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Efficient synthesis of protected 3′-deoxyadenosine and 3′-deoxyguanosine from adenosine and guanosine

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Abstract—Highly efficient synthesis of protected 3′-deoxyadenosine and 3′-deoxyguanosine from adenosine and guanosine were described. The 2′,3′-diol of protected adenosine and guanosine were reacted with α-acetoxyisobutyryl bromide to yield 9-(2′-*O*-acetyl-3′-bromo-5′-*O*-*tert*-butyldiphenylsilyl-3′-deoxy-β-D-xylofuranosyl)-6-*N*-benzoyl adenine and 9-(2′-*O*-acetyl-3′-bromo-5′-*O*-*tert*-butyldiphenylsilyl-3′-deoxy-β-D-xylofuranosyl)-2-*N*-(*N*′,*N*′-dimethylaminomethylene) guanine and subsequently heated with tri-*n*-butyltin hydride in the presence of 2,2′-azobisisobutyronitrile to afford the protected 3′-deoxyadenosine and 3′-deoxyguanosine in 66–73% over all yield. © 2001 Elsevier Science Ltd. All rights reserved.

Modified nucleosides play an important role in the development of genetic therapies such as antigene and antisense strategies.[1] 3′-Deoxyribonucleosides are known to posses potential antiviral and antitumor activities.[2] The first isolated nucleotide antibiotic was 3′-deoxyadenosine, that is known as cordycepin which inhibits *Bacillus subtilis*, *avian tubercle bacillus* and *Ehrlich ascites* tumor cells.[2a] 3′-Deoxynucleotides have been incorporated into oligonucleotides to form 2′, 5′-linked oligodeoxynucleotide that selectively binds with complementary DNA or RNA.[3] The 2′, 5′-linked oligonucleotides are stable to most of the nucleases that hydrolyze the natural DNA, making them potential candidates for diagnostic and therapeutic antisense applications.[4] A number of methods to prepare 3′-deoxyadenosine and several synthetic approaches for 3′-deoxyguanosine have been described.[5] The most efficient route of 3′-deoxyguanosine synthesis in five steps with 50% overall yield from guanosine was reported by He and Bischofberger.[6] The efficient route of 3′-deoxyadenosine synthesis in three steps with 53% overall yield from adenosine was reported by Robins et al.[7] Norman and Reese have described that the preparation of 2′, 5′-di-*O*-acetyl-3′-deoxyadenosine was in 41% overall yield from adenosine.[8] Herein, we report an efficient synthetic route to prepare protected 3′-deoxyadenosine and 3′-deoxyguanosine in very high yield from corresponding nucleosides.

Moffatt et al. reported that adenosine reacted with α-acetoxyisobutyryl bromide to generate 2′-*O*-acetyl-3′(2′)-deoxy-3′(2′)-bromo-5′-dioxolone-adenosine mixtures.[9] We modified the Moffatt's reaction by protecting 5′-hydroxy and exo-amino groups of ribonucleotides prior reacting with α-acetoxyisobutyryl bromide. The *tert*-butyldiphenylsilyl (TBDPS) group was chosen as a protection group for 5′-hydroxy and benzoyl group for the 6-amino group of adenosine. The adenosine (**1**) was first converted into 6-*N*-benzoyl-adenosine **2** in 96% yield[10] by treating with trimethylsilyl chloride, benzoyl chloride, and 1.0 M ammonium hydroxide, respectively and then treated with *tert*-butyldiphenylsilyl chloride to give 6-*N*-benzoyl-5′-*O*-*tert*-butyldiphenylsilyl-adenosine (**3**) in 99% yield. To a suspension of **3** (915 mg, 1.5 mmol) in acetonitrile (45 ml) containing a trace amount of water (22 μl, 1.2 mmol), α-acetoxyisobutyryl bromide (0.66 ml, 4.5 mmol) was added slowly at 0°C. The mixture was stirred at 0°C for 2.5 h and at room temperature for 7 h when the reaction gave a clear solution. The mixture was concentrated to about 5 ml under reduced pressure and 150 ml of ethyl acetate was added. The solution was washed with cold saturated sodium bicarbonate (2×50 ml), water (50 ml), and brine (50 ml). The aqueous solution was extracted with dichloromethane (2×50 ml) and the combined organic layers were dried over anhydrous sodium sulfate. After evaporation, the crude product was purified by flash silica gel column eluted with a gradient (0–5%) methanol–chloroform to give **4** as a white foam solid (900 mg, yield = 84.1%).[11] Several methods, such as H_2/Raney Ni and H_2/Pd-C (10%), have been tried for the reductive cleavage of

