Abstract: An improved protocol for the transformation of ribonucleosides into 2′,3′-dideoxynucleoside and 2′,3′-didehydro-2′,3′-dideoxynucleoside derivatives, including the anti-HIV drugs stavudine (d4T), zalcitabine (ddC) and didanosine (ddI), was established. The process involves radical deoxygenation of xanthate using environmentally friendly and low-cost reagents. Bromoethane or 3-bromopropanenitrile was the alkylating agent of choice to prepare the ribonucleoside 2′,3′-bissxanthates. In the subsequent radical deoxygenation reaction, tris(trimethylsilyl)silane and 1,1′-azobis(cyclohexanecarbonitrile) were used to replace hazardous Bu₃SnH and AIBN, respectively. In addition, TBAF was substituted for camphorsulfonic acid in the deprotection step of the 5′-O-silyl ether group, and an enzyme (adenosine deaminase) was used to transform 2′,3′-didehydroadenosine into 2′,3′-dideoxyinosine (ddI) in excellent yield.

Keywords: 2′,3′-dideoxynucleosides; 2′,3′-didehydro-2′,3′-dideoxynucleosides; synthesis; zalcitabine (ddC); didanosine (ddI); stavudine (d4T)

1. Introduction

Emerging viruses continue to be a global threat to human health. During the past 25 years, human immunodeficiency virus (HIV), the cause of AIDS, reached virtually every corner of the globe, with 680,000 dying of HIV-related illnesses worldwide in 2020 [1]. More than two-thirds of people infected with HIV live in Asia and Africa. Despite substantial progress in the development of anti-HIV drugs, only 20% of low- and middle-income countries in need of these drugs are receiving them. Among the different anti-HIV chemotherapeutic agents known, the Nucleoside Reverse Transcriptase Inhibitors (NRTI, Figure 1) represent an important class.

Since Mitsuya et al. [2] identified 3′-azido-2′,3′-dideoxythymidine (zidovudine, AZT) as a potent antiviral agent against HIV-1, other nucleoside derivatives showing activity against this virus, such as ddl, ddC, d4T, 3TC, FTC, ABV and TDF, have been successfully developed [3,4]. Most of these compounds are 2′,3′-dideoxynucleosides or 2′,3′-didehydro-2′,3′-dideoxynucleosides and are characterized by lacking hydroxyl groups at the 2′- and 3′-positions.

Various methodologies are reported in the literature for the synthesis of the title compounds. These protocols require formation of the glycosidic bonds [5–11], the Eastwood procedure [12,13], the Corey–Winter synthesis [14–18], the Barton–McCombie deoxygenation [16,19–22], the Garegg–Samuelsson reaction [23], photoinduced deoxygenations [24,25], reductive elimination [13,26–35], or metathesis reaction [36,37]. However, careful review of the literature indicated that the majority of these protocols are not amenable for large-scale production to meet the global demand of antiviral nucleosides. Particularly, some of the...
methods described involve difficult control of diastereoselectivity in glycosidic bond formation, reagents that are expensive or not environmentally friendly, or partial nucleoside decomposition with loss of the pyrimidine base.

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{T} & \quad \text{N}_3 \\
\text{Zidovudine (AZT)} & \\
\text{HO} & \quad \text{O} & \quad \text{B} \\
\text{B} = \text{Hypoxanthine} & \quad \text{Didanosine (ddI)} & \quad \text{B} = \text{C} & \quad \text{Zalcitabine (ddC)} & \quad \text{B} = \text{C} & \quad \text{Lamivudine (3TC)} & \quad \text{B} = 5\text{-FC} & \quad \text{Emtricitabine (FTC)}
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{OH} \\
\text{Stavudine (d4T)} & \\
\text{HO} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{NH}_2 \\
\text{Abacavir (ABV)} & \\
\text{HO}_2\text{C} & \quad \text{C} & \quad \text{CO}_2\text{H} \\
\text{Tenofor visopropyl fumarate (TDF)}
\end{align*}
\]

\textbf{Figure 1.} Several approved NRTIs against HIV.

Considering the ongoing challenge of HIV infections in underdeveloped countries, among NRTIs, ddI, ddC and d4T are the most affordable drugs for poor patient populations in Asia and Africa. Our objective is to develop improved protocols that are simple, inexpensive, safe and industrially benign for the large-scale syntheses of these three nucleoside derivatives and their analogs, with different heterocyclic bases. For that purpose, we develop a procedure that involves a Barton–McCombie deoxygenation and the use of commercial ribonucleosides as starting materials.

