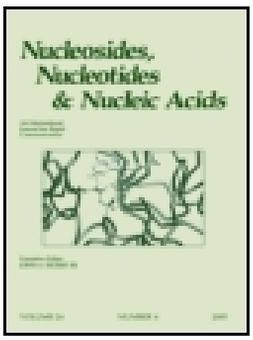

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A practical synthesis of xylo- and arabinofuranoside precursors by diastereoselective reduction using *Corey-Bakshi-Shibata* catalyst

Lynn M. Utley, Jessica Maldonado, and Ahmed M. Awad

Department of Chemistry, California State University Channel Islands, Camarillo, California, USA

ABSTRACT

The *Corey-Bakshi-Shibata* (CBS) catalyst provides an efficient mechanism to reduce ketones and achieve desired enantiopure alcohols. Herein, the diastereoselective reduction of C-2′ and C-3′-keto ribofuranoside derivatives to the corresponding arabino- and xylofuranosides in greater than 95% diastereomeric excess is reported. The stereo-directed substitution with an azido group as well as the synthesis of prodrugs cytarabine and vidarabine are also described. The reported strategy offers superior diastereoselectivity, shorter reaction times, and obviates cooling required with comparable protocols involving achiral reductants.

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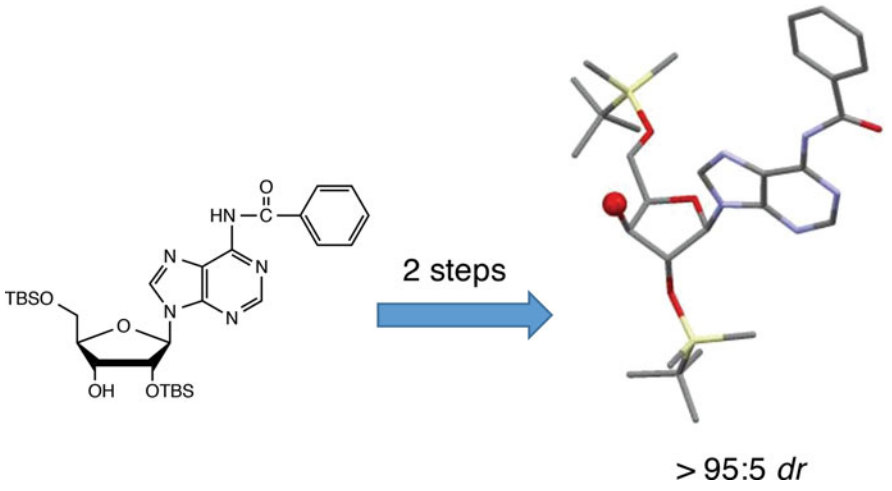
nucleoside analogues; nucleoside drugs and prodrugs; keto-nucleosides; xylo- and arabinofuranosides; Corey-Bakshi-Shibata catalyst; diastereoselective reduction; oxazaborolidine

GRAPHICAL ABSTRACT



Introduction

With deliberate chemical modifications, nucleoside analogs elicit therapeutic effects by inhibition of cancer cell growth and disruption of viral replication.[1,2] Several

CONTACT Ahmed M. Awad ahmed.awad@csuci.edu Department of Chemistry, California State University Channel Islands, One University Drive, Camarillo, CA 93012, USA.
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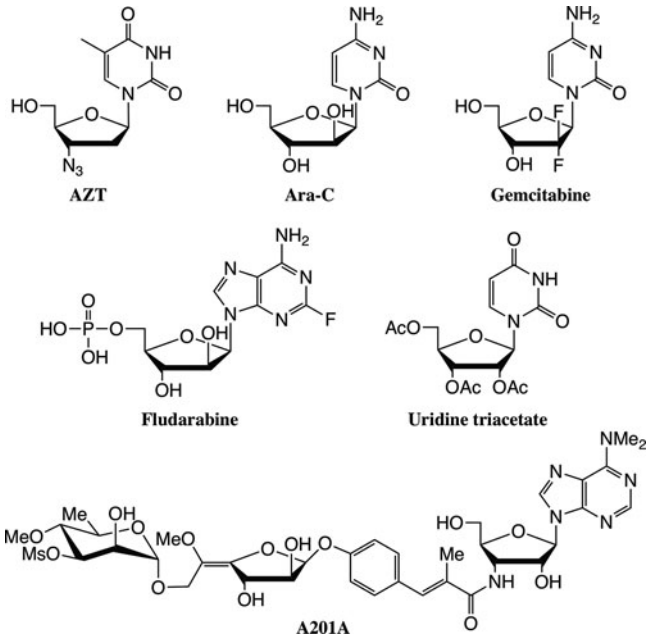


Figure 1. Structures of important nucleoside drugs/prodrugs represent analogs that require specific stereochemistry at the chiral C-2′ and C-3′ positions.

nucleoside drugs and prodrugs have been approved for cytotoxic therapy and for treatment of hepatitis, HIV, and HSV (Figure 1). 3′-azidothymidine (AZT) was the first antiretroviral treatment for HIV and is also used to treat several human cancers.[3] Cytarabine (Ara-C) is an arabinofuranoside currently used for treatment of acute myeloid leukemia.[4] Gemcitabine, another pyrimidine derivative, has activity pertaining to several solid tumors including pancreatic, breast, lung, and ovarian cancers.[5] Fludarabine is a purine analog used for treatment of malignant blood disorders,[5] and most recently, uridine triacetate has been approved for treatment of hereditary orotic aciduria (HOA) and as an antidote for certain types of chemotherapy.[6] A nucleoside antibiotic, A201A, with potent antibacterial activities has also been reported.[7]

