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Citation for final published version:

Ferrari, Valentina ORCID: https://orcid.org/0000-0003-1895-8906, Serpi, Michaela ORCID: https://orcid.org/0000-0002-6162-7910, McGuigan, Christopher ORCID: https://orcid.org/0000-0001-8409-710X and Pertusati, Fabrizio ORCID: https://orcid.org/0000-0003-4532-9101 2015. Chemoselective N-deacetylation of protected nucleosides and nucleotides promoted by the Schwartz’s reagent. Nucleosides, Nucleotides & Nucleic Acids 34 (11), pp. 799-814. 10.1080/15257770.2015.1075552 file

Publishers page: http://dx.doi.org/10.1080/15257770.2015.1075552
<http://dx.doi.org/10.1080/15257770.2015.1075552>

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To cite this article: Valentina Ferrari, Michaela Serpi, Christopher McGuigan & Fabrizio Pertusati (2015): Chemoselective N-Deacetylation of Protected Nucleosides and Nucleotides Promoted by Schwartz's Reagent, Nucleosides, Nucleotides and Nucleic Acids, DOI: 10.1080/15257770.2015.1075552

To link to this article: http://dx.doi.org/10.1080/15257770.2015.1075552

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CHEMOSELECTIVE N-DEACETYLATION OF PROTECTED NUCLEOSIDES AND NUCLEOTIDES PROMOTED BY SCHWARTZ’S REAGENT

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Protection and deprotection strategies involving the N-acetyl group are widely utilized in nucleoside and nucleotide chemistry. Herein, we present a mild and selective N-deacetylation methodology, applicable to purine and pyrimidine nucleosides, by means of Schwartz’s reagent, compatible with most of the common protecting groups used in nucleoside chemistry.

Keywords Chemoselective; N-deacetylation; Schwartz reagent; nucleoside; prodrugs; protecting groups

1. INTRODUCTION

The chemistry of metallocenes rapidly expanded in the 1970s with organozirconocene emerging as one of the most useful classes of transition metal derivatives for use in organic synthesis. One important reagent belonging to this class of organometallic compounds is the chlorobis(cyclopentadienyl)hydrido-zirconium, also called zirconocene hydrochloride but better known as Schwartz’s reagent. Wailes and Weigold were the first to prepare 1 and, subsequently, Schwartz and many other scientists exploited its potential in the functionalization of organic compounds. Selected examples of the utility of this reagent in organic synthesis are depicted in Figure 1. Schwartz’s reagent is most often used in the hydrozirconation of triple and double bonds (Figure 1,
FIGURE 1 Selected organic transformations involving the Schwartz’s reagent.

Reaction a). However, its use in this reaction is sometimes hampered by the functional group compatibility of the process that is limited by the oxophilic, hard Lewis-acid character of the Schwartz reagent.

This characteristic has been therefore exploited in other useful synthetic organic transformations such as the chemoselective reduction of tertiary amides to aldehydes (Figure 1, Reaction b) and the reduction of secondary amides to N-substituted imines (Figure 1, Reaction c). The latter transformation, when performed with most other metal hydride reagents, results either in over-reduction of the imine to give the corresponding amine or in the reductive cleavage of the amide. Interestingly, 1 has also been employed as a reducing agent for phosphine oxides to the corresponding phosphines (Figure 1, Reaction d). Recently, Bhat and co-workers reported a very mild and useful deacetylation procedure of acetamides involving reagent 1. The methodology proved to be very efficient for aromatic, heteroaromatic, and aliphatic amides and moreover no epimerization was observed during the N-deacetylation of chiral acetamides.

The amine functionality is present in many compounds of biological interest, for instance natural products and pharmaceuticals. Nucleoside and nucleotide chemistry frequently involves protecting procedures at the amine and hydroxyl groups and benefit of selective deprotection methods, in order to obtain the target compound efficiently without any side reactions. N-Acetyl protection is one of the most widely used in nucleoside and nucleotide chemistry. However, the requirement of strong base or acid and/or high reaction temperatures during the deprotection step (N-deacetylation) is often not compatible with some nucleosidic substrates and especially their prodrugs. Harsh conditions are also likely to yield fully deprotected...
products, an outcome often undesired. Zinc bromide\cite{11} and hydrazine hydrate\cite{12} were initially reported as selective and mild N-deacetylating agents for nucleosides, although their compatibility with other protecting groups was not explored broadly. Our goal was the identification of a selective N-deacetylation methodology involving mild reaction conditions that could be applied to a broad spectrum of differently protected nucleosides. Therefore, we became immediately interested in Bhat’s methodology\cite{8} and in its possible application in nucleoside chemistry. To the best of our knowledge, no attempt to use Schwartz’s reagent in the N-deacetylation of nucleosides and their prodrugs has been previously reported. Herein, we would like to report our efforts directed at deacetylation of N-acetyl purine and pyrimidine nucleoside analogues bearing a variety of protecting groups (PGs) at the hydroxyl moiety, commonly used in nucleoside chemistry, such as O-acetyl, O-tert-butyloxycarbonyl, O-tert-butyldimethylsilyl, O-tetrahydropyranyl, O-benzoyl, and O-isopropylidene groups, with the aim of evaluating the ability of reagent 1 to selectively remove the acetyl group from the amino moiety, leaving the other PGs untouched.