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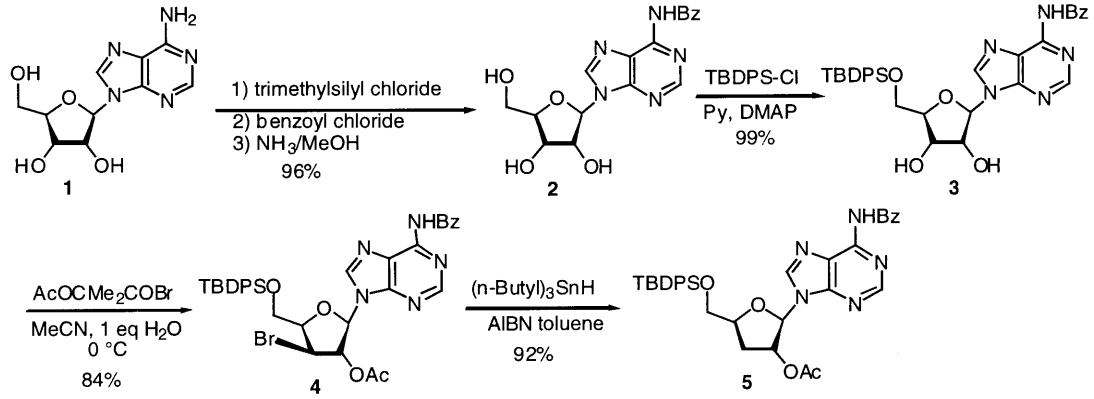
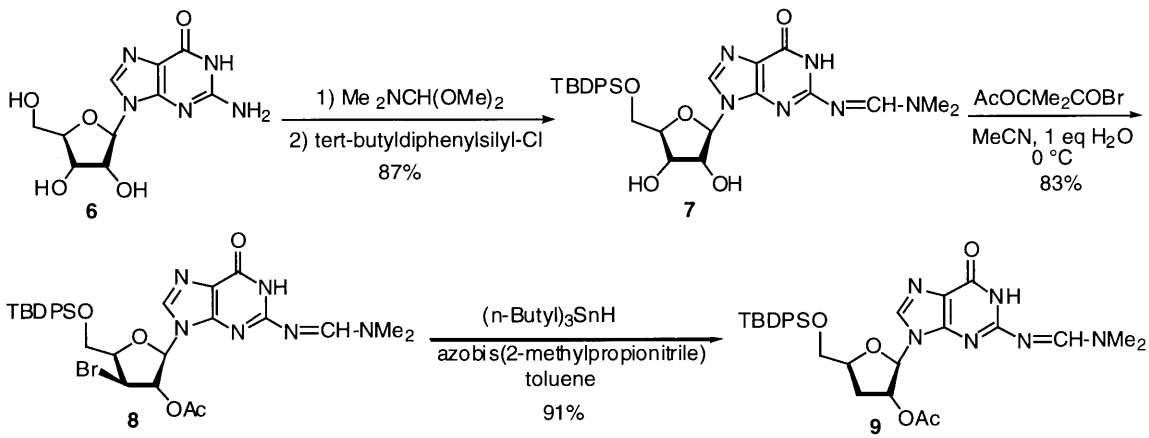


Scheme 1.

3′-bromo group of **4** but gave poor yield or side products. When **4** was heated with an excess tri-*n*-butyltin hydride in the presence of 2,2′-azobisisobutyronitrile (AIBN) in toluene solution, a protected 3′-deoxyadenosine (**5**) was obtained in high yield but a trace amount of *N*-benzoyl cleaved product was formed after prolonged heating. The compound **4** (500 mg, 0.7 mmol) was first dissolved in dry toluene (10 ml) under an atmosphere of argon and then tri-*n*-butyltin hydride (0.57 ml, 2.1 mmol) and 2,2′-azobisisobutyronitrile (9.8 mg, 0.06 mmol) were added at room temperature. The stirred reaction mixture was heated to 95°C. After 50 min, the starting material was disappeared monitored by ESI-MS. The solvent was removed under reduced pressure, the crude product was purified by flash silica gel column eluted with 0.1–3% methanol–methylene chloride to afford **5** as a white solid (410 mg, 92% yield) (73% from **1**) (Scheme 1).[12]

9-(2′-*O*-Acetyl-5′-*O*-*tert*-butyldiphenylsilyl-3′-β-D-2-(*N*′, *N*′-dimethylaminomethylene) xylofuranosyl) guanine (**9**) was prepared by a similar synthetic route as described above for **5**. Guanosine was first protected by *N*,*N*-dimethylaminomethylene at 2-amino of guanine and TBDPS at 5′-hydroxy group, and then reacted with α-acetoxyisobutyryl bromide,[13] finally treated with tri-*n*-butyltin hydride and a catalytic amount of AIBN to give the desired product (Scheme 2). Briefly, guanosine **6** was reacted with *N*,*N*-dimethylformamide dimethyl acetal in acetonitrile to give 2-(*N*,*N*-dimethylaminomethylene) guanosine in 97% yield and then treated with *tert*-butyldiphenylsilyl chloride to give **7** in 90% yield. Compound **7** was reacted with α-acetoxyisobutyryl bromide to yield **8** (83%).[14] The compound **8** (190 mg, 0.28 mmol) was dissolved in toluene (10 ml) under an atmosphere of argon and tri-*n*-butyltin hydride (0.23 ml, 0.84 mmol) and 2,2′-azobisisobutyronitrile were added, and heated to 95°C for 2 h. The pure product **9** (154 mg, 91%) was obtained after silica gel chromatography purification (66% overall from **6**).[15]