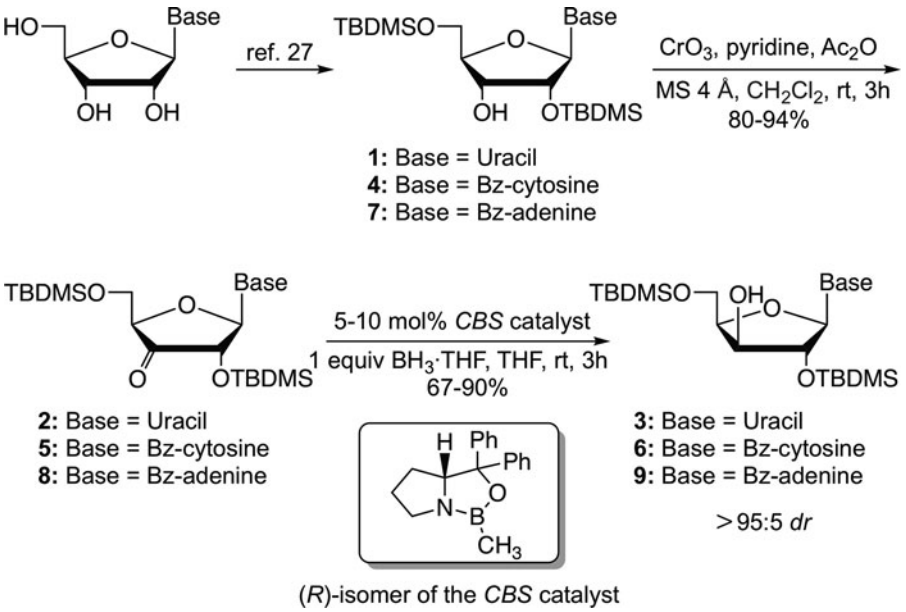
A key step in the synthesis of such analogs is to convert the 2′/3′-hydroxyl groups on the ribose moiety into desired modifications with retention of the configuration. Several approaches have been investigated, including the formation of anhydro intermediate for pyrimidine nucleosides,[8] lyxo-epoxides which can be opened selectively at the C-2′ or C-3′,[9] modification of the D-xylose sugar prior to addition of the nitrogenous base,[10] or reduction of 3′-oxime nucleoside to 3′-hydroxyamino that are subject to a catalytic reduction to form 3′-amino analogs.[11]

The main goal of this work is to develop an efficient and economical route to synthesize xylo- and arabinofuranosides from commercially available ribonucleosides. These molecules may serve as effective precursors for achieving desired stereochemistry at C-2′ and C-3′ positions during further synthesis of important nucleoside analogs such as fluoro-, azido-, and amino derivatives.[12]

Xylofuranosides have also been reported as excellent precursors for the synthesis of potential nucleic acid therapeutics such as guanidine-linked DNA/RNA antisense and antigene therapy[13], N3′→P5′ phosphoramidates/*thio*-phosphoramidates,[14] and xylonucleic acids (XyloNA).[15]

Results and discussion

The methodology in this study involves inversion of configuration at the 2′/3′-positions of ribonucleosides by a two-step process, oxidation to keto-nucleoside followed by diastereoselective reduction of the carbonyl group (Scheme 1). The oxidation/reduction/substitution sequence has been described as an effective route for stereocontrolled synthesis of nucleoside analogs.[16] Robins and co-workers showed that stirring of protected keto-nucleosides with sodium triacetoxyborohydride (generated in situ from sodium borohydride and acetic acid) in acetic acid at low temperature for 48 h resulted in hydride delivery at the α-face with high stereoselectivity.[17] A similar reaction procedure has been applied to synthesize 3′-aminoacylamino-3′-deoxyadenosine, an analog of the antibiotic puromycin.[18] However, the addition and reaction of the keto-nucleoside were carried out at an external cooling bath temperature of 8°C and the reaction was subject to mechanical stirring for 2.5 days. The double inversion strategy to alter the stereochemistry of the 2′/3′-hydroxyl groups was also reported to synthesize 2′-/3′-aspartyl or glutamyl adenosine.[19] Dess–Martin periodinane was used as an oxidant for the conversion of both 2′- and 3′-hydroxyl groups of the ribose into keto-adenosine intermediates. The reduction of the 3′-keto analog with excess $NaBH(OAc)_3$, generated in situ at 0°C, provided the ribo (minor) and xylo (major) diastereomers, as the hydride preferentially attacked



Scheme 1. Synthesis of xylofuranoside derivatives.

the less sterically hindered α-face. The same method was described in the synthesis of the nucleoside antibiotic 5′-*O*-[*N*-(salicyl)sulfamoyl]-adenosine (SAL-AMS) that involves the incorporation of fluorine at the 2′ and 3′ positions.[20] Other optimized protocols to a more efficient stereoselective reduction of keto-nucleosides involved the use of commercial $NaHB(OAc)_3$ in acetonitrile containing a minimal amount of acetic acids. A much shorter reaction time (4 h) was reported, but the reaction proceeded at a very low temperature (−78°C to −18°C).[21] In addition, $NaHB(OAc)_3$ is expensive and required greater quantity (2.4 equivalent) for complete conversion.

To facilitate the diastereoselective reduction of keto-nucleosides, we investigated the use of *Corey-Bakshi-Shibata* oxazaborolidine (CBS) as a catalyst. CBS-oxazaborolidine has been reported as a chiral catalyst that mediates the borane reduction of ketones to secondary alcohols with excellent enantioselestivity.[22] With one stereogenic center, CBS-oxazaborolidine exists as two enantiomers, (*S*)-(−)-2-methyl-CBS-oxazaborolidine and (*R*)-(+)-2-methyl-CBS-oxazaborolidine. The (*S*)-Me-CBS delivers a hydride ion to the *Re* face of the carbonyl, while the (*R)*-Me-CBS delivers the hydride ion to the *Si* face, thus allowing for enantioenriched alcohol formation.[23] The CBS enantioselective reduction is practical, as the preparation of the catalyst is quick, it is easy to handle, and inexpensive reagents are involved.[24] It has been reported that ketones, which are susceptible to noncatalytic reduction by BH_3, can be reduced to chiral alcohols by up to 90% *ee* using electronically tuned-CBS catalyst with BH_3.[25] We utilized the (*R*)-Me-CBS enantiomer of the catalyst to reduce both 2′-keto and 3′-keto nucleosides. This catalytic hydrogenation produced the corresponding arabino and xylo structures for both pyrimidine and purine nucleosides in an excellent yield with high diastereoselectivity (greater than 95:5 *dr*, Figure 2). In addition, the reduction was completed in 2 h at room temperature. These results suggest that our method to stereospecifically