2. RESULTS AND DISCUSSION

Our investigation began with the preparation, according to literature procedures, of differently substituted N-acetyl-2′-deoxycytidine (2a-c) and N-acetylcytidine (2d-g), as indicated in Table 1. With all the O-protected nucleosides in hand, we proceeded to test the deacetylation reaction. First, compound 2a was subjected to the action of three equivalents of reagent 1 in a THF solution, under a nitrogen atmosphere, for 30 minutes (Table 1, Entry 1). Pleasingly, we were able to isolate after aqueous work-up and column chromatography compound 3a in 57% yield, where only the N-acetyl group was removed. Delighted by this result, we directed our efforts towards other protecting groups. Application of these conditions to 2b, once again, led to the selective removal of the acetyl group from the amino moiety without affecting the silicon protected hydroxyl groups and yielding 3b in 49% yield (Table 1, Entry 2).

Similar results were obtained testing the compatibility of Schwartz’s reagent with other protecting groups such as tetrahydropyranyl, tertbutoxycarbonyl, benzoyl, and isopropylidene (Table 1, Entries 3–7). In all examples, the O-protecting groups were unaffected by this procedure, and only the acetyl group on the nucleobase was removed, affording the desired compounds in moderate to good yields (39–70%), along with the recovery of unreacted starting material. Attempts to increase the yield of the desired N-deacetylated nucleoside either by increasing the equivalents of 1 (up to six) or by adding it portionwise over a period of three hours, proved to be unsuccessful and some amount of starting material was always recovered.
TABLE 1  Deacetylation reaction of differentially protected $N$-acetyl-$2'$-deoxycytidines and $N$-acetylcytidines, promoted by Schwartz reagent

![Chemical Reaction Diagram]

| Entry | Cpd | $R_1$ | $R_2$ | $R_3$ | I (eq) | Temp ($^\circ$C) | Time (h) | Prod. Yield (%) | Recovered SM (%) |
|-------|-----|-------|-------|-------|-------|---------------|----------|-----------------|-----------------|
| 1     | 2a  | H     | Ac    | Ac    | 3     | rt            | 0.5      | 3a              | 57              | 40              |
| 2     | 2b  | H     | TBDMS | TBDMS | 3     | rt            | 0.5      | 3b              | 49              | 33              |
| 3     | 2c  | H     | THP   | THP   | 3     | rt            | 3        | 3c              | 68              | 20              |
| 4     | 2d  | OH    | Boc   | Boc   | 3     | rt            | 0.5      | 3d              | 39              | 55              |
| 5     | 2e  | OAc   | Ac    |      | 3     | rt            | 3        | 3e              | 70              |                |
| 6     | 2f  | Obz   | Bz    |      | 3     | rt            | 3        | 3f              | 53              | 41              |
| 7     | 2g  | CMe$_2$ | H    |      | 3     | rt            | 3        | 3g              | 55              | 38              |
| 8     | 2a  | H     | Ac    | Ac    | 6     | 70            | 12       | 3a              | 55              | 42              |
| 9     | 2a  | H     | Ac    | Ac    | 3     | 70            | 12       | 3a              | 48              | 39              |

(Table 1, Entry 8). Incrementing the temperature up to 70$^\circ$C did not enhance the yield (Table 1, Entry 9). Subsequently, we decided to broaden the scope of the methodology by testing it on examples of other pyrimidine and purine nucleoside derivatives bearing different PGs (Table 2). Lamivudine was acetylated on both oxygen and amine groups and the resulting $N,O$-diacetylated compound 2h was then submitted to the deacetylating protocol (Table 2, Entry 1). As expected, the acetyl group was removed only from the nitrogen on the nucleobase, leaving the $O$-acetyl group untouched.

