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From Adenosine to 3′-Deoxyadenosine: Development and Scale Up

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Abstract:

A manufacturing process has been developed suitable for the production of 3′-deoxyadenosine (cordycepin, 3′-dA) in 20% yield from adenosine. The chemistry involves conversion of adenosine to isomeric 2′,3′-bromoacetates with isolation of the desired isomer in high purity. Acidic hydrolysis followed by hydrogenolysis afforded product with a purity of ≥99%. Unlike routes reported in the literature, intermediates are isolated as solids, thus avoiding the use of chromatography for isomer separation and final product purification.

Introduction

Cordycepin (3′-deoxyadenosine, 3′-dA, **1**) is a naturally occurring antibiotic first isolated from the fungus *Cordyceps militaris*.[2] Being a 3′-deoxy nucleoside, its mode of action is due to the chain-terminating ability at the 3′-terminus during RNA synthesis. We have recently become interested in this compound and decided to embark on a program aimed at developing a route suitable for the large-scale manufacture of 3′-dA.

A number of methods for the synthesis of 3′-dA exist in the literature. These routes can be classified as belonging to one of three types of synthesis: total synthesis from non-nucleoside derivatives,[3−5] metal hydride reduction of the 2′,3′-anhydro derivative,[6−8] and reduction of the 3′-halo derivatives using both noble metal catalysts[9,10] and tin hydrides.[11,12] Since we were interested in obtaining samples that were free from the α-anomer as well as having low levels of the 2′-deoxy derivative, we focused our attention on the latter two approaches which would use natural adenosine as the starting material.

Results and Discussion

We embarked on a two-prong approach aimed at developing a scaleable process for the manufacture of 3′-dA. Central to this approach was the use of 2-acetoxyisobutyryl bromide (AIB, Mattock's bromide) for the conversion of adenosine to the corresponding adenosine bromoacetates **2** and **3**. Robins has demonstrated the utility of Mattock's bromide as a reagent for the conversion of natural nucleosides into various derivatives, including deoxy- derivatives.[12−16] Several industrial based labs have also published work using this reagent for the synthesis of deoxynucleosides.[17−20] In developing our route, it was planned that the generated bromoacetates **2** and **3** could be used as common intermediates in either of our approaches, as outlined in Scheme 1. The major concern for both routes was selectivity. To proceed via the anhydro intermediate **4**, we would capitalize on the convergence of both isomeric bromoacetates to a common intermediate, but then we would need to address the regioselectivity of epoxide ring opening. A synthesis based on reduction then hydrolysis is also prone to certain pitfalls. As pointed out succinctly by Chattopadhyaya,[7] in approaches based on reduction of the halo-sugars, extensive purification is required prior to reduction, or a separation of 2′- and 3′-deoxyadenosine must be done at the last stage. Considering that we were aiming at scaling up to our pilot plant, a process that involved careful chromatography was not a suitable candidate.

In Chattopadhyaya's synthesis of 3′-dA, the isomeric bromo-acetates were converted to the common 2′-3′-anhydroadenosine **4** by treatment with Amberlite (OH^-) resin. Although the remaining steps to his synthesis would be cumbersome on-scale due to successive protection, reduction, and deprotection steps and two back-to-back purifications on silica gel, we believed that his approach provided a good starting point for process development.

Approach One: Epoxide Reduction. Epoxide **4** was conveniently prepared from adenosine via a two-step process. Addition of neat AIB to a suspension of adenosine in acetonitrile followed by a basic work up afforded a mixture of bromoacetates **2** and **3**. Rapid conversion to epoxide **4**