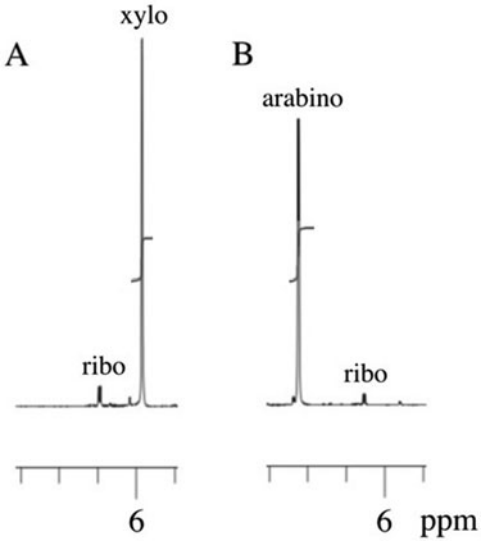


Figure 2. Relative ratio of the ^{1}H-NMR H-1′ signals for the diastereomeric crude mixture of A) compound **9** and B) compound **15**.

reduce keto-nucleosides is more practical and convenient than the reported sodium triacetoxyborohydride protocols.

As shown in Scheme 1, commercially available purine and pyrimidine nucleosides were converted to corresponding xylofuranoside analogs. Adenosine and cytidine were first protected on the exocyclic amino group to produce N^6-benzoyladenosine and N^4-benzoylcytidine, respectively, according to the described method.[26] TBDMS protecting group was then selectively introduced to the C-2′ and C-5′ hydroxyls of uridine, N^4-benzoylcytidine, and N^6-benzoyladenosine to form 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)nucleoside derivatives **1**, **4**, and **7**, respectively.[27] The inversion of configuration at the 3′-position of these compounds was accomplished by oxidation of the C-3′ alcohol followed by CBS-catalyzed enantioselective reduction of the formed ketones. Compounds **1**, **4**, and **7** were treated with 1.5 equivalents of chromium trioxide in a mixture of pyridine and acetic anhydride to form the corresponding 3′-keto nucleoside derivatives **2**, **5**, and **8**, respectively. Initially, the oxidation was carried out using 3.0 equiv of CrO_3 and 6.0 equiv of Ac_2O as previously reported.[11] However, a much higher reaction yield (80% for **8** and >90% for **2** and **5**) was obtained when the reagents were reduced to 1.5 equiv of CrO_3 and 2.0 equiv of Ac_2O. This modified protocol minimized the possibility of a chromium-nucleoside complex formation, and accordingly no need to explore alternative oxidants such as Pfitzner–Moffatt or Dess–Martin periodinane was proposed. We then examined the reduction of the formed carbonyl group using CBS as a chiral catalyst. CBS has been reported as an efficient catalyst during the synthesis of important biomolecules, including the formation of glycosyl α-amino acids synthons by stereocontrolled reduction of glycosyl α-ketoesters,[28] and the synthesis of steroidal glycosides, saundersiosides.[29] However, the catalyst was not effective in the stereoselective preparation of all four isomers of β- and γ-hydroxy α-amino acids,[30] in which enzymatic kinetic resolution was the method of choice.[31] In our study, the enantioselective reduction of the 3′-keto derivatives **2**, **5**, and **8** was performed using the (*R*)-Me-CBS in a 10 mol% and 1 equivalent of BH_3 in anhydrous THF as a solvent. The NMR data of crude mixtures showed that each catalytic chiral reduction afforded the xylofuranose ribonucleosides **3**, **6**, and **9** with a high level of diastereoselectivity (>95:5 *dr*, Figure 2A). High reaction yields were obtained and pure compounds were confirmed by HRMS, ^{1}H NMR, ^{13}C NMR and X-ray crystallography. Figure 3 represents the X-ray structure for compound **9** in which the crystal structure revealed the β-D-xylo configuration. Moreover, to determine the minimum mol% of catalyst required for the diastereoselective reduction of the carbonyl group, 5 mol% of the CBS catalyst was evaluated. The NMR data of the crude product showed that 5 mol% can be used to catalyze the reduction, however, further purification was needed to remove the limited amount of unreacted keto-ribonucleoside derivatives.

The resulting xylofuranosides provide precursor molecules for further modification at C-3′ to synthesize analogs that have potential applications in pharmacotherapeutics. We demonstrated the conversion of the 3′-hydroxy group of compound **9** into an azide via the 3′-*O*-mesylate activation of the alcohol (Scheme 2). The silyl

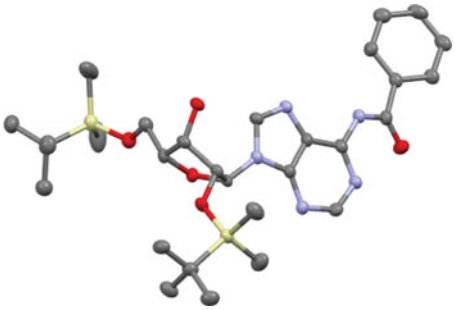
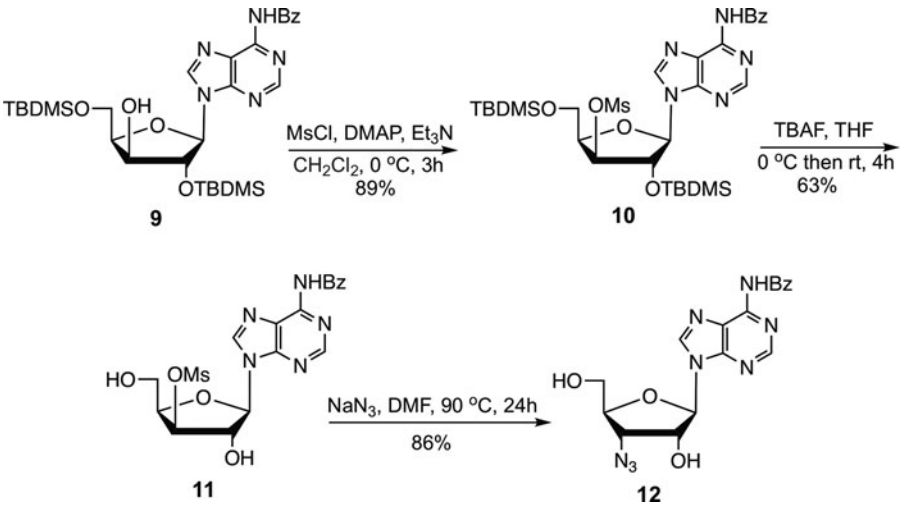