$N$-acetyl-$O$-trityl-lamivudine 2i was found to be a poor substrate for this protocol (Table 2, Entry 2). The desired product 3i was obtained only in 25% isolated yield, most probably due to the partial trityl group instability to the reaction conditions. No starting material was isolated in this case.

When the protocol was tested on purine nucleoside analogues, reagent 1 proved efficient in removing the acetyl group selectively from the amine group on both the guanine ring of peracetylated acyclovir 2j and the adenine ring of $N$-acetyl-$5'$-$O$-acetyl-$2'$,$3'$-$O$-isopropylidene adenosine 2k, affording 3j and 3k respectively in 47% and 76% isolated yields (Table 2, Entries 3,4).

Finally, $N,N$-diacetyl-$2'$,$3'$-isopropylidene adenosine 2l was submitted to the optimized protocol. In this case Schwartz’s reagent was able to remove both $N$-acetyl groups, affording compound 3k in 53% yield, with only traces of mono-$N$-acetylated derivative 2k.
### Table 2: N-deacetylation of protected pyrimidine and purine nucleosides, promoted by Schwartz's reagent

| Entry | Compound | Product | Yield (%) |
|-------|----------|---------|-----------|
| 1     | ![Image](2h.png) | ![Image](3h.png) | 56        |
| 2     | ![Image](2i.png) | ![Image](3i.png) | 25        |
| 3     | ![Image](2j.png) | ![Image](3j.png) | 47        |
| 4     | ![Image](2k.png) | ![Image](3k.png) | 76        |

(Continued on next page)
TABLE 2  N-deacetylation of protected pyrimidine and purine nucleosides, promoted by Schwartz’s reagent (Continued)

| Entry | Compound | Product | Yield (%) |
|-------|----------|---------|-----------|
| 5     | ![Diagram of compound 2](image1.png) | ![Diagram of product 3](image2.png) | 53        |

2.1. In Situ Generation of the Schwartz’s Reagent and Yield Improvement

At the same time we were conducting our investigations, Snieckus et al.\textsuperscript{6c} reported a practical method to generate Schwartz’s reagent in situ using Li(O\textsubscript{t-Bu})\textsubscript{3}AlH, demonstrating the advantage of this procedure both in reducing tertiary amides to aldehydes and in hydrozirconation reactions, in comparison to the use of the commercial Schwartz’s reagent. We, therefore, decided to assess this efficient procedure in the deacetylation of nucleoside 2\textsubscript{g} in order to be able to compare the in situ methods with the use of the preformed 1 (Scheme 1). Therefore, to a THF solution of 2\textsubscript{g} and 1.5 equivalents of Cp\textsubscript{2}ZrCl\textsubscript{2} in THF, solid Li(O\textsubscript{t-Bu})\textsubscript{3}AlH was added in one portion and the mixture was stirred for 40 minutes. Aqueous workup, followed by column chromatography, afforded compound 3\textsubscript{g} in 80\% isolated yield, demonstrating a yield improvement from the previous 55\%, possibly due to the partial air, light, and moisture sensitivity of 1, which are reported to be responsible for the reduction of its effectiveness with time.\textsuperscript{13}

2.2. Schwartz’s Reagent N-Deacetylation Applied to Nucleoside Phosphoroamidate

Nucleoside analogues (NAs) are an important class of molecules accounting for half of all antiviral drugs currently on the market and a number of anticancer agents that are widely used.\textsuperscript{14} NAs mostly require phosphorylation to be active. Unfortunately, many nucleoside analogues are not phosphorylated effectively in vivo, and thus their therapeutic potential is often quite limited. Using various approaches, the ionizable phosphate group can be masked by derivatization, generating prodrugs with increased biological activity.\textsuperscript{15} Among different nucleoside monophosphate prodrug strategies is
the phosphoroamidate prodrug approach (ProTide), consisting of an amino acid ester moiety linked via P–N bond to a nucleoside aryl phosphate.\[16\] Several leading pharmaceutical companies have applied this technology for antiviral and anticancer treatments. Gilead has just launched on the market its anti-HCV ProTide, Sofosbuvir (PSI-7977),\[17\] whereas Nucana Biomed has taken to trial a gemcitabine ProTide (NUC-1031), for patients with advanced solid tumours.\[18\] Considering the importance that the ProTide technology is assuming in the antiviral and anticancer scenarios, we were interested in checking if Schwartz's reagent is compatible with the phosphoroamidate motif and whether this protocol can be used at later stage in the synthesis of this class of prodrugs.