\section*{2. Results and Discussion}

The selective removal of the hydroxyl groups at the 2\(^\prime\)- and 3\(^\prime\)-positions of the ribonucleoside requires appropriate protection of the 5\(^\prime\)-OH group. Due to prior experience in our group \cite{38,39}, we decided to carry out the regioselective enzymatic acylation of the primary hydroxyl with acetonoxime levulinate as an acylating agent and \textit{Candida antarctica} lipase B (CAL-B) as the catalyst. The reactions were performed in THF at 250 rpm, varying the number of equivalents of the acyl donor, the temperature and the substrate concentration, depending on the starting nucleoside (Scheme 1).

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{B} & \quad \text{HO} \\
\text{1} & & \text{HO} & \quad \text{B} & \quad \text{HO} \\
& \quad \text{CAL-B, THF} & \text{250 rpm} & \rightarrow & \quad \text{LevO} \\
\text{B} & \text{= U (a), T (b), C (c), C\text{\textsuperscript{5\prime}} (d), A (e), Hypoxanthine (f)}
\end{align*}
\]

\textbf{Scheme 1.} Regioselective enzymatic acylation of 1.

Enzymatic acylation of \(\beta\)-D-uridine (1a) and \(\beta\)-D-5-methyluridine (1b) with 3 equiv of acetonoxime levulinate at 30 °C in the presence of CAL-B afforded the 5\(^\prime\)-O-levuliny esters 2a and 2b with excellent regioselectivity and high yields in short reaction times (entries 1 and 2, Table 1). However, the reaction with \(\beta\)-D-cytidine (1c) is slower, and complete conversion is not achieved, despite using long reaction times, 55 °C instead 30 °C, more dilute conditions, a large excess of acylating agent (9 vs. 3 equiv), and a higher ratio of 1c:CAL-B, 1:2 (w/w). This resulted in the undesired acylation of the secondary hydroxyl
group (entry 3, Table 1). The low reactivity was attributed to the poor solubility of the starting nucleoside in the reaction mixture. Next, the enzymatic acylation reaction of the base-protected cytidine was attempted. A complete conversion was observed when the same process was carried out with Nβ-benzoyl-β-D-xylopyranosyluridine (1d), giving rise to the acylated derivative 2d, with total selectivity and 93% yield (entry 4, Table 1). A moderate selectivity and absence of complete conversion was also observed when the substrate was adenosine (1e), which was attributed to the low solubility of this compound in the reaction medium (entry 5, Table 1). In the case of inosine (1f), 90 h of reaction time was needed to achieve complete conversion, and although the formation of other acylation products occurred in a low ratio (entry 6, Table 1), compound 2f was obtained in low yield after column chromatography purification.

Table 1. Regioselective enzymatic acylation of ribonucleosides 1.

| Entry | Substrate | T (°C) | conc (M) | t (h) | 1 (%) | 2 (%) | Other Acylated Compounds (%) |
|-------|-----------|--------|----------|-------|-------|-------|-----------------------------|
| 1     | 1a        | 30     | 0.1      | 2     | -     | >97   | (80)                        |
| 2     | 1b        | 30     | 0.1      | 2.5   | -     | >97   | (78)                        |
| 3     | 1c        | 55     | 0.025    | 54    | 26    | 53    | (50)                        |
| 4     | 1d        | 55     | 0.025    | 24    | -     | >97   | (93)                        |
| 5     | 1e        | 55     | 0.025    | 48    | 10    | 70    | (42)                        |
| 6     | 1f        | 55     | 0.025    | 90    | -     | 87    | (40)                        |

*a* Based on 1H-NMR signal integration. b Percentage of isolated yields are given in parenthesis. c 3 equiv of acetonoxime levulinate and ratio 1:CAL-B, 1:1 (w/w). d 9 equiv of acetonoxime levulinate and ratio 1:CAL-B, 1:2 (w/w).

Next, transformation of the 5’-O-levulinyl ribonucleoside 2a into the corresponding bisxanthate was carried out by reaction with carbon disulfide followed by alklylation with bromoethane, a safer and cheaper reagent than other alkylating agents previously used, such as iodomethane or 3-bromopropanenitrile (Scheme 2) [16]. However, the desired bisxanthate 3a was obtained in a low 25% yield because compound 4a, resulting from the reaction at the primary hydroxyl, which was deprotected under the reaction conditions (NaOH 5 M), was formed as a by-product. Although different bases (inorganic: t BuOK, K2CO3; organic: DIPEA, DBU) were studied as alternatives, the appropriate conditions to carry out the reaction were not found, and the levulinyl group was not pursued as protecting group for the 5’-position.

