd, $J = 12.01$, 1.76 Hz, 1H, 4′-H), 4.95 (dd, $J = 7.86$, 4.64 Hz, 1H, 2′-H), 4.29 (d, $J = 4.64$ Hz, 1H, 3′-H), 4.18 (s, 1H, OH), 3.93 (dd, $J = 13.07$, 1.76 Hz, 1H, 5′-H), 3.70 (dd, $J = 13.07$, 12.01 Hz, 1H, 5′-H), 0.16 (s, 9H), −0.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9 (2C), 152.9 (1C), 151.7 (1C), 151.5 (1C), 145.1 (1C), 133.7 (2C), 133.1 (2C), 129.4 (4C), 129.2 (1C), 128.8 (4C), 90.7 (1C), 89.5 (1C), 73.6 (1C), 73.5 (1C), 62.9 (1C), 0.29 (3C), −0.61 (3C); HRMS $[M+H]^+$, Found: 620.2446, $C_{30}H_{38}O_6N_5Si_2$ requires m/z 620.2360.

***N*^{6},*N*^{6}-dibenzoyladenosine (7).** After adenosine (7.5 mmol) was silylated and benzoylated (Sch. 4), water (8 mL) was added to cleave the TMS groups. The resulting mixture was stirred at r.t. for 30 min and subsequently diluted with 100 mL CH_2Cl_2 and washed with brine (40 mL). After separation, the aqueous layer was further extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and evaporated at reduced pressure. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH = 100:1 to 100:4) yielded **7** as a white solid (3.53 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.14 (s, 1H), 7.79 (dd, $J = 7.26$, 1.11 Hz, 4H, arom. H), 7.47 (td, $J = 7.42$, 1.11 Hz, 2H, arom. H), 7.33 (dd, $J = 7.42$, 7.26 Hz, 4H, arom. H), 5.80 (d, $J = 6.88$ Hz, 1H, 1′-H), 5.45 (d, $J = 9.59$, 1H, 4′-H), 4.68 (dd, $J = 6.88$, 5.86 Hz, 1H, 2′-H), 4.43 (d, $J = 5.86$ Hz, 1H, 3′-H), 4.14 (s, br, 2H, 2 × OH), 3.79 (d, $J = 12.54$ Hz, 1H, 5′-H), 3.70 (s, br, 1H, OH), 3.56 (dd, $J = 12.54$, 9.59 Hz, 1H, 5′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (2C), 152.1 (1C), 151.8 (1C), 151.6 (1C), 145.1 (1C), 133.5 (2C), 133.4 (2C), 129.5 (4C), 128.9 (4C), 128.4 (1C), 91.0 (1C), 87.3 (1C), 73.9 (1C), 71.8 (1C), 62.7 (1C); HRMS $[M+H]^+$, Found: 476.1603, $C_{24}H_{22}O_6N_5$ requires m/z 476.1570.