Phosphoroamidate 5 was synthesized from 2g and (2S)-cyclohexyl 2-((chloro(naphthalen-1-yloxy)phosphoryl)amino)propanoate 4 in 40% yield (Scheme 2), according to a previously described method.\[16\] Phosphoroamidate 5 was then treated with three equivalents of the Schwartz's reagent, yielding the corresponding deacetylated prodrug 6 in 65% isolated yield.
3. CONCLUSIONS

In conclusion, we have demonstrated that the general and mild method for the deacetylation of N-acetyl group developed by Bhat et al. can be successfully applied to purine and pyrimidine nucleosides, with diverse O-protection. Moreover, we have shown that Schwartz’s reagent is compatible with the phosphoramide moiety and can be used for N-deacetylation reaction in the later stages of the synthesis of this class of nucleoside monophosphate prodrugs. Lastly, we have proved that modification of the reported procedure\cite{6c} involving in situ generation of Schwartz’s reagent leads to yield improvement and is promising of similar results on other nucleoside substrates.

4. EXPERIMENTAL SECTION

**General information.** All anhydrous solvents were purchased from Sigma-Aldrich. All commercially available reagents were used without further purification. Schwartz reagent was purchased from Sigma-Aldrich or prepared in situ as described and all nucleosides used as starting materials were purchased from Carbosynth. All reactions were performed under an Argon atmosphere, unless otherwise stated. $^1$H NMR (500 MHz), $^{13}$C NMR (125 MHz), and $^{31}$P NMR (202 MHz) spectra were recorded on a Bruker Avance 500 MHz spectrometer at 25ºC. Chemical shifts (δ) are quoted in parts per million (ppm) relative to internal CD$_3$OD (δ 3.34 $^1$H NMR, δ 49.86 $^{13}$C NMR) and CDCl$_3$ (δ 7.26 $^1$H NMR, δ 77.36 $^{13}$C NMR) or external 85% H$_3$PO$_4$ (δ 0.00 $^{31}$P NMR). Coupling constants (J) are given in Hertz. The following abbreviations are used in the assignment of NMR signals: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), multiplet (m), broad singlet (bs), doublet of doublet (dd), and doublet of triplet (dt). High and low-resolution mass spectrometry analyses were performed on a Bruker microTof-LC system.

**Standard procedure for the N-deacetylation reaction.**\cite{8} To a stirred solution of N-acetyl nucleoside (100 mg) in anhydrous THF (2 mL), Schwartz’s reagent (3–6 eq.) is added at room temperature and the reaction mixture is stirred for 0.5–3 hours. Water is then added to quench the reaction. The resulting solution is extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic layer is washed with brine solution and dried over anhydrous Na$_2$SO$_4$, filtered and evaporated to afford the crude product, which is purified by silica gel column chromatography to finally afford pure deacetylated nucleoside.

**N-Deacetylation reaction via in situ generation of Schwartz’s.**\cite{6c} To a solution of N-acetyl nucleoside (100 mg) and Cp$_2$ZrCl$_2$ (1.5 equiv) in THF (2 mL) at rt, solid LiAlH(OtBu)$_3$ (1.5 equiv) was rapidly added. The resulting solution was stirred at rt for 40 minutes and the reaction was monitored by TLC analysis. Water is then added to quench the reaction. The resulting
solution is extracted with CH₂Cl₂ (2 × 5 mL). The combined organic layer is washed with brine solution and dried over anhydrous Na₂SO₄, filtered and evaporated to afford the crude product, which is purified by silica gel column chromatography to finally afford pure deacetylated nucleoside.

3′,5′-O-Bis(acetyl)-2′-deoxycytidine (3a). Prepared from 2a [20a,b] according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH₂Cl₂/MeOH from 98/2 to 95/5 to give 3a [20c] as a white solid (0.050 g, 57% yield). ¹H NMR (500 MHz) CDCl₃ δH 2.08 (3H, s, OCOCH₃), 2.09 (3H, s, OCOCH₃), 2.19–2.12 (1H, m, H-2′a), 2.58 (1H, dd, J = 4.0, 14.0 Hz, H-2′b), 4.24–4.26 (1H, m, H-4′), 4.32 (2H, d, J = 12.5 Hz, H-5′), 5.18–5.19 (1H, m, H-3′), 6.11 (1H, d, J = 6.5 Hz, H-5), 6.22 (1H, t, J = 6.5 Hz, H-1′), 7.57 (1H, d, J = 6.5 Hz, H-6). ¹³C NMR (125 MHz) CDCl₃ δC 20.90, 20.98 (CH₃), 38.24 (CH₂-′), 63.82 (CH₂-′), 74.12 (C-3′), 82.63 (C-4′), 88.18 (C-1′), 95.87 (C-5), 142.25 (C-6), 170.32 (C-O), 155.15 (C-2), 164.90 (C-4); MS (ES⁺) m/z (312) [M+1]; HRMS (ES⁺) m/z found 312.1192 [calcd for C₁₃H₁₈N₃O₆⁺ (M+H)⁺ 312.1190].