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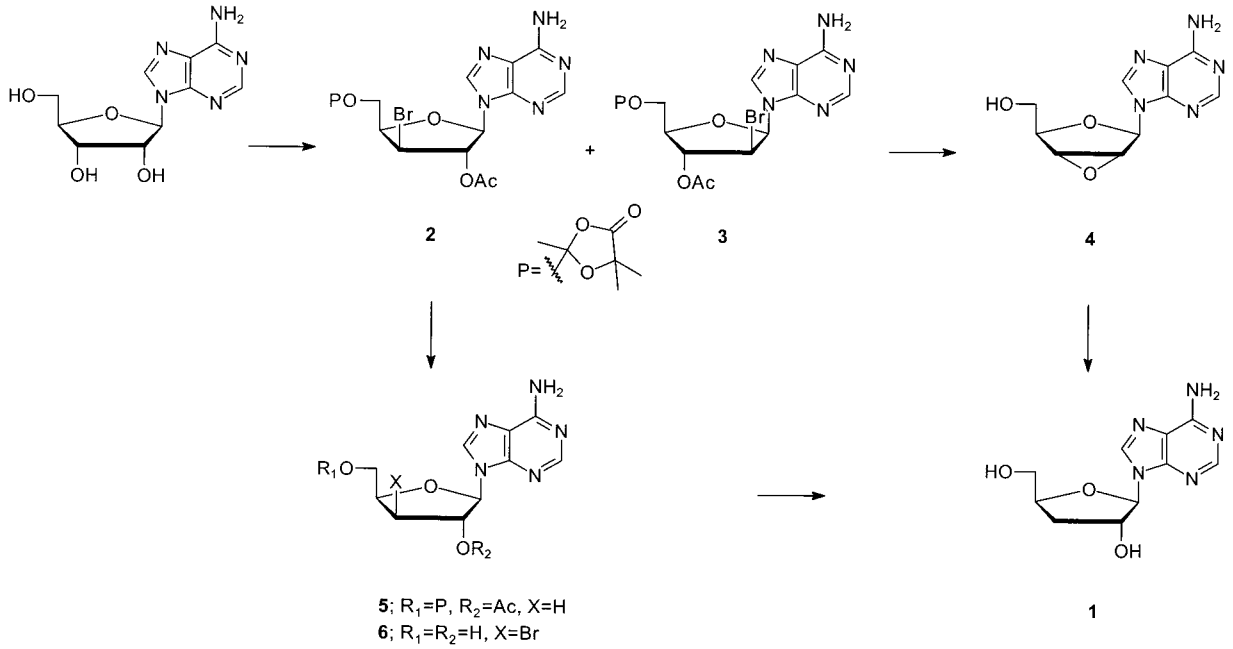
Scheme 1



was achieved by switching the solvent to methanol and adding potassium carbonate. Epoxide **4** was isolated as a solid, following partial concentration of the stock solution.

Although Chattopadhyaya protected the 5′-hydroxyl group as a 4-methoxytriphenylmethyl ether prior to $LiAlH_4$-mediated reduction,[7] we chose to skip this on the basis of Robins' report of regioselective ring opening of the epoxide with super-hydride.[6] Although $LiAlH_4$ did reduce the anhydro intermediate **4**, it was not selective, and chromatography on silica gel was required. Other hydride reagents could have been examined, but the dilute nature of most commercial solutions of borohydrides, which would limit throughput, and the possibility of chromatographic purification were considered as marks against this approach.

Approach Two: Bromoacetate Reduction. While working on approach one, it was noticed that a thick slurry formed while concentration of the stock solution of bromoacetates **2** and **3** was being done. Filtration of this slurry and analysis of the solid revealed that the desired isomer **2** had precipitated in a purity of ≥98%. Although the recovery was rather poor (∼ 30%) with significant losses of the desired isomer to the mother liquor, we decided to investigate the reduction of **2**. The rather fortuitous precipitation of the desired isomer in high purity would remove any troublesome purification at later stages.

It was soon discovered, however, that we could not take advantage of this serendipitous purification. The bromoacetate **2**, once precipitated, was quite insoluble in solvents commonly used for hydrogenolysis with heterogeneous catalysts. To further complicate matters, once dissolved, the desired reduction was quite slow with pressures of up to 30 psi hydrogen, and the dominant reduction pathway was reduction of the glycosyl bond, as evident by the large amount of adenine detected in the reaction mixtures. On the basis of the indication of poor conversion of **2** to **5**, it was clear that another strategy was required.

Approach Three: Bromoacetate Hydrolysis and Reduction. We reasoned that the poor hydrogenolysis performance was the result of two factors: Large groups at the 1′- and 5′-positions that prevented good contact of the substrate and catalyst and poor solubility in solvents commonly used for hydrogenolysis. We speculated that removal of the 5′-dioxolanyl and 2′-acetyl groups would allow for greater solubility in polar protic solvents, as well as create a less congested area for the interaction between the substrate and catalyst.

Although there were reports in the literature on the selective hydrolysis of compounds related to bromoaceteate **2** to bromodeoxy derivatives similar to **6** under basic conditions using ammonia,[21] in our hands we managed to form only epoxide **4**. On the basis of these difficulties, acidic conditions were examined.