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REFERENCES

1. (a) Doudna, J.A.; Szostak, J.W.; Rich, A.; Usman, N. J. Org. Chem. **1990**, *55*, 5547; (b) Rosemeyer, H.; Krecmerova, M.; Seela, F. Helv. Chim. Acta **1991**, *74*, 2054; (c) Fu, D.-J.; McLaughlin, L.W. Biochemistry **1992**, *31*, 10941; (d) Seela, F.; Worner, K.; Rosemeyer, H. Helv. Chim. Acta **1994**, 77, 883; (e) Cui, Z.; Zhang, L.; Zhang, B. Tetrahedron Lett. **2001**, *42*, 561.
2. (a) Schulhof, J.C.; Molko, D.; Teoule, R. Tetrahedron Lett. **1987**, *28*, 51; (b) Schulhof, J.C.; Molko, D.; Teoule, R. Nucleic Acids Res. **1987**, *15*, 397; (c) Chaix, C.; Duplaa, A.M.; Molko, D.; Teoule, R. Nucleic Acids Res. **1989**, *17*, 7381; (d) Chaix, C.; Molko, D.; Teoule, R. Tetrahedron Lett. **1989**, *30*, 71.
3. (a) Wu, T.; Ogilvie, K.K. Tetrahedron Lett. **1988**, *29*, 4249; (b) Wu, T.; Ogilvie, K.K.; Pon, R.T. Nucleic Acids Res. **1989**, *17*, 3501.
4. (a) Pirrung, M.C.; Fallon, L. J. Org. Chem. **1998**, *63*, 241; (b) Song, Q.; Wang, W.; Fischer, A.; Zhang, X.; Gaffney, B.L.; Jones, R.A. Tetrahedron Lett. **1999**, *40*, 4153.
5. (a) Watanabe, K.A.; Fox, J.J. Angew. Chem. Int. Edn. Engl. **1966**, *5*, 579; (b) Takaku, H.; Shimada, Y.; Morita, Y.; Hata, T. Chem. Lett. **1976**, 19; (c) Steinfeld, A.S.; Naider, F.; Becker, J.M. J. Chem. Research (S) **1979**, *129*; (d) Igolen, J.; Morin, C. J. Org. Chem. **1980**, *45*, 4802; (e) Finlay, M.; Debiard, J.P.; Guy, A.; Molko, D.; Teoule, R. Synthesis **1983**, 303; (f) Kaskar, B.; Markovac, A. J. Heterocyclic Chem. **1989**, *26*, 1531; (g) Nahar, P. Tetrahedron Lett. **1997**, *38*, 7253.
6. (a) Rammler, D.H.; Khorana, H.G. J. Am. Chem. Soc. **1962**, *84*, 3112; (b) Schaller, H.; Weimann, G.; Lerch, B.; Khorana, H.G. J. Am. Chem. Soc. **1963**, *85*, 3821; (c) Cole, A.G.; Gani, D. J. Chem. Soc. Perkin Trans. 1 **1995**, 2685.
7. (a) Ti, G.S.; Gaffney, B.L.; Jones, R.A. J. Am. Chem. Soc. **1982**, *104*, 1316; (b) Sung, W.L.; Narang, S.A. Can. J. Chem. **1982**, *60*, 111; (c) McLaughlin, L.W.; Piel, N.; Hellmann, T. Synthesis **1985**, *322*.
8. (a) Goodwin, J.T.; Osborne, S.E.; Scholle, E.J.; Glick, G.D. J. Am. Chem. Soc. **1996**, *118*, 5207; (b) Marwood, R.D.; Riley, A.M.; Jenkins, D.J.; Potter, B.V.L. J. Chem. Soc. Perkin Trans. 1 **2000**, 1935; (c) Marwood, R.D.; Correa, V.; Taylor, C.W.; Potter, B.V.L. Tetrahedron:Asymmetry **2000**, *11*, 397.
9. (a) Welch, C.-J.; Chattopadhyaya, J. Acta Chem. Scand. **1983**, *B 37*, 147; (b) Matsuzaki, J.-I.; Hotoda, H.; Sekine, M.; Hata, T. Tetrahedron Lett. **1984**, *25*, 4019; (c) Sekine, M.; Fujii, M.;

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Nagai, H.; Hata, T. Synthesis **1987**, 1119; (d) Ly, D.; Sanii, L.; Schuster, G.B. J. Am. Chem. Soc. **1999**, *121*, 9400.

10. (a) De, N.C.; Chheda, G.B. J. Carbohydrates Nucleosides Nucleotides **1979**, *6*, 371; (b) Parmentier, G.; Schmitt, G.; Dolle, F.; Luu, B. Tetrahedron **1994**, *50*, 5361; (c) Cummins, L.; Owens, S.; Risen, L.; Lesnik, E.; Freier, S.; McGee, D.; Guinosso, C.; Dan Cook, P. Nucleic Acids Res. **1995**, *23*, 2019; (d) Cramer, H.; Pfleiderer, W. Helv. Chim. Acta **1996**, *79*, 2114; (e) Kittaka, A.; Kuze, T.; Asakura, T.; Ito, K.; Miyasaka, T.; Inoue, J.-I. Bioorg. Med. Chem. Lett. **1998**, *8*, 3207.
11. (a) Inoue, H.; Hayase, Y.; Imura, A.; Iwai, S.; Miura, K.; Ohtsuka, E. Nucleic Acids Res. **1987**, *15*, 6131; (b) Akiyama, T.; Nishimoto, H.; Ozaki, S. Bull. Chem. Soc. Jpn. **1990**, *63*, 3356; (c) Roy, S.K.; Tang, J.-Y. Organic Process Research & Development **2000**, *4*, 170.

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