3′,5′-O-Bis(tert-butyldimethylsilyl)-2′-deoxycytidine (3b). Prepared from 2b [20a,b] according to N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH₂Cl₂/MeOH from 98/2 to 95/5 to give 3b [20c] as a white solid (0.044 g, 49%). ¹H NMR (500 MHz) CDCl₃ δH 0.12 (6H, s, 2 × CH₃), 0.15 (6H, s, 2 × CH₃), 0.91 (9H, s, C(CH₃)₃), 0.98 (9H, s, C(CH₃)₃), 2.09–2.13 (1H, m, H-2′a), 2.35–2.40 (1H, m, H-2′b), 3.83 (1H, dd, J = 2.5, 11.5 Hz, H-5′a), 3.92 (1H, dd, J = 3.0, 11.0 Hz, H-5′b), 3.93–3.96 (1H, m, H-4′), 4.47–4.49 (1H, m, H-3′), 5.89 (1H, d, J = 7.5 Hz, H-5), 6.24 (1H, t, J = 6.0 Hz, H-1′), 7.97 (1H, d, J = 7.5 Hz, H-6); ¹³C NMR (125 MHz) CDCl₃ δC −4.92, −4.58 (SiCH₃), 17.93, 18.94 (C(CH₃)₃), 26.04, 26.22 (C(CH₃)₃), 42.13 (C-2′), 62.04 (C-5′), 70.44 (C-3′), 85.80 (C-1′), 87.25 (C-4′), 94.26 (C-5), 141 (C-6), 155.94 (C-2), 165.87 (C-4); MS (ES⁺) m/z 456 [M+1]; HRMS (ES⁺) m/z found 456.2710 [calcd for C₁₃H₂₀N₃O₄Si₂⁺ (M+H)⁺ 456.2708].

3′,5′-O-Bis(tetrahydropyranyl)-2′-deoxycytidine (3c). Prepared from 2c [21] according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH₂Cl₂/MeOH from 98/2 to 95/5 to give 3c as a white solid (0.061 mg, 68%). ¹H NMR (500 MHz) CD₂OD δH 1.44–1.48 (8H, m, CH₂ Py), 1.61–1.76 (4H, m, CH₂ Py), 2.34–2.50 (1H, m, H-2′b), 1.95–2.12 (1H, m, H-2′a), 3.43–3.47 (2H, m, CH₂O Py), 3.51 (0.25H, dd, J = 3.0, 11.0 Hz, H-5′b), 3.53 (0.25H, dd, J = 3.0, 11.5 Hz, H-5′b), 3.54–3.61 (0.5H, dt, J = 3.9, 16.5 Hz, H-5′b), 3.71–3.82 (2H, m, CH₂O Py), 3.80–3.86 (0.5, m, H-5′a), 3.90–3.95 (0.5H, m, H-5′a), 4.07–4.11 (0.5H, m, H′4), 4.13–4.15 (0.25H, m, H-4′), 4.17–4.19 (0.25H, m, H-4′), 4.29–4.31 (0.25H, m, H-3′), 4.34–4.36 (0.5H, m, H-3′), 4.40–4.41 (0.25H, m, H-3′), 4.55–4.67 (2H, m,
CHO Py), 5.77–5.80 (1H, m, H-5), 6.11–6.16 (1H, m, H-1'), 7.88 (0.25H, d, J = 7.5 Hz, H-6), 7.89 (0.25H, d, J = 7.5 Hz, H-6), 7.94 (0.25H, d, J = 7.5 Hz, H-6), 7.97 (0.25H, d, J = 7.0 Hz, H-6); 13C NMR (125 MHz) CD3OD δC 20.47, 20.50, 20.68, 20.77 (CH3 Py), 26.51, 26.55 (CH2 Py), 31.69, 31.75, 31.94, 32.01 (CH2 Py), 39.54, 39.71, 40.82, 40.98 (C-2'), 63.69, 63.73, 63.75, 63.92 (CH2O), 68.50, 68.42, 68.49, 68.80 (C-5'), 77.39, 77.82, 78.25 (C-3'), 85.41, 85.47, 85.97, 85.18 (C-4'), 87.65, 87.83, 87.87, 87.97 (C-1'), 95.80, 95.90 (C-5), 99.29, 99.36, 99.79, 99.88, 100.14, 100.33, 100.97, 101.03 (CH Py), 142.38, 142.81 (C-6), 158.17 (C-2), 167.63 (C-4); MS (ES+) m/z = 396 [M+1]. HRMS (ES+) m/z found 396.2127 [calcd for C19H33N8O6+(M+H)+ 396.2129].