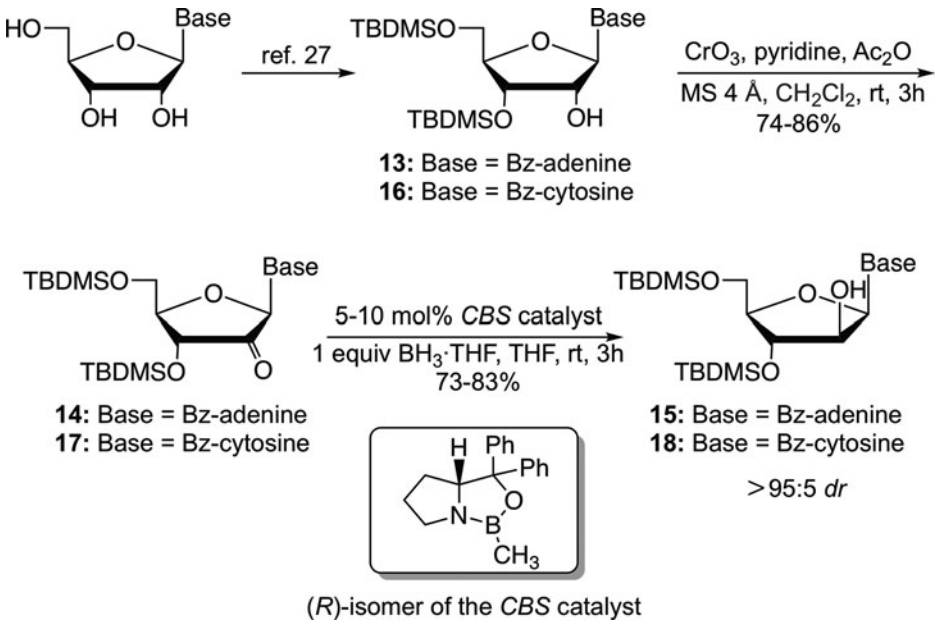
Figure 3. X-ray structure of N^6-benzoyl-9-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl] adenine (**9**).

groups of the mesylated analog **10** were removed with tetrabutylammonium fluoride (TBAF). The deprotected product **11** was subject to an S_N2 nucleophilic attack by azide group using NaN_3 to form the desired azido derivative **12**, which was confirmed by HRMS and its NMR analysis was in agreement with the reported data.[32] This provides an alternative and efficient method to synthesize 3′-azido ribonucleosides, especially with purine nucleosides in which the nucleophilic substitutions on the secondary alcohols are stereochemically challenging.[27]

We applied the CBS-catalyzed diastereoselective reductive approach to produce arabinoside precursors for the synthesis of nucleoside prodrugs vidarabine and cytarabine (Scheme 3). Benzoyl group was used to protect the N^6 and N^4-amino moieties of adenosine and cytidine, respectively. TBDMS was applied to block C-3′ and C-5′ hydroxyls of the ribose sugar resulting in formation of *N*-benzoyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)ribonucleosides **13** and **16**. Oxidation of the latter compounds with CrO_3 in a mixture of pyridine and acetic anhydride afforded the corresponding 2′-keto derivatives **14** and **17**, respectively. When the oxidation was conducted without protection of the amino group on the adenine moiety, it has



Scheme 2. Synthesis of N^6-benzoyl-3′-azido-3′-deoxyadenosine.



Scheme 3. Synthesis of arabinofuranoside derivatives.

been reported that the 2′-keto adenosine derivative exists as an equilibrium mixture of the ketone and its hydrate form. The DFT calculations suggested the origin of the formation of the 2′-ketone hydrate via the internal hydrogen bond network, which was not observed in the 3′-keto isomer.[19] The NMR and HRMS data indicated that this has not been an issue in our case and no ketone hydrate was detected. The electron-withdrawing benzoyl protective group might decrease the electron density of the purine ring, thus reducing the tendency for H-bonding and prevent the formation of the 2′,2′-diol. The diastereoselective hydrogenation of the carbonyl using 10 mol% (*R*)-Me-CBS and 1 equivalent of $BH_3 \cdot THF$ in anhydrous THF afforded the arabinofuranose nucleosides **15** and **18** in a high level of diastereoselectivity (>95:5 *dr*, Figure 2B). Removal of the protecting groups from **15** produces the antiviral nucleoside prodrug, vidarabine (Ara-A) which is used for treatment of HSV,[33] while deprotection of **18** yields the cytotoxic nucleoside prodrug, cytarabine (Ara-C) which is used as a chemotherapy agent in the treatment of acute leukemias.[34]

To examine the extent in which the diastereoselectivity is governed by the chiral catalyst, the reduction of keto-ribonucleosides was carried out in absence of the catalyst as well as by using the (*S*)-Me-CBS-oxazaborolidine enantiomer of the catalyst (Table 1). In contrast to the *R*-CBS, under the same reaction conditions, reductions in the absence of catalyst and by the *S*-CBS enantiomer were comparatively ineffective. While all reactions elicited the xylofuranoside in high diastereomeric ratio (>95:5), only the *R*-CBS enantiomer produced a significantly high total yield. These results indicate that although the hydride preferentially attacks the less sterically hindered α-face of the keto substrate (>95% xylo formation), the stereocontrolled reduction is accomplished and considerably accelerated by the chiral catalyst.