After considerable optimization, we found that the hydrolysis worked best using methanol as the solvent and concentrated HCl as the acid source. Rather than using a catalytic amount of acid, 5 mol equiv were found to be optimal. This reaction was the most interesting and least robust step of the process. The reaction proceeds in three distinct stages that are easily observed by HPLC (Scheme 2). The 5′-dioxolanoyl group of **2** is first converted to an acetate (**7**), which is then hydrolyzed to provide **8**. The intermediacy of **7** was determined by an independent synthesis of **7** from **8**. The last step involves hydrolysis of the remaining 2′-acetate to afford **6**, which was isolated as the hydrochloride salt. This reaction appears to require a fine balance of acid, water content, and reaction temperature. If either the acid concentration, water content, or reaction temperature was too low, then the reaction did not go to completion, and the isolated product was the hydrochloride salt of intermediate **8**. Increasing the reaction temperature

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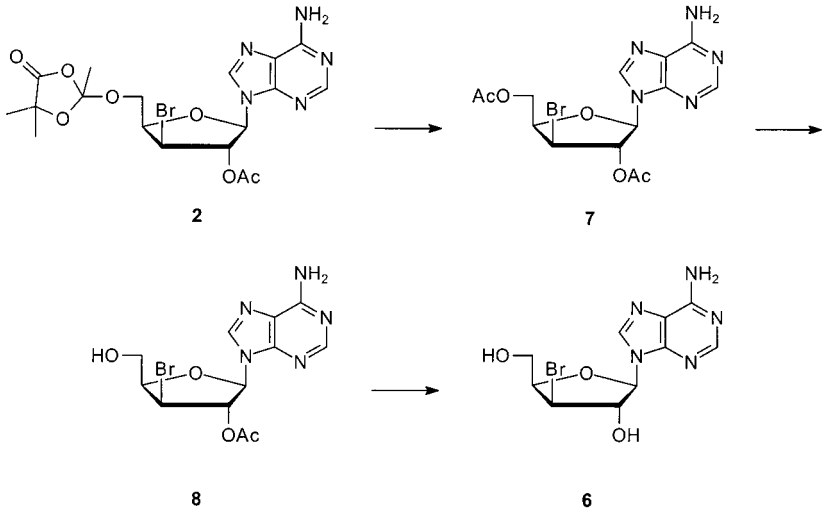
Scheme 2



while keeping the acid concentration and water content low led to hydrolysis of **8** followed by rapid depurination. A considerable effort was directed towards developing a robust process for this stage. Although the reaction time was longer than desired, increased stir out periods did not have a negative impact on the product yield or purity, provided the reaction temperature was maintained between 20 and 25 °C. Following these reaction conditions led to an in-process adenine content of less than 5%, and ≤0.1% in the final product.

With a method in hand that provided the desired 3′-dA precursor in a purity of 98%, being remarkably free of the 2′-dA precursor, we set out to convert the penultimate product to 3′-dA. Attempts to carry the hydrochloride salt of **6** forward through the hydrogenolysis resulted in limited success. In cases where a reaction did occur, cleavage of the glycosyl bond and generation of adenine became a significant pathway. An intensive program was initiated, aimed at finding reaction conditions that would buffer the reaction, with the goal of minimizing the amount of adenine formed during the hydrogenolysis. After considerable experimentation, it was discovered that that addition of 4−5 mol equiv of sodium acetate to a solution of **6** in 50/50 ethanol/water (w/w) effected smooth hydrogenolysis of the carbon−bromine bond. Under these conditions, adenine formation was kept to a minimum (typically ≤5%) when palladium on carbon was used as the catalyst. As an added benefit, the product precipitated from the filtered stock solution upon standing.

Although the current process had the advantage of avoiding chromatographic purification at all stages and provided the final product in a purity >95%, the overall yield was only ∼10%. However, the majority of the losses were encountered at the first stage of the reaction when the pure bromoacetate **2** was isolated in a yield of ∼30%. It was believed that improvements at this stage of the reaction would have a dramatic impact on yield. It was also realized that this stage was also the weakest point in the process since the purity of the product isolated set the stage for the purity of the final product.