5',3'-O-Bis-(tert-butoxycarbonyl)-cytidine (3d). Prepared from 2d[22] according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH2Cl2/MeOH from 98/2 to 95/5 to give 3d as a white solid (0.035 g, 39% yield). 1H NMR (500 MHz) CD3OD δH 1.47 (9H, s, C(CH3)3), 1.50 (9H, s, C(CH3)3), 3.77 (1H, dd, J = 3.0, 12.5 Hz, H-5'), 3.88 (1H, dd, J = 2.5, 12.5 Hz, H-5'), 4.22–4.20 (1H, m, H-4'), 5.27 (1H, dd, J = 5.5 Hz, J = 5.5 Hz, H-3'), 5.32 (1H, dd, J = 4.0, 4.0 Hz, H-2'), 5.90 (1H, dd, J = 7.5 Hz, H-5), 6.10 (1H, d, J = 4.5 Hz, H-1'), 8.0 (1H, d, J = 7.5 Hz, H-6); 13C NMR (125 MHz) CD3OD δC 27.96, 28.02 (C(CH3)3), 31.70 (C(CH3)3), 61.96 (C-5'), 74.17 (C-3'), 77.25 (C-2'), 83.93 (C-4'), 89.64 (C-1'), 95.80 (C-5), 143.07 (C-6), 153.61, 153.89 (COCH(CH3)3), 158.17 (C-2), 167.63 (C-4); MS (ES+) m/z = 444 [M+1]. HRMS (ES+) m/z found 444.1973 [calcd for C19H33N8O6+(M+H)+ 444.1977].

Cytidine 2', 3', 5'-triacetate (3e). Prepared from 2e[19a,10b] according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH2Cl2/MeOH from 98/2 to 95/5 to give 3e[10b] as a white solid (0.063 g, 70% yield). 1H NMR (500 MHz) CD3OD δH 2.10 (3H, s, COCH3), 2.11 (3H, s, COCH3), 2.12 (3H, s, COCH3), 4.34–4.40 (3H, m, H4', H5'), 5.41 (dd, J = 5.0, 5.9 Hz, H1', H3'), 5.48 (dd, J = 4.6, 6.0 Hz, 1H, H3'), 5.96 (1H, d, J = 7.5 Hz, H5), 5.98 (1H, d, J = 4.6 Hz, H1'), 7.69 (1H, d, J = 7.5 Hz, H6); 13C NMR (125 MHz) CD3OD δC 20.40 (COCH3), 20.45 (COCH3), 20.69 (COCH3), 64.32 (C5'), 71.68 (C3'), 74.69 (C2'), 80.99 (C4'), 91.09 (C1'), 96.76 (C5), 143.23 (C6), 157.91 (C4), 167.82 (C2), 171.35 (COCH3), 171.39 (COCH3), 172.19 (COCH3); MS (ES+) m/z (370 [M+1]. HRMS (ES+) m/z found 370.1243 [calcd for C13H29N3O9+(M+H)+ 370.1245].

Cytidine 2', 3', 5'-tribenzoate (3f). Prepared from 2f[23a,b] according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH2Cl2/MeOH from 98/2 to 96/4 to give 3f[23c] as a white solid (0.049 g,
53% yield). $^1$H NMR (500 MHz) CD$_3$Cl $\delta$H 2.12 (3H, s, COCH$_3$), 4.63 (1H, dd, $J = 3.9, 12.2$ Hz, H5$'$), 4.72–4.68 (1H, m, H4$'$), 4.76 (1H, dd, $J = 2.8, 12.2$ Hz, H5$'$), 5.74–5.78 (1H, m, H2), 5.79–5.84 (1H, m, H3$'$), 6.31 (1H, d, $J = 4.2$ Hz, H1$'$), 7.31–7.24 (5H, m, Ph, H5), 7.37–7.42 (2H, m, Ph), 7.43–7.49 (2H, m, Ph), 7.50–7.55 (1H, m, Ph), 7.81–7.89 (5H, m, Ph, H6), 7.98–8.08 (2H, m, Ph), 9.58 (1H, br s, NHCOCH$_3$).