Table 1. Borane reduction of keto-nucleosides **2** and **8** in absence of CBS catalyst and with (*R*) or (*S*)-CBS enantiomers.

compound	CBS catalyst	yield (%)*
3	—	36
3	*R*	90
3	*S*	42
9	—	22
9	*R*	67
9	*S*	25

*all reactions produced the corresponding xylofuranoside in *dr* > 95:5

Conclusion

In summary, we have developed an economical and efficient method for the diastereopure synthesis of arabino and xylofuranosides using the CBS chiral catalyst to reduce the corresponding keto-ribonucleosides. Our method has proven successful in both pyrimidine and purine nucleosides, providing a facile solution to achieve desired stereochemistry in nucleoside drug/prodrug design that contributes to a wide range of medicinal and biological applications. Moreover, this approach would be particularly useful in the commercial scale manufacturing of nucleoside analogs, in which the commercially available starting materials are considerably expensive. Furthermore, we applied this method in the synthesis of current pharmaceuticals, vidarabine and cytarabine. We believe that this method may serve biomedical science as an efficient approach to synthesize nucleoside building blocks for antigene and antisense therapeutics.

Experimental

General procedures

^{1}H and ^{13}C NMR spectra were recorded on a 500MHz Varian instrument using $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and coupling constants (J) are given in Hz. Thin layer chromatography (TLC) was carried out on Silica Gel 60 F_{254} pre-coated plates and visualization of the products was performed under UV light. Silica gel used for column chromatography was Scientific Silica Gel (particle size 0.035–0.070 mm). ESI mass spectra were recorded on Micromass QTOF2 Quadrupole/Time of Flight Tandem mass spectrometer with Turbo Ion Spray ionization source. X-ray Crystallography was measured at 100K with Cu K-alpha radiation. The data collection and cell determination was done by Bruker Apex II software. Program Shelx were used for the structure determination and refinements. All reactions were performed under nitrogen atmosphere using anhydrous solvents.

General procedure for oxidation of compounds (1), (4), and (7). Pyridine (18.0 mmol) was added dropwise to a mixture of CrO_3 (9.0 mmol) and molecular sieves 4 Å beads (5 g) in CH_2Cl_2 (25 mL) at 0°C. After 30 min Ac_2O (12.0 mmol)

was added and the mixture was stirred at 0°C for another 15 min. To this mixture was added a solution of the protected nucleoside **1**, **4**, or **7** (6.0 mmol) in CH_2Cl_2 (15 mL) at room temperature. After the mixture was stirred at room temperature for further 3 h, the reaction mixture was poured into EtOAc (250 mL) and stirred for 40 min at room temperature. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to dryness. The crude was then redissoved in EtOAc, washed with 5% $NaHCO_3$, and dried over anhydrous Na_2SO_4. The mixture was then concentrated under reduced pressure and purified by silica gel column chromatography (30% ethyl acetate in hexanes for **2**, and 40% ethyl acetate in hexanes for **5** and **8**) to afford pure compounds **2**, **5**, and **8**, respectively.

1-[2′,5′-Bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuran-3′-ulosyl]uracil (**2**) (94% yield) as a white foam. HRMS (ESI) m/z Calcd for $C_{21}H_{38}N_2O_6NaSi_2$ $(M+Na)^+$ 493.2166, found 493.2148. ^{1}H NMR (500 MHz, $CDCl_3$) 9.18 s, 1H (NH); 7.83 d, 1H, $J = 7.8$ (H-6); 6.26 d, 1H, $J = 7.8$ (H-1′); 5.8 d, 1H, $J = 7.8$ (H-5); 4.23 s, 1H (H-2′); 4.16 d, 1H, $J = 7.8$ (H-4′); 3.91–3.90 m, 2H, (H-5′); 0.89 s, 9H, ($SiC(CH_3)_3$); 0.85 s, 9H ($SiC(CH_3)_3$); 0.09 s, 3H ($SiCH_3$); 0.08 s, 3H ($SiCH_3$); 0.05 s, 3H ($SiCH_3$); −0.004 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz, $CDCl_3$) 208.3, 162.7, 150.2, 139.0, 103.7, 84.8, 81.9, 62.8, 25.7, 25.4, 18.2, 18.1, −4.8, −5.4, −5.6, −5.8.

N^4-Benzoyl-1-[2′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuran-3′-ulosyl]cytosine (**5**) (92% yield) as a white foam. HRMS (ESI) m/z Calcd for $C_{28}H_{43}N_3O_6NaSi_2$ $(M+Na)^+$ 596.2588, found 596.2566. ^{1}H NMR (500 MHz, $CDCl_3$) 8.75 s, 1H (NH); 8.22 d, 1H $J = 7.3$ (H-6); 7.92–7.51 m, 6H (BzH and H-5); 6.43 d, 1H $J = 7.9$ (H-1′); 4.28 br s, 1H (H-2′); 4.21 d, 1H $J = 7.3$ (H-4′); 3.98–3.92 m, 2H (H-5′); 0.91 s, 9H ($SiC(CH_3)_3$); 0.85 s, 9H ($SiC(CH_3)_3$); 0.11 s, 3H ($SiCH_3$); 0.07 s, 3H ($SiCH_3$); 0.04 s, 3H ($SiCH_3$); 0.00 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz, $CDCl_3$) 208.4, 133.4, 129.1, 127.6, 86.3, 82.0, 78.7, 62.8, 25.8, 25.4, 18.2, 18.2, 0.0, −4.9, −5.4, −5.5, −5.7.