![Scheme 2](image)

Scheme 2. Transformation of 5’-O-Lev-uridine into bisxanthates.

Therefore, we elected 5’-O-tert-butyldimethylsilyl (TBS) as the protecting group of choice due to low cost, high regioselectivity and stability during base treatment. Various ribonucleosides 1 were regioselectively protected at the primary hydroxyl as silyl ethers by treatment with TBSCI and imidazole in DMF for 12 h at room temperature (Scheme 3), furnishing the 5’-O-TBS protected nucleosides 5 in high to excellent yields (Table 2). TBS-protected nucleosides 5 were pure enough to carry forward into the next step without further purification by column chromatography. Next, the conversion of 5 to 6 was carefully optimized using the correct combination of the solvent, base, and reaction temperature. The ideal reaction condition calls for the reaction of 5 with CS2 in the presence of 3 M aqueous NaOH solution and DMF as solvent for 30 min at 0 °C, and subsequent in situ
alkylation with bromoethane for 20 min, affording bisxanhtanes 6a–f in high yields. It is important to note that compounds 6 were isolated with suitable purity by thorough washing with heptane, avoiding chromatographic purification. We expect the two-step simple chromatography-free protocol for the synthesis of bisxanhtanes 6a–f will be conducive for scale-up.

Scheme 3. Synthesis of 2′,3′-didehydro-2′,3′-dideoxyxynucleosides and 2′,3′-dideoxyxynucleosides. Synthesis of d4T, ddC and ddI. Reagents and conditions: (a) TBSCI, imidazole, DMF, rt, 12 h; (b) (1) CS2, 3 M NaOH, DMF, 0 °C, 30 min; (2) EtBr, 0 °C → rt, 20 min; (c) Method A: Bu3SnH, AIBN, MeCN, reflux, 1 h; Method B: (Me3Si)3SiH, ACHN, MeCN, reflux, 1 h (7a,b,d,e) or 6 h (7f); (d) Method A: TBAF, THF, 0 °C → rt, 1 h; Method B: (–)-CSA, MeOH, 0 °C → rt, 1 h; (e) H2, 10% Pd-C, MeOH, rt, 2 h.

Table 2. Reaction yields of 5, 6, 7, 8 and 9.

| B   | 1→5 | 5→6 | 6→7 | 7→8 | TBAF | (–)-CSA | 8→9 |
|-----|-----|-----|-----|-----|------|---------|-----|
| a = U | 93  | 82  | 60  | 65  | 95   | 92      | 82  |
| b = T | 85  | 81  | 60  | 75  | 90   | 95      | 87  |
| c = C | 91  | 75  | 35  | ND  | -    | -       | 70  |
| d = C\textsuperscript{Bz} | 80  | 72  | 60  | 40  | 90   | ND      | -   |
| e = A | 85  | 90  | 60  | 77  | 95   | ND      | 88  |
| f = Hypoxanthine | 80  | 70  | ND  | 80  | 75   | ND      | 80  |

\* From 8d. \* See Scheme 4. ND, not the desired product. -, reaction not performed.

Scheme 4. Synthesis of Zalcitabine (ddC) from 8d.

Next, we tested the reduction of Bisxanhtanes 6 using conventional conditions to ensure the formation of desired nucleosides 7. Using tributyltin hydride (Bu3SnH) and 2,2′-azobis(2-methylpropionitrile) (AIBN) in refluxing acetonitrile furnished 7a,b,d,e in moderate yield (60%) and 7c in low yield (35%) (Table 2). Interestingly, conversion of the hypoxanthine derivative 6f resulted in a mixture of products difficult to separate and identify. Next, we sought to find a replacement for the traditional reducing agent Bu3SnH, which is toxic, expensive and difficult to remove from the reaction mixture. We elected to use tris(trimethylsilyl)silane [(Me3Si)3SiH] \[40,41\] as a greener, non-toxic reagent for reduction. We also replaced hazardous AIBN with a safer radical initiator 1,1′-azobis(cyclohexanecarbonitrile) (ACHN), which has a longer half-life than AIBN. Under optimized reaction conditions, reduction of bisxanhtanes 6 with green reagents afforded improved yields for uracil, thymine and adenine derivatives furnishing 7a, 7b and 7e.
The signals of the

Therefore, we opted to reverse the sequence of the reactions, first carrying out the

performing hydrogenation under the same conditions, isolating the drug zalcitabine (\(9c\)) in high yields. The reaction of the

\(8d\) benzoyl deprotection by treating

\(8d\) with 92% and 95% yield, respectively. However, this protocol is not suitable for

purine derivatives due to the cleavage of the glycosidic bond in the acidic reaction medium. Other TBS deprotection methods using povidone-iodine (PVP-1) \([44]\) or phosphomolybdic acid \([45]\) were not successful.