$^{13}$C NMR (125 MHz) CD$_3$Cl $\delta$C 63.92 (C5$'$), 71.20 (C3$'$), 74.45 (C2$'$), 80.15 (C4$'$), 89.25 (C1$'$), 95.45 (C5), 129.40 (C-Ar), 129.71 (CH-Ar), 129.85 (CH-Ar), 129.97 (CH-Ar), 133.49 (CH-Ar), 133.61 (CH-Ar), 133.62 (CH-Ar), 141.36 (C6), 155.28 (C5), 165.33 (COPh), 165.37 (COPh), 165.39 (C4), 166.14 (COPh); MS (ESI$^+$) m/z found 272.0701 [calcd for C$_{12}$H$_{18}$N$_3$O$_5$S$^+$ (M+H)$^+ 284.1241$].

$^{2'}$, $^{3'}$-O-Isopropylidene-cytidine (3g). Prepared from 2g$^{[24a,b]}$ according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH$_2$Cl$_2$/MeOH from 98/2 to 95/5 to give 3g$^{[24c]}$ as a white solid (0.043g, 49% yield). Prepared according to the in situ Schwartz’s reagent generation procedure for the deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH$_2$Cl$_2$/MeOH from 98/2 to 95/5 to give 3g as a white solid (0.070g, 80% yield). $^1$H NMR (500 MHz) CD$_3$OD $\delta$H 1.25 (3H, s, CH$_3$), 1.45 (3H, s, CH$_3$), 3.62 (1H, dd, $J = 4.5, 12.0$ Hz, H-5$'$a), 3.69 (1H, dd, $J = 3.5, 12.0$ Hz, H-5$'$b), 4.11–4.13 (1H, m, H-4$'$), 4.72–4.74 (1H, m, H-3$'$), 4.78–4.80 (1H, m, H-2$'$), 5.75 (1H, s, H-1$'$), 5.81 (1H, d, $J = 7.5$ Hz, H-5), 7.73 (1H, d, $J = 7.5$ Hz, H-6); $^{13}$C NMR (125 MHz) CD$_3$OD $\delta$C 25.55 (CCH$_3$)$_2$, 27.55 (CCH$_3$)$_2$, 63.19 (C5$'$), 82.25 (C3$'$), 86.40 (C2$'$), 88.69 (C4$'$), 95.45 (C1$'$), 96.20 (C5), 115.03 (CCH$_3$)$_2$, 144.42 (C6), 154.90 (C2), 167.82 (C4).MS (ESI$^+$) m/z = (284 [M+1]).HRMS (ES$^+$) m/z found 284.1243 [calcd for C$_{12}$H$_{18}$N$_3$O$_5$S$^+$ (M+H)$^+ 284.1241$].