N^6-Benzoyl-9-[2′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuran-3′-ulosyl]adenine (**8**) (80% yield) as a pale yellow foam. HRMS (ESI) m/z Calcd for $C_{29}H_{43}N_5O_5NaSi_2$ $(M+Na)^+$ 620.2700, found 620.2675. ^{1}H NMR (500 MHz, $CDCl_3$) 9.12 s, 1H (NH); 8.82 s, 1H (H-8); 8.36 s, 1H (H-2); 8.05–7.52 m, 5H (BzH); 6.23 d, 1H, $J = 8.3$ (H-1′); 4.94 d, 1H, $J = 7.8$ (H-2′); 4.33 br s, 1H (H-4′); 4.01–3.96 m, 2H (H-5′); 0.92 s, 9H ($SiC(CH_3)_3$); 0.72 s, 9H ($SiC(CH_3)_3$); 0.11 s, 3H ($SiCH_3$); 0.08 s, 3H ($SiCH_3$); −0.01 s, 6H (($Si(CH_3)_2$); ^{13}C NMR (500 MHz, $CDCl_3$) 208.2, 140.9, 132.8, 128.9, 127.9, 85.2, 82.5, 77.9, 62.4, 25.6, 23.8, 21.0, 18.3, 18.0, 14.2, −4.8, −5.5, −5.6.

General procedure for CBS reduction of compounds (2), (5), and (8). To a solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst (0.019 g, 0.067 mmol) in THF (0.5 mL) was added BH_3, 1 M in THF (0.670 mL, 0.670 mmol). The resulting solution was stirred for 30 min. A solution of **2**, **5**, or **8** (0.670 mmol) in THF (1.0 mL) was then added dropwise over 30 min., and the resulting solution was stirred at room temperature for 3 hours. The reaction was cooled on ice and quenched with 1 mL of methanol. After concentration under reduced pressure, the residue was purified by

silica gel column chromatography (25% ethyl acetate in hexanes for **3**, and 40% ethyl acetate in hexanes for **6** and **9**) to afford pure compounds **3**, **6**, and **9**, respectively.

1-[2′,5′-Bis-O-(tert-butyldimethylsilyl)-β-D-xylofuranosyl]uracil (**3**) (90% yield) as a white foam. HRMS (ESI) m/z Calcd for $C_{21}H_{40}N_2O_6NaSi_2$ $(M+Na)^+$ 495.2323, found 495.2310. ^{1}H NMR (500 MHz, $CDCl_3$) 8.86 s, 1H (NH); 7.90 d, 1H, $J = 8.3$ (H-6); 5.73 s, 1H (H-1′); 5.62 d, 1H, $J = 8.3$ (H-5); 4.45 d, 1H, $J = 1.5$ (OH-3′); 4.31–4.19 m, 2H, (H-5′); 4.20 br s, 1H (H-2′); 4.17 br s, 1H (H-3′); 4.15 br s, 1H (H-4′); 0.92 s, 9H ($SiC(CH_3)_3$); 0.88 s, 9H ($SiC(CH_3)_3$); 0.16 s, 3H ($SiCH_3$); 0.15 s, 3H ($SiCH_3$); 0.14 s, 3H ($SiCH_3$); 0.11 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz, $CDCl_3$) 163.4, 150.2, 140.9, 101.0, 92.3, 81.9, 80.7, 78.4, 62.9, 25.7, 25.6, 18.0, 17.9, 0.0, −4.8, −5.2, −5.6, −5.8.

N^4-Benzoyl-1-[2′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-xylofuranosyl]cytosine (**6**) (75% yield) as a white foam. HRMS (ESI) m/z Calcd for $C_{28}H_{45}N_3O_6NaSi_2$ $(M+Na)^+$ 598.2745, found 598.2716. ^{1}H NMR (500 MHz, $CDCl_3$) 9.36 s, 1H (NH); 8.30 d, 1H, $J = 7.4$ (H-6); 7.97–7.49 m, 5H (BzH); 7.43 d, 1H, $J = 7.4$ (H-5); 6.04 d, 1H, $J = 8.8$ (H-1′); 5.75 br s, 1H (OH-3′); 4.34 d, 1H, $J = 3.4$ (H-3′); 4.17 d, 1H, $J = 8.8$ (H-2′); 4.09 br s, 1H (H-4′); 4.01–3.96 m, 2H (H-5′); 0.89 s, 9H ($SiC(CH_3)_3$); 0.88 s, 9H ($SiC(CH_3)_3$); 0.12 s, 3H ($SiCH_3$); 0.07 s, 3H ($SiCH_3$); 0.06 s, 3H ($SiCH_3$); 0.04 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz, $CDCl_3$) 153.9, 128.8, 127.2, 123.2, 100.9, 83.5, 81.9, 81.5, 81.1, 78.4, 75.0, 62.9, 62.7, 41.0, 25.8, 25.5, 25.4, 18.2, 18.1, 0.0, −4.6, −5.3, −5.6, −5.8.

N^6-Benzoyl-9-[2′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-xylofuranosyl]adenine (**9**) (67% yield) as a pale yellow foam. HRMS (ESI) m/z Calcd for $C_{29}H_{45}N_5O_5NaSi_2$ $(M+Na)^+$ 622.2857, found 622.2827. ^{1}H NMR (500 MHz, $CDCl_3$): 9.03 s, 1H (NH); 8.80 s, 1H (H-8); 8.30 s, 1H (H-2); 8.30–7.54 m, 5H (BzH); 5.97 d, 1H, $J = 0.90$ (H-1′); 5.60 d, 1H, $J = 6.3$ (OH-3′); 4.50 br s, 1H (H-2′); 4.28 q, 1H, $J = 3.9$ (H-3′); 4.18 d, 1H, $J = 3.9$ (H-4′); 4.25–4.07 m, 2H (H-5′); 0.90 s, 9H ($SiC(CH_3)_3$); 0.90 s, 9H ($SiC(CH_3)_3$); 0.10 s, 3H ($SiCH_3$); 0.09 s, 3H ($SiCH_3$); 0.08 s, 3H ($SiCH_3$); −0.004 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz, $CDCl_3$) 164.5, 152.3, 150.8, 149.7, 142.6, 132.8, 128.9, 127.8, 92.2, 83.1, 82.3, 78.2, 62.3, 26.0, 25.8, 25.6, 25.6, 18.3, 17.9, −4.8, −4.9, −5.4, −5.5.