Hydrogenation of \(2',3',3'-didehydro-2',3'-dideoxynucleosides\) \(8\) using palladium on carbon in methanol at room temperature afford the corresponding \(2',3',3'-dideoxynucleosides\) \(9a,b,e,f\) in high yields. The reaction of the \(N^1\)-benzoylcytidine derivative \(8d\) was carried out under similar conditions, but it resulted in the formation of a mixture of products. Therefore, we opted to reverse the sequence of the reactions, first carrying out the \(N^1\)-benzoyl deprotection by treating \(8d\) with an aqueous ammonia solution at 55 °C and then performing hydrogenation under the same conditions, isolating the drug zalcitabine (\(9c\)) with a 70% yield (Scheme 4).

Additionally, the drug didanosine (\(9f\)) was obtained via enzymatic deamination of adenosine analogue \(9e\) (Scheme 5) \([46]\). Treatment of \(9e\) with adenosine deaminase (ADA) in a 0.10 M phosphate buffer (pH 7) and 3% DMSO provides the \(2',3'-dideoxynucleoside\) \(9f\) in an almost quantitative yield (95%) after 3 h of reaction.

![Scheme 5. Synthesis of Didanosine (ddI) through enzymatic deamination of 9e.](image)

The structure of the synthesized compounds was determined by NMR spectroscopy. The signals of the \(^1\)H and \(^{13}\)C-NMR spectra of the nucleoside derivatives are fully assigned on the basis of \(^1\)H and \(^{13}\)C chemical shifts, proton coupling constants, and two-dimensional \(^1\)H-\(^1\)H (COSY) and \(^1\)H-\(^{13}\)C spectra (HSQC and HMBC). As an illustrating example, the identification of zalcitabine (\(9c\)) was performed as follows. The protons H1', H4', H5', H5 and H6 are assigned by \(^1\)H-NMR. Subsequent analysis of the \(^1\)H-\(^{13}\)C HSQC experiment leads to identification of the corresponding carbons. Several multiplets at 1.6–2.5 ppm in the \(^1\)H-NMR spectrum are assigned, but not identified, to the hydrogens H2' and H3'. In addition, the signals at 24.7 and 31.9 ppm in the \(^{13}\)C-NMR spectrum are assigned to C2' and C3'. A correlation cross-peak in the \(^1\)H-\(^{13}\)C HMBC experiment between the H5' protons and the carbon at 24.7 ppm allows the assignment of C3'. This has been corroborated by a correlation cross-peak between H1' and C3'. Further analysis of the \(^1\)H-\(^{13}\)C HSQC experiment leads to unambiguously identification of H2 and H3. Finally, a correlation cross-
peak between H1′ and the signal at 157.3 ppm in the 1H-13C HMBC experiment allows the assignment of C2, being the signal of the 13C-NMR spectrum at 165.9 ppm, which does not appear in the DEPT-135 experiment, identified as C4. The COSY experiment validates the assignment made. It is worth mentioning the three-bond correlation of H1′ with the two hydrogens H2′, but not with H3′, as well as the three-bond correlation of H4′ with the two hydrogens of H3′, but not with H2′.

3. Materials and Methods

3.1. General

All chemical reagents were purchased from Aldrich, Sigma, Merck, Acros or Alfa Aesar, and used without further purification. Thin-layer chromatography (TLC) was carried out on aluminum-backed Silica-Gel 60 F254 plates. The spots were visualized with UV light. Column chromatography was performed using Silica Gel (60 Å, 230 × 400 mesh).