Process Optimization

Having observed that the 3′-bromo-3′-deoxy isomers **6** and **8** precipitated so readily from solution during the hydrolysis, it was decided to investigate skipping the filtration at stage one and to carry a stock solution of isomeric bromoacetates **2** and **3** forward. After the starting adenosine disappeared (by TLC) the reaction mixture was quenched and converted to a methanol stock solution. Hydrochloric acid was then added and the reaction mixture stirred at room temperature until the starting material **2** and intermediate **7** were each below 1% (by HPLC). It was also convenient, and much faster, to monitor the reaction using ^{1}H NMR. The 1′- and 2′-protons of **2** appeared at 6.2 and 5.9 ppm, respectively. Although there were very minor changes in the chemical shifts of these protons as the hydrolysis proceeded from **2** to **8** via **7**, significant changes occurred once the 2′-acetate was removed. Both the 1′ and 2′-protons were shifted upfield to 5.9 and 4.9 ppm, respectively. From an in-process control standpoint, it was convenient to observe the region of the spectrum between 5.9 and 6.2 ppm as it slowly converged to a single doublet. The reaction solvent did not interfere with this region of the spectrum; therefore no sample workup was required. Addition of a few drops of the reaction mixture to d_6-DMSO allowed us to determine when the reaction was complete, at which time the reaction mixture was cooled (0−5 °C) and filtered. The isolated solid was determined to be the desired product **6**; however, it was significantly contaminated with adenine, adenosine, and the undesired 2′-bromodeoxy isomer. The elevated levels of adenine and adenosine pointed towards an incomplete reaction at stage one and caused us to reexamine that stage of the process.

Isolation of the major products formed in the reaction of adenosine and AIB using column chromatography showed that in addition to the isomeric 5′-dioxolanyl bromoacetates **2** and **3**, there was also a mixture of 2′,3′-bromoacetates that had a free OH group at the 5′-position (**8** and its 2′/3′-isomer), which is consistent with reports in the literature.[12,22] Although

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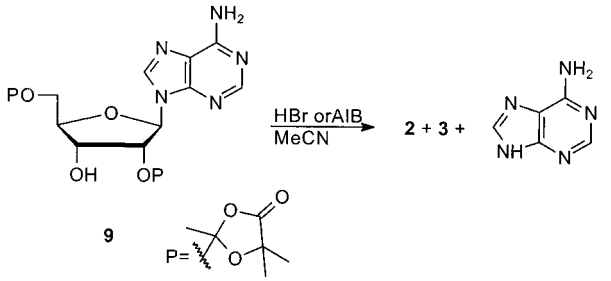
Scheme 3



our reaction was conducted under anhydrous conditions, we did not see any evidence for the formation of the 2′,3′,5′-tris(dioxolanon-2-yl) byproduct as suggested by others.[12,22] However, we did isolate material that appeared to have two dioxolanonyl groups present (**9**). The absence of the tris-(dioxolanon-2-yl) byproduct indicated that hydrolysis of **9** was likely the source of the observed adenosine. We speculated that **9** could be an intermediate in the formation of **2** and **3** and were gratified to see that treatment of **9** with HBr resulted in conversion to **2**, **3**, and adenine (Scheme 3). Since an aqueous work up followed stage one, it was reasoned that running stage one at a slightly higher temperature (∼30 °C) would result in conversion of intermediate **9** to either product or adenine. If adenine were formed, it would be conveniently removed by the aqueous work up. By limiting the amount of **9** carried forward, the adenosine and adenine generated during the hydrolysis should be controlled.

It was also discovered during the stage one development that the reaction worked better in a 50/50 (w/w) mixture of acetonitrile/ethyl acetate, and addition of one back-extraction of the aqueous layer with ethyl acetate increased the recovery of the desired product. The additional back-extraction also increased the adenine content, but incorporation of a brine wash effectively removed it. Conversion of this acetonitrile/EtOAc mixture to a methanol stock solution followed by addition of concentrated HCl afforded, after the appropriate stir out period, the desired product in a yield of 61% over the two steps. This compares with a yield of 35−40% if the intermediate bromoacetate was isolated. Unfortunately, HPLC analysis of the isolated product showed that it was contaminated with 15−20% of the unwanted 2′-bromodeoxy isomer.

The final process development occurred when it was decided to use the modified reaction conditions discussed above and isolate the bromoacetate intermediate **2**. The optimized process afforded **2** in a 50% yield, and a purity of ≥98%. The isolated product **2** was hydrolyzed to **6** under the conditions previously described in yields of 70−75% with no detrimental impact on product purity.

Having improved the yield to the penultimate intermediate, the next stage was to carry the isolated solid forward through the hydrogenolysis and purify the final product. Upon further scale up of the hydrogenolysis, it was necessary to increase the pressure and temperature to 50 psi and 50 °C, respectively, to get good conversions of **6** to **1**. These changes in the reaction conditions did not adversely affect the adenine content.