N^6-Benzoyl-9-[2′,5′-bis-O-(tert-butyldimethylsilyl)-3′-O-mesyl-β-D-xylofuranosyl]adenine (**10**). To a solution of **9** (1.2 g, 2.0 mmol) in anhydrous methylene chloride (20 mL) were added DMAP (0.12 g, 1.0 mmol) and Et_3N (2.8 mL, 20 mmol). The mixture was cooled to 0°C for 15 min. MsCl (0.4 mL, 5.0 mmol) was added dropwise and the mixture was stirred under N_2 at 0°C for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude mixture was purified by silica gel column chromatography (50% ethyl acetate in hexanes) to afford compound **10** (1.2 g, 89%). HRMS (ESI) m/z Calcd for $C_{30}H_{48}SSi_2N_5O_7$ $(M+H)^+$ 678.2813, found 678.2843. ^{1}H NMR (500 MHz, $CDCl_3$): 9.18 s, 1H (NH); 8.72 s, 1H (H-8); 8.27 s, 1H (H-2); 8.00–7.45 m, 5H (BzH); 6.20 d, 1H, $J = 1.40$ (H-1′); 4.95 t, 1H, $J = 2.4$ (H-3′); 4.84 t, 1H $J = 2.0$ (H-2′); 4.54 q, 1H,

$J = 3.9$ (H-4′); 3.54–4.20 m, 2H, (H-5′); 2.94 s, 3H (SCH_3); 0.90 s, 9H ($SiC(CH_3)_3$); 0.88 s, 9H ($SiC(CH_3)_3$); 0.11 s, 3H ($SiCH_3$); 0.10 s, 3H ($SiCH_3$); 0.09 s, 3H ($SiCH_3$); 0.06 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz, $CDCl_3$) 164.6, 152.8, 151.7, 149.4, 142.6, 140.8, 132.8, 132.7, 128.9, 127.8, 90.2, 83.1, 82.0, 81.2, 79.8, 78.2, 62.2, 60.2, 38.2, 31.5, 25.9, 25.8, 25.6, 25.5, 18.3, 17.8, −4.9, −5.0, −5.2, −5.3.

N^6-Benzoyl-9-(3′-O-mesyl-β-D-xylofuranosyl)adenine (**11**). To a solution of **10** (1.00 g, 1.48 mmol) in anhydrous THF (10 mL), tetra-n-butylammonium fluoride (1M in THF, 3.75 mL, 3.75 mmol) was added dropwise over 30 min at 0°C and the mixture was stirred under N_2 at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was re-suspended in EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The crude mixture was purified by silica gel column chromatography (10% methanol in ethyl acetate) to afford white crystals of pure compound **11** (0.42 g, 63%). HRMS (ESI) m/z Calcd for $C_{18}H_{20}O_7N_5S$ $(M+H)^+$ 450.1083, found 450.1071. ^1H NMR (500 MHz, DMSO): 11.24 s, 1H (NH); 8.77 s, 1H (H-8); 8.52 s, 1H (H-2); 7.65–7.52 m, 5H (BzH); 6.49 d, 1H, $J = 4.9$ (H-1′); 5.19 d, 1H, $J = 4.9$ (OH-2′); 5.15 t, 1H, $J = 4.9$ (OH-5′); 4.90 t, 1H, $J = 3.4$ (H-3′); 4.55 d, 1H, $J = 2.5$ (H-2′); 4.44 q, 1H, $J = 4.8$ (H-4′); 3.52–3.76 m, 2H, (H-5′); 3.27 s, 3H (SCH_3); ^{13}C NMR (500 MHz, DMSO) 166.1, 152.3, 150.9, 142.7, 132.9, 128.9, 126.0, 88.4, 83.1, 81.8, 80.9, 77.8, 61.3, 59.5, 59.1, 58.2, 55.4, 38.1.

N^6-Benzoyl-3′-azido-3′-deoxyadenosine (**12**). To a solution of **11** (0.25 g, 0.56 mmol) in anhydrous DMF (3 mL), sodium azide (0.29 g, 4.48 mmol) was added and the reaction mixture was heated under N_2 at 90°C for 24 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (5% methanol in ethyl acetate) to afford compound **12** (0.19 g, 86%). HRMS (ESI) m/z Calcd for $C_{17}H_{17}O_4N_8$ $(M+H)^+$ 397.1373, found 397.1367. ^1H NMR (500 MHz, DMSO): 11.21 s, 1H (NH); 8.26 s, 1H (H-8); 8.11 s, 1H (H-2); 7.48–7.99 m, 5H (BzH); 5.91 d, 1H, $J = 4.9$ (H-1′); 4.95 t, 1H, $J = 5.4$ (H-3′); 4.57 d, 1H, $J = 4.9$ (H-2′); 4.28 q, 1H, $J = 4.8$ (H-4′); 3.62–3.70 m, 2H, (H-5′).

*General procedure for oxidation of compounds (**13**) and (**16**).* Pyridine (18.0 mmol) was added dropwise to a mixture of CrO_3 (9.0 mmol) and molecular sieves 4 Å beads (5 g) in CH_2Cl_2 (25 mL) at 0°C. After 30 min Ac_2O (12.0 mmol) was added and the mixture was stirred at 0°C for another 15 min. To this mixture was added a solution of the protected nucleoside **13** or **16** (6.0 mmol) in CH_2Cl_2 (15 mL) at room temperature. After the mixture was stirred at room temperature for further 3 h, the reaction mixture was poured into EtOAc (250 mL) and stirred for 40 min at room temperature. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to dryness. The crude was redissoved in EtOAc, washed with 5% $NaHCO_3$, and dried over anhydrous Na_2SO_4. The mixture was then concentrated under reduced pressure and purified by silica gel column chromatography (40% ethyl acetate in hexanes for **14**, and 30% ethyl acetate in hexanes for **17**) to afford pure compounds **14** and **17**, respectively.