Candida antarctica lipase type B (CAL-B, Novozyme 435, immobilized by adsorption in Lewatit, 9120 PLU/g) was purchased from Novozymes. Adenosine deaminase (ADA, 2–5 units/mg, intestinal bovine source, lyophilized) was purchased from Creative Enzymes. Anhydrous THF was added to an Erlenmeyer flask containing ribonucleoside 1 (0.2 mmol), acetonoxime levulinate and CAL-B (acylating agent equiv, enzyme ratio, concentration, temperature, and reaction time are indicated in Table 1) under nitrogen. The reaction crude was purified by column chromatography (gradient eluent: 2–5% MeOH/CH2Cl2). The enzyme was filtered and washed with CH2Cl2 and MeOH, and the solvents were removed under reduced pressure. The reaction crude was purified by column chromatography (gradient eluent: 2–5% MeOH/CH2Cl2), obtaining the corresponding acylated ribonucleosides 2a–f (yields are indicated in Table 1).

5′-O-Levulinyl-β-d-uridine (2a). White solid, mp: 60–62 °C. Rf: 0.32 (10% MeOH/CH2Cl2). HRMS (ESI+, m/z): Calcd. for C14H19N2O8 [M + H]+: 343.1136. Found: 343.1131.

5′-O-Levulinyl-β-d-5-methyluridine (2b). White solid, mp: 134–136 °C. Rf: 0.33 (10% MeOH/CH2Cl2). HRMS (ESI+, m/z): Calcd. for C15H21N2O8 [M + H]+: 357.1292. Found: 357.1279.

5′-O-Levulinyl-β-d-cytidine (2e). White solid, mp: 53–55 °C. Rf: 0.35 (20% MeOH/CH2Cl2). HRMS (ESI+, m/z): Calcd. for C14H20N3O7 [M + H]+: 342.1296. Found: 342.1295.

N4-Benzoyl-5′-O-levulinyl-β-d-cytidine (2d). White solid, mp: 193–195 °C. Rf: 0.47 (10% MeOH/CH2Cl2). HRMS (ESI+, m/z): Calcd. for C21H24N3O8 [M + H]+: 446.1563. Found: 446.1564.

5′-O-Levulinyl-β-d-adenosine (2e). White solid, mp: 116 °C (decompose). Rf: 0.26 (10% MeOH/CH2Cl2). HRMS (ESI+, m/z): Calcd. for C15H20N3O6 [M + H]+: 366.1408. Found: 366.1406.

5′-O-Levulinyl-β-d-inosine (2f). White solid, mp: 54–56 °C. Rf: 0.44 (20% MeOH/CH2Cl2). HRMS (ESI+, m/z): Calcd. for C15H19N4O7 [M + H]+: 367.1248. Found: 367.1253.
3.3. Synthesis of 5

To a solution of ribonucleoside 1 (0.4 M for 1a–f and 0.2 M for 1c–f) in anhydrous DMF were added imidazole (2.4 equiv) and TBSCI (1.2 equiv). The mixture was stirred at rt for 12 h. Then, the residue was poured into EtOAc and washed with water. The organic phase was dried, filtered, and evaporated under reduced pressure. Compounds 5 were obtained with sufficient purity for the next step and the following yields: 93% for 5a, 85% for 5b, 91% for 5c, 80% for 5d, 85% for 5e and 80% for 5f. If desired, a chromatographic column could be performed (gradient eluent: 5–10% MeOH/CH₂Cl₂).

5′-O-(tert-Butyldimethylsilyl)-β-D-uridine (5a). White solid, mp: 94–96 °C. Rf: 0.41 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₅H₂₇N₂O₅Si [M + H]⁺: 359.16329. Found: 359.16332.

5′-O-(tert-Butyldimethylsilyl)-β-D-5-methyluridine (5b). White solid, mp: 197–198 °C. Rf: 0.35 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₆H₂₀N₂O₃Si [M + H]⁺: 373.1789. Found: 373.1790.

5′-O-(tert-Butyldimethylsilyl)-β-D-cytidine (5c). Colorless foam. Rf: 0.52 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₅H₂₈N₂O₃Si [M + H]⁺: 358.1798. Found: 358.1791.

N₄-Benzoyl-5′-O-(tert-butyldimethylsilyl)-β-D-cytidine (5d). White solid, mp: 86–88 °C. Rf: 0.47 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₂₂H₃₁N₃O₆Si [M + H]⁺: 462.2055. Found: 462.2048.

5′-O-(tert-Butyldimethylsilyl)-β-D-adenosine (5e). White solid, mp: 178–179 °C. Rf: 0.33 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₆H₂₈N₄O₄Si [M + H]⁺: 382.1911. Found: 382.1902.