With conditions that allowed for smooth hydrogenolysis, the remaining challenge was to develop an isolation method that would remove the high salt load. It was found that addition of ethyl acetate to the filtered reaction mixture and partial concentration of the organic layer afforded the product as a white solid. Analysis of the final product revealed it to be 99.0% pure, with a 2′-dA and adenine content of 0.1 and 0.2%, respectively, as well as being 0.4% ash by weight.

In conclusion, an efficient process for the conversion of adenosine to 3′-deoxyadenosine that is amendable to further scale up has been developed. The yield from adenine is 20%, and unlike other preparations of 3′-dA, this one is remarkably free of column chromatography. All intermediates are isolated as filterable solids, following minimal workups. The final product is extremely pure and obviates the need for any further purification.

Experimental Section

Adenosine and acetoxyisobutyryl bromide were purchased from commercial suppliers. All reactions were conducted under a nitrogen atmosphere. Purity is reported as area percentage HPLC performed under the following conditions: column, Phenomenex Luna C18(2), 5 μm, 250 × 4.6 mm; solvent, MeCN, phosphate buffer (pH = 6.0); flow rate, 1.0 mL/min; detection, 260 nm. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded at 200 and 50 MHz using a Varian Gemini spectrometer or at 300 and 75 MHz on a Bruker AM-300 spectrometer. Electrospray mass spectra were determined at the University of Alberta.

5′-[2,5,5-Trimethyl-1,3-dioxolan-4-on-2-yl]-3′-bromo-3′-deoxy-2′-*O*-acetyl Adenosine (2). Adenosine (0.3 kg, 1.12 mol) was suspended in equal amounts of acetonitrile and ethyl acetate (1.30 kg each) in a 5 L reactor equipped with a water-cooled condenser, nitrogen line, addition funnel, thermocouple probe, and overhead agitator. The pot temperature was adjusted to 25−30 °C, and Mattock's bromide (0.66 kg, 3.16 mol, 2.8 equiv) was added at a rate keeping the temperature below 35 °C (Caution: Exotherm). When the addition was complete, the reaction mixture was agitated at 30 °C until complete by HPLC (typically 5−6 h). The reaction mixture, which was still a slurry, was cooled to room temperature and was quenched into a solution of potassium bicarbonate (0.5 kg) and water (1.05 L) (Caution: CO_2 evolved). The mixture was allowed to agitate for 1 h, and then the lower aqueous layer was separated and extracted with ethyl acetate (0.75 kg). The combined organic layers were washed with a 10% brine solution (450 mL), and the aqueous layer was discarded. The remaining organic layer was concentrated and then coevaporated with ethyl acetate (100 mL). The total dissolved solids (TDS) was adjusted to 30−35% by the addition or removal of ethyl acetate. Heptane (0.9 kg) was added to the slurry and the mixture was cooled to 0−5 °C for ∼1 h. The slurry was then filtered and the solids pulled dry, then transferred to a vacuum oven and dried overnight at 40−50 °C. The product was obtained as a white solid in a yield of 52% (0.29 kg) and a purity of 98.5% (HPLC). ^{1}H NMR ($CDCl_3$, 200 MHz) 1.45 (s, 3H), 1.50 (s, 3H), 1.74 (s, 3H), 2.11 (s, 3H), 3.86 (m, 2H), 4.50 (m, 1H), 4.94 (m, 1H), 5.92 (m, 1H), 6.14 (d, J = 3 Hz), 7.40 (br, 2H), 8.12 (s, 1H), 8.22 (s, 1H) ppm; mp 163−165 °C (lit. 171 °C)[9]

3′-Bromo-3′-deoxyadenosine Hydrochloride (6). Bromoacetate **2** (220 g, 0.44 mol) was suspended in methanol (880 g) in a 2 L reactor. Concentrated HCl (216.8 g, 2.2 mol, 5 equiv) was charged slowly, keeping the temperature below 20 °C (Caution: exotherm). The temperature was then maintained at 20−25 °C, and the slurry was agitated until the reaction was complete, as monitored by NMR or HPLC. Typically this reaction required 2−4 days to go to completion. The slurry was then cooled to 0−5 °C for ∼1 h and then filtered. After drying in a vacuum oven at 40 °C for 16 h, the product was isolated as a white solid (113.02 g, 70.1%) in a purity of 97.8% (HPLC). ^{1}H NMR (DMSO, 300 MHz) 3.72 (dd, J = 12.5, 6.0 Hz, 1H), 3.81 (dd, J = 12.5, 6.0 Hz, 1H), 4.40 (q, J = 6.0 Hz 1H), 4.59 (dd, J = 6.0, 3.5 Hz, 1H), 4.78 (t, J = 3.5 Hz, 1H), 5.94 (d, J = 3.5 Hz, 1H), 8.54 (s, 1H), 8.62 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO) 52.56, 61.64, 79.94, 80.35, 88.41, 117.64, 140.82, 144.41, 147.25, 149.59 ppm; IR (KBr) 3200 (br), 1695 cm^{-1}; mp. 172 °C (dec); EIMS (*m*/*z*,%) 330.0 (M^+, 100), 332 (M^+ + 2, 99).