N^6-Benzoyl-9-[3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuran-2′-ulosyl]adenine (**14**) (74% yield) as a pale yellow foam. HRMS (ESI) m/z Calcd for $C_{29}H_{43}N_5O_5NaSi_2$ $(M+Na)^+$ 620.2700, found 620.2675. ^{1}H NMR (500 MHz, $CDCl_3$) 9.07 s, 1H (NH); 8.69 s, 1H (H-8); 8.05 s, 1H (H-2); 8.01–7.51 m, 5H (BzH); 5.89 s, 1H (H-1′); 5.20 d, 1H, $J = 8.8$ (H-3′); 4.12–3.80 m, 3H (H-4′ and H-5′); 0.95 s, 9H ($SiC(CH_3)_3$); 0.82 s, 9H ($SiC(CH_3)_3$); 0.25 s, 3H ($SiCH_3$); 0.21s, 3H ($SiCH_3$); 0.02 s, 3H ($SiCH_3$); −0.09 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz, $CDCl_3$) 207.0, 152.9, 142.2, 132.8, 128.9, 127.9, 80.5, 80.1, 71.5, 61.0, 26.0, 25.7, 25.7, 25.6, 18.3, 18.2, −4.3, −5.2, −5.4, −5.5.

N^4-Benzoyl-1-[3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuran-2′-ulosyl]cytosine (**17**) (86% yield) as a white foam. HRMS (ESI) m/z Calcd for $C_{28}H_{43}N_3O_6NaSi_2$ $(M+Na)^+$ 596.2588, found 596.2564. ^{1}H NMR (500 MHz, $CDCl_3$) 8.80 s, 1H (NH); 7.88 br s, 1H (H-6); 7.63–7.50 m, 5H (BzH); 7.49 s, 1H (H-5); 5.25 s, 1H (H-1′); 4.79 d, 1H $J = 7.8$ (H-3′); 4.03–3.95 m, 3H (H-4′ and H-5′); 0.92 s, 9H ($SiC(CH_3)_3$); 0.90 s, 9H ($SiC(CH_3)_3$); 0.20 s, 3H ($SiCH_3$); 0.16 s, 3H ($SiCH_3$); 0.07 s, 6H ($Si(CH_3)_2$); ^{13}C NMR (500 MHz, $CDCl_3$) 205.8, 133.4, 133.2, 129.1, 127.5, 100.1, 89.8, 86.1, 82.7, 82.4, 71.0, 70.9, 63.1, 60.3, 26.0, 25.9, 25.7, 18.5, 18.4, 18.2, 18.0, −4.3, −5.2, −5.3, −5.5.

General procedure for CBS reduction of compounds (14) and (17). To a solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst (0.019 g, 0.067 mmol) in THF (0.5 mL) was added BH_3, 1 M in THF (0.670 mL, 0.670 mmol). The resulting solution was stirred for 30 min. A solution of **14** or **17** (0.670 mmol) in THF (1.0 mL) was then added dropwise over 30 min., and the resulting solution was stirred at room temperature for 3 hours. The reaction was cooled on ice and quenched with 1 mL of methanol. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (40% ethyl acetate in hexanes) to afford pure compounds **15** and **18**, respectively.

N^6-Benzoyl-9-[3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-arabinofuranosyl] adenine (**15**) (73% yield) as a pale yellow foam. HRMS (ESI) m/z Calcd for $C_{29}H_{45}N_5O_5NaSi_2$ $(M+Na)^+$ 622.2857, found 622.2836. ^{1}H NMR (500 MHz, $CDCl_3$): 9.12 s, 1H (NH); 8.80 s, 1H (H-8); 8.47 s, 1H (H-2); 8.04–7.50 m, 5H (BzH); 6.45 d, 1H, $J = 2.5$ (H-1′); 4.80 d, 1H $J = 10.3$ (OH-2′); 4.35 br s, 1H (H-2′); 4.14–4.11 m, 2H (H-3′ and H-4′); 4.00–3.82 m, 2H (H-5′); 0.95 s, 9H ($SiC(CH_3)_3$); 0.94 s, 9H ($SiC(CH_3)_3$); 0.16 s, 6H ($Si(CH_3)_2$); 0.15 s, 6H ($Si(CH_3)_2$); ^{13}C NMR (500 MHz, $CDCl_3$) 164.6, 152.6, 151.7, 149.2, 142.8, 133.8, 132.7, 128.8, 127.9, 86.3, 85.5, 78.1, 76.3, 63.3, 25.9, 25.8, 18.4, 18.0, 0.0, −4.6, −4.9, −5.4, −5.7.

N^4-Benzoyl-1-[3′,5′-bis-O-(tert-butyldimethylsilyl)-β-D-arabinofuranosyl] cytosine (**18**) (83% yield) as a white foam. HRMS (ESI) m/z Calcd for $C_{28}H_{45}N_3O_6NaSi_2$ $(M+Na)^+$ 598.2745, found 598.2723. ^{1}H NMR (500 MHz, $CDCl_3$) 9.26 s, 1H (NH); 7.81 d, 1H, $J = 7.3$ (H-6); 7.59–7.42 m, 6H (BzH and H-5); 6.20 d, 1H, $J = 3.9$ (H-1′); 4.34 br s, 1H (H-3′); 4.22 t, 1H, $J = 9.8$ (H-2′); 4.00 br s, 1H (H-4′); 3.98–3.80 m, 2H (H-5′); 0.95 s, 9H ($SiC(CH_3)_3$); 0.89 s, 9H ($SiC(CH_3)_3$); 0.016 s, 6H ($Si(CH_3)_2$); 0.13 s, 3H ($SiCH_3$); 0.10 s, 3H ($SiCH_3$); ^{13}C NMR (500 MHz,

$CDCl_3$) 162.5, 145.9, 133.4, 133.1, 131.9, 128.9, 128.6, 128.3, 127.4, 127.3, 87.8, 85.5, 84.4, 77.4, 76.0, 62.4, 25.9, 25.7, 18.4, 18.0, −4.4, −5.0, −5.4, −5.5.

Conflicts of interest

The authors declare no conflict interest.

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