5′-O-(tert-Butyldimethylsilyl)-β-D-inosine (5f). White solid, mp: 229–230 °C. Rf: 0.17 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₆H₂₇N₄O₅Si [M + H]⁺: 383.1745. Found: 383.1743.

3.4. Synthesis of 6

To a solution of 5′-O-silyl protected ribonucleosides 5 and CS₂ (7 equiv) in DMF (0.4 M) at 0 °C, an aqueous 3 M NaOH solution (3 equiv) was added dropwise. After being stirred for 30 min at this temperature, bromoethane (15 equiv) was added dropwise, and stirring continued for 20 min at rt. Then, the residue was poured into EtOAc and washed with water. The organic phase was dried, filtered, and evaporated under reduced pressure. The resulting solid was thoroughly washed with heptane to afford compounds 6 with suitable purity, avoiding chromatographic purification. Yields: 82% for 6a, 81% for 6b, 75% for 6c, 72% for 6d, 90% for 6e and 70% for 6f.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-bis-O-[(ethylthio)thiocarbonyl]-β-D-uridine (6a). White solid, mp: 102–104 °C. Rf: 0.45 (40% EtOAc/hexane). HRMS (ESI⁺, m/z): Calcd. for C₂₁H₃₈N₂O₅S₄Si [M + H]⁺: 567.1142. Found: 567.1133.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-bis-O-[(ethylthio)thiocarbonyl]-β-D-5-methyluridine (6b). White solid, mp: 131–132 °C. Rf: 0.50 (40% EtOAc/hexane). HRMS (ESI⁺, m/z): Calcd. for C₂₂H₄₁N₂O₅S₄Si [M + H]⁺: 581.1298. Found: 581.1292.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-bis-O-[(ethylthio)thiocarbonyl]-β-D-cytidine (6c). White solid, mp: 99–101 °C. Rf: 0.35 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₂₁H₃₈N₂O₅S₄Si [M + H]⁺: 566.1302. Found: 566.1295.

N₄-Benzoyl-5′-O-(tert-butyldimethylsilyl)2′,3′-bis-O-[(ethylthio)thiocarbonyl]-β-D-cytidine (6d). White solid, mp: 140–141 °C. Rf: 0.25 (40% EtOAc/hexane). HRMS (ESI⁺, m/z): Calcd. for C₂₃H₄₀N₃O₅S₄Si [M + H]⁺: 670.1564. Found: 670.1558.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-bis-O-[(ethylthio)thiocarbonyl]-β-D-adenosine (6e). White solid, mp: 164–165 °C. Rf: 0.18 (50% EtOAc/hexane). HRMS (ESI⁺, m/z): Calcd. for C₂₂H₃₉N₃O₄S₄Si [M + H]⁺: 590.1414. Found: 590.1409.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-bis-O-[(ethylthio)thiocarbonyl]-β-D-inosine (6f). White solid, mp: 201–203 °C. Rf: 0.36 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₂₂H₃₈N₄O₅S₄Si [M + H]⁺: 591.1254. Found: 591.1239.
3.5. Synthesis of 7

3.5.1. Method A: Bu₃SnH

To a solution of 6 in anhydrous MeCN (0.13 M) at reflux was added dropwise a solution of Bu₃SnH (4 equiv) and AIBN (0.4 equiv) in anhydrous MeCN (0.5 M). After being stirred for 1 h at this temperature, the solvent was removed under vacuum, and the residue was purified by column chromatography (gradient eluents: 40–50% EtOAc/hexane for 7a,b; 70% EtOAc/hexane-EtOAc for 7d; 2–5% MeOH/CH₂Cl₂ for 7c,e) to afford 7a, 7b, 7d and 7e in 60% yield and 7c in 35% yield.

3.5.2. Method B: (Me₅Si)₂SiH

To a solution of 6 in anhydrous MeCN (0.13 M) at reflux, was added dropwise a solution of (Me₅Si)₂SiH (4 equiv) and 1,1′-azobis(cyclohexanecarbonitrile) (0.4 equiv) in anhydrous MeCN (0.5 M). The mixture was stirred for 1 h (6a–e) or 6 h (6f) at this temperature. Next, the solvent was removed under vacuum, and the residue was purified by column chromatography (gradient eluents: 40–50% EtOAc/hexane for 7a,b; 70% EtOAc/hexane-EtOAc for 7d; 2–5% MeOH/CH₂Cl₂ for 7f) to afford 7 (65% for 7a, 75% for 7b, 40% for 7d, 7% for 7e and 80% yield for 7f).