TBDPS or acetyl group of **5** and **9** can be selectively deprotected with appropriate reagent. 5′-TBDPS group of **5** and **9** was removed quantitatively with 1.0 M tetra-*n*-butylammonium fluoride (TBAF) in THF at 0°C. 2′-Acetyl group of **5** and **9** was deprotected with 0.5–1.0N ammonia in methanol in ~100% yield. Thus, the **5** and **9** can be easily converted to corresponding phosphoramidites for solid-phase oligonucleotide synthesis using standard coupling protocols.[16] This synthetic route can be enhanced to preparative scale for preparing 3′-deoxynucleosides.



Scheme 2.

Acknowledgements

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11. Compound **4**: $R_f = 0.50$ (chloroform: methanol = 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 9H), 2.19 (s, 3H), 4.04 (m, 2H), 4.47–4.39 (m, 2H), 5.75 (s, 1H), 6.28 (d, $J = 2.0$ Hz, 1H), 8.01–7.37 (m, 15H), 8.33 (s, 1H), 8.74 (s, 1H), 9.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 20.7, 26.8, 50.2, 64.5, 81.5, 82.8, 88.0, 123.3, 127.9, 128.0, 128.6, 130.0, 132.6, 132.7, 133.7, 135.5, 141.1, 149.8, 151.5, 152.8, 165.2, 169.1; ESI-Mass (m/e): 736.2 (M+Na)$^+$; 738.2 (M+Na+2)$^+$.
12. Compound **5**: $R_f = 0.45$ (chloroform: methanol = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 9H), 2.12 (s, 3H), 2.14–2.18 (m, 1H), 2.66–2.73 (m, 1H), 3.77 (dd, $J = 4.03$, 11.74 Hz, 1H), 4.02 (dd, $J = 3.30$, 11.74 Hz, 1H), 4.51 (m, 1H), 5.67 (m, 1H), 6.20 (d, $J = 1.47$ Hz, 1H), 7.30–7.55 (m, 9H), 7.61–7.64 (m, 4H), 8.00 (m, 2H), 8.28 (s, 1H), 8.73 (s, 1H), 9.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 21.2, 27.1, 32.4, 64.7, 78.3, 81.6, 89.7, 123.6, 128.0, 128.1, 128.9, 130.1, 132.9, 133.0, 134.0, 135.7, 141.7, 149.9, 151.4, 153.0, 165.11, 170.3; ESI-MS positive ion 636.1 (M +1)$^+$, 658.3 (M+Na)$^+$.
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14. Compound **8**: $R_f = 0.65$ (chloroform: methanol = 85:15); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 9H), 2.22 (s, 3H), 3.10 (s, 3H), 3.18 (s, 3H), 4.03 (m, 2H), 4.37 (d, $J = 3.6$ Hz, 1H), 4.43 (m, 1H), 5.94 (d, $J = 1.8$ Hz, 1H), 6.12 (s, 1H), 7.72–7.38 (m, 10H), 7.83 (s, 1H), 8.64 (s, 1H), 8.81 (br, 1H). The ^{1}H NMR spectrum is coincident with that reported in the literature.[13]
15. Compound **9**: $R_f = 0.44$ (chloroform: methanol = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 9H), 2.02–2.07 (m, 1H), 2.12 (s, 3H), 2.34–2.41 (m, 1H), 3.06 (s, 3H), 3.13 (s, 3H), 3.76 (dd, $J = 4.03$, 11.37 Hz, 1H), 3.93 (dd, $J = 3.66$, 11.37 Hz, 1H), 4.49 (m, 1H), 5.82 (m, 1H), 5.96 (d, $J = 1.1$ Hz, 1H), 7.33–7.41 (m, 6H), 7.61–7.66 (m, 4H), 7.81 (s, 1H), 8.62 (s, 1H), 9.72 (br, s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 21.3, 27.1, 32.3, 35.3, 41.6, 65.0, 77.7, 81.6, 89.4, 121.1, 128.1, 130.1, 133.0, 135.7, 136.1, 149.7, 157.2, 158.4, 159.0, 170.0; ESI-MS positive ion: 603.2 (M+1)$^+$, 625.3 (M+Na)$^+$; negative ion, 601.4 (M−1)$^-$.
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