3′-Deoxyadenosine (1). A solution of bromide **6** (100 g, 0.27 mol) and sodium acetate (111.91 g, 1.37 mol, 5 equiv) in ethanol (500 g) and distilled water (500 g) was prepared and filtered through a glass fiber filter paper to remove a small amount of insoluble material. Palladium on carbon (5%, 50% water wet) was charged to the solution, and the slurry was charged to a 5 L Parr glass-lined pressure vessel. The reactor was flushed with nitrogen three times, then charged to 30 psi hydrogen. The reaction mixture was agitated at 250 rpm and 25 °C for 44 h, after which time, in-process analysis had showed that the rate of the reaction had slowed dramatically. The pressure was then increased to 50 psi, and after another 4 h, the rate had not changed significantly. The temperature was then increased to 50 °C, and agitation continued until the reaction was complete (another 21 h). The atmosphere inside the reactor was then converted from hydrogen to nitrogen, and the contents were discharged. The catalyst was removed by filtration over a Celite bed, blanketed with nitrogen (Caution: Dry catalyst is pyrophoric), and the clear yellow stock solution was extracted with ethyl acetate (1L). The organic layer was concentrated under reduced pressure to a volume of 180−200 mL (45 °C bath temperature) and methanol (150 mL) was charged. The slurry was cooled to 5 °C and agitation continued ∼ 1 h, and then the slurry was filtered and dried to afford the product as a white solid (36.0 g, 52.5%), which was 99.0% pure by HPLC and had an ash content of 0.4 wt %. Another crop of product could be isolated from the mother liquor, which increased the yield to over 60%; however, the purity was lower (96% by HPLC), and the ash content was also higher (3.5%). ^{1}H NMR (d_6-DMSO, 200 MHz) 1.95 (m, 1H), 2.21 (m, 1H), 3.60 (m, 2H), 4.30 (m, 1H), 4.55 (m, 1H), 5.82 (s, 1H), 7.22 (s, 1H), 8.15 (s, 1H), 8.28 (s, 1H) ppm; mp 224−226 °C (lit. 224 °C). [9]

3′-Bromo-3′-deoxy-2′,5′-di(*O*-acetyl) Adenosine (7). ^{1}H NMR ($CDCl_3$, 200 MHz) 2.12 (s, 3H), 2.20 (s, 3H), 4.50 (m, 4H), 5.65 (br, 2H), 5.72 (s, 1H), 6.24 (d, J = 3.0 Hz), 8.29 (s, 1H), 8.35 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 20.66, 20.75, 49.29, 64.91, 78.50, 83.13, 87.66, 119.58, 138.52, 149.73, 153.41, 155.7, 169.14, 170.43 ppm; mp 163−165 °C (lit. 166−167 °C).[23]

3′-Bromo-3′-deoxy-2′-*O*-acetyl Adenosine Hydrochloride (8). ^{1}H NMR (200 MHz, DMSO) 2.05 (s, 3H), 3.80 (m, 2H), 4.40 (q, J = 6.0 Hz), 4.50 (br, 4H), 4.90 (t, J = 6.0 Hz), 5.90 (t, J = 6.0 Hz), 6.21 (d, J = 6.0 Hz), 8.5 (s, 1H), 8.62 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO) 20.45, 49.19, 62.24, 81.31, 81.43, 86.64, 118.51, 141.28, 145.98, 148.16, 150.87, 169.42 ppm; IR (KBr) 1210, 1690, 1730, 2700 (br), 3000 (br) cm^{-1}; EIMS (*m*/*z*, %) 372.0 (M^+ + H, 100%), 374.0 (M^+ + 2 + H, 99%); mp 160 °C (dec).

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