5′-O-(tert-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-β-D-uridine (7a). White solid, mp: 166–168 °C. Rf: 0.16 (40% EtOAc/hexane). HRMS (ESI⁺, m/z): Calcd. for C₁₅H₂₅N₂O₄Si [M + H]⁺: 325.1578. Found: 325.1573.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-β-D-uridine (7b). White solid, mp: 169–171 °C. Rf: 0.29 (40% EtOAc/hexane). HRMS (ESI⁺, m/z): Calcd. for C₁₅H₂₅N₂O₄Si [M + H]⁺: 339.1735. Found: 339.1729.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-β-D-cytidine (7c). White solid, mp: 176–178 °C. Rf: 0.52 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₅H₂₅N₂O₄Si [M + H]⁺: 343.1738. Found: 343.1743.

N⁴-Benzyloxy-5′-O-(tert-butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-β-D-cytidine (7d). White solid, mp: 137–138 °C. Rf: 0.19 (40% EtOAc/hexane). HRMS (ESI⁺, m/z): Calcd. for C₂₂H₃₀N₃O₄Si [M + H]⁺: 428.2000. Found: 428.1993.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-β-D-adenosine (7e). White solid, mp: 118–120 °C. Rf: 0.48 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₅H₂₅N₂O₄Si [M + H]⁺: 348.1850. Found: 348.1848.

5′-O-(tert-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-β-D-inosine (7f). White solid, mp: 178–180 °C. Rf: 0.36 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₁₅H₂₅N₂O₄Si [M + H]⁺: 349.1690. Found: 349.1690.

3.6. Synthesis of 8

3.6.1. Method A: TBAF

TBAF (2 equiv, 1.0 M in THF) was added dropwise to a stirred solution of 7 (1 equiv) in anhydrous THF (0.1 M) at 0 °C. After 5 min, the ice bath was removed, and the reaction mixture was stirred at rt for 1 h. Next, the solvent was removed under vacuum, and the residue was purified by column chromatography (5% MeOH/CH₂Cl₂ for 8a,b,d; 15% MeOH/CH₂Cl₂ for 8e,f) to afford 8a,e in 95%, 8b,d in 90%, and 8f in 75% yields.

3.6.2. Method B: (–)-CSA

(–)-CSA (1 equiv) was added to a solution of 7 in anhydrous MeOH (0.1 M) at 0 °C, and the reaction was stirred at rt for 1 h. Solid NaHCO₃ was then added, and the mixture was stirred for a further 5 min. Next, the solvent was removed under vacuum, and the residue was purified by column chromatography (5% MeOH/CH₂Cl₂) to afford 8a in 92% and 8b in 95% yields.

2′,3′-Didehydro-2′,3′-dideoxy-β-D-uridine (8a). White solid, mp: 154–155 °C. Rf: 0.40 (10% MeOH/CH₂Cl₂). HRMS (ESI⁺, m/z): Calcd. for C₉H₁₀N₂O₄ [M + Na]⁺: 233.0533. Found: 233.0537.
2',3'-Didehydro-3'-deoxy-β-D-5-thymidine (8b). White solid, mp: 165–166 °C. $R_f$: 0.42 (10% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_{10}$H$_{13}$N$_2$O$_4$ [M + H$^+$]: 225.0870. Found: 225.0873.

N$^4$-Benzoyl-2',3'-didehydro-2',3'-dideoxy-β-D-cytidine (8d). White solid, mp: 280 °C (decompose). $R_f$: 0.66 (10% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_{16}$H$_{16}$N$_3$O$_4$ [M + H$^+$]: 314.1135. Found: 314.1140.

2',3'-Didehydro-2',3'-dideoxy-β-D-adenosine (8e). White solid, mp: 185–186 °C. $R_f$: 0.24 (10% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_{10}$H$_{12}$N$_4$O$_2$ [M + H$^+$]: 234.0986. Found: 234.0984.

2',3'-Didehydro-2',3'-dideoxy-β-D-inosine (8f). White solid, mp: >300 °C. $R_f$: 0.19 (10% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_{10}$H$_{11}$N$_4$O$_3$ [M + H$^+$]: 235.0826. Found: 235.0826.

3.7. Synthesis of 9

A flask containing 8 and 10% Pd/C (0.1 equiv) was exposed to a positive pressure of hydrogen gas (balloon). Anhydrous MeOH (0.02M) was added, and the mixture was stirred vigorously for 2 h under a hydrogen atmosphere. The suspension was filtered on Celite$^{65}$ and washed with MeOH, and the solvent was removed under vacuum. The crude was purified by column chromatography (gradient eluent 2–10% MeOH/CH$_2$Cl$_2$) to afford 9a in 82%, 9b in 87%, 9e in 88%, and 9f in 80% yields.

2',3'-Dideoxy-β-D-uridine (9a). White solid, mp: 116–117 °C. $R_f$: 0.42 (10% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_9$H$_{15}$N$_2$O$_4$ [M + H$^+$]: 213.0870. Found: 213.0875.

3'-Deoxy-β-D-5-thymidine (9b). White solid, mp: 155–156 °C. $R_f$: 0.44 (10% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_{10}$H$_{15}$N$_2$O$_4$ [M + H$^+$]: 227.1026. Found: 227.1032.

2',3'-Dideoxy-β-D-adenosine (9e). White solid, mp: 160–163 °C. $R_f$: 0.28 (10% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_{10}$H$_{13}$N$_4$O$_3$ [M + H$^+$]: 237.0982. Found: 237.0989.

3.7.1. Synthesis of Zalcitabine (9c)

A suspension of 8d (50 mg, 0.16 mmol) in an aqueous 32% NH$_3$ solution (2.5 mL) was stirred at 55 °C for 12 h. The solvent was removed under vacuum. Then, a mixture of the resulting residue and 10% Pd/C (17 mg) was exposed to a positive pressure of hydrogen gas (balloon). Anhydrous MeOH (8 mL) was added, and the mixture was stirred vigorously for 2 h under a hydrogen atmosphere. The suspension was filtered on Celite$^{65}$ and washed with MeOH, and the solvent was removed under vacuum. The crude was purified by column chromatography (20% MeOH/CH$_2$Cl$_2$) previously packed with silica gel using a 10% Et$_3$N solution in MeOH/CH$_2$Cl$_2$ (2:8, v/v). Compound 9c was isolated in 70% yield.

2',3'-Dideoxy-β-D-cytidine (9c). White solid, mp: 208–210 °C. $R_f$: 0.27 (20% MeOH/CH$_2$Cl$_2$). HRMS (ESI$^+$, m/z): Calcd. for C$_9$H$_{14}$N$_3$O$_3$ [M + H$^+$]: 212.1030. Found: 212.1034.

3.7.2. Synthesis of Didanosine (9f)

To a suspension of 9e (40 mg, 0.17 mmol) in a phosphate buffer solution pH 7 (0.8 mL) and 3% of DMSO, to promote dissolution, 2 mg of adenosine deaminase dissolved in the same buffer (0.2 mL) was added. The reaction was stirred at 250 rpm and 30 °C for 3 h. The crude was purified by column chromatography (10% MeOH/CH$_2$Cl$_2$) to afford 9f in 95% yield.

4. Conclusions

We report an economical and green synthesis of 2',3'-dideoxynucleoside and 2',3'-didehydro-2',3'-dideoxynucleoside derivatives of uracil, thymine, cytosine, adenine and hypoxanthine through deoxygenation of the corresponding 2',3'-O-bissanthe ribonucleosides. This protocol involves the use of tris(trimethylsilyl)silane [(Me$_3$Si)$_3$SiH] instead of Bu$_3$SnH, which is toxic, expensive and difficult to remove from the reaction mixture,
as a radical-based reducing agent. We also replaced potentially explosive AIBN with 1,1′-azobis(cyclohexanecarbonitrile) (ACHN) as a safer alternative. In addition, for the deprotection of silyl ethers at the 5′-position of the nucleosides, we were able to substitute TBAF for camphorsulfonic acid as a more sustainable reagent, in pyrimidine derivatives. The use of (Me$_3$Si)$_2$SiH in the deoxygenation of bixanthane hypoxanthine derivative allows easy access to 2′,3′-didehydro-2′,3′-dideoxynucleosides. As an alternative synthesis, this nucleoside was also obtained in excellent yield via enzymatic deamination of 2′,3′-dideoxyadenosine with adenosine deaminase. It is important to emphasize that these protocols may have potential industrial application for the synthesis of three of the most demanding anti-HIV drugs: stavudine (d4T), zalcitabine (ddC) and didanosine (ddl).

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27133993/s1, 1H and 13C-NMR data with their assignment for all compounds. Level of purity is indicated by the inclusion of copies of 1H, 13C, and DEPT NMR spectra; in addition, some 2D NMR experiments are shown, which were used to assign the peaks.

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