O-Acetyl-lamivudine (3h). Prepared from 2h$^{[19a,25]}$ according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH$_2$Cl$_2$/MeOH from 98/2 to 95/5 to give 3h$^{[25]}$ as a white solid (0.048g, 56% yield). $^1$H NMR (500 MHz) CD$_3$OD $\delta$H 1.90 (3H, s, COCH$_3$), 2.95 (1H, dd, $J = 3.0, 12.5$ Hz, H4$'$), 3.35 (1H, dd, $J = 5.5, 12.5$ Hz, H4$'$), 4.20 (1H, dd, $J = 3.0, 12.5$ Hz, CH$_2$OH), 4.35 (1H, dd, $J = 5.0, 12.5$ Hz, CH$_2$OH), 5.20 (1H, dd, $J = 3.5, 5.0$ Hz, H-2$'$), 5.70 (1H, d, $J = 7.5$ Hz, H-5), 6.10 (1H, dd, $J = 3.5, 5.5$ Hz, H-5$'$), 7.68 (1H, d, $J = 7.5$ Hz, H-6); $^{13}$C NMR (125 MHz) CD$_3$OD $\delta$C 20.62 (CH$_3$), 38.15 (C-4$'$), 65.64 (CH$_2$OH), 84.44 (C-2$'$), 89.11 (C-5$'$), 96.03 (C-6), 142.49 (C-5), 157.83 (C-2), 167.72 (C-4), 172.08 (COCH$_3$); MS (ESI$^+$) m/z = 272 [M+1]. HRMS (ES$^+$) m/z found 272.0701 [calcd for C$_{10}$H$_{14}$N$_3$O$_4$S$^+$ (M+H)$^+ 272.0700$].
O-Trityl-lamivudine (3i). Prepared from 2i\textsuperscript{[26]} according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH\textsubscript{2}Cl\textsubscript{2}/MeOH from 98/2 to 95/5 to give 3i as a white solid (0.023 g, 25% yield). \textsuperscript{1}H NMR (500 MHz) CDCl\textsubscript{3} \( \delta \)H 3.09 (1H, dd, \( J = 2.5, 12.5 \) Hz, H-4'), 3.44 (1H, dd, \( J = 5.5, 12.5 \) Hz, H-4'), 3.49 (2H, d, \( J = 3.5 \) Hz, CH\textsubscript{2}OH), 5.19 (1H, t, \( J = 3.5 \) Hz, H-2'), 5.38 (1H, d, \( J = 7.0 \) Hz, H-5), 6.27 (1H, dd, \( J = 3.0, 5.5 \) Hz, H-5'), 7.26–7.15 (10H, m, Ph), 7.39–7.37 (5H, m, Ph), 7.93 (1H, d, \( J = 7.0 \) Hz, H-6); \textsuperscript{13}C NMR (125 MHz) CDCl\textsubscript{3} \( \delta \)C 36.72 (C-4'), 84.75 (C-5'), 84.88 (C-Ph), 91.12 (C-5), 124.39, 125.59, 126.23 (CH-Ph), 139.06 (C-6), 140.08 (C-Ph), 153.01 (C-2), 163.16 (C-4); MS (ESI+) m/z = 472 [M+1]. HRMS (ESI+) m/z found 472.1685 [calcd for C\textsubscript{27}H\textsubscript{26}N\textsubscript{3}O\textsubscript{5}S\textsuperscript{+} (M+H)\textsuperscript{+} 472.1689].

O-Acetyl-acyclovir (3j). Prepared from 2j\textsuperscript{[19a,27a]} according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH\textsubscript{2}Cl\textsubscript{2}/MeOH from 98/2 to 95/5 to give 3j\textsuperscript{[27b]} as a white solid (0.041 g, 47%). \textsuperscript{1}H NMR (500 MHz) (CD\textsubscript{3})\textsubscript{2}SO \( \delta \)H 1.95 (3H, s, COCH\textsubscript{3}), 3.65 (2H, dd, \( J = 7.0, 7.5 \) Hz, CH\textsubscript{2}O), 4.10 (2H, dd, \( J = 5.0, 6.0 \) Hz, CH\textsubscript{2}O), 6.55 (2H, s, NCH\textsubscript{2}O), 7.80 (1H, s, H-8), 10.65 (1H, brs, NH); \textsuperscript{13}C NMR (125 MHz) (CD\textsubscript{3})\textsubscript{2}SO \( \delta \)C 20.53 (CH\textsubscript{3}), 62.70 (NCH\textsubscript{2}), 66.48 (CH\textsubscript{2}O), 71.80 (NCH\textsubscript{2}O), 116.45 (C-5), 137.62 (C-8), 151.39 (C-4), 153.92 (C-2), 156.71 (C-6), 170.22 (COCH\textsubscript{3}); MS (ESI+) m/z = 268 [M+1]. HRMS (ES\textsuperscript{+}) m/z found 268.1044 [calcd for C\textsubscript{10}H\textsubscript{14}N\textsubscript{5}O\textsubscript{4} \textsuperscript{+} (M+H)\textsuperscript{+} 268.1040].

5'-O-Acetyl-2',3'-O-isopropylidene-adenosine (3k). Prepared from 2k\textsuperscript{[19a,28]} or 2i\textsuperscript{[19a]} according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH\textsubscript{2}Cl\textsubscript{2}/MeOH from 98/2 to 95/5 to give 3k as a white solid (0.068 g, 76% from 2k; 0.034 g, 53% from 2i). \textsuperscript{1}H NMR (500 MHz) CD\textsubscript{3}Cl \( \delta \)H 1.33 (3H, s, CH\textsubscript{3}), 1.55 (3H, s, CH\textsubscript{3}), 1.92 (3H, s, COCH\textsubscript{3}), 4.15 (1H, dd, \( J = 6.2 \) Hz, 11.7 Hz, H5'), 4.29 (1H, dd, \( J = 4.4 \) Hz, 11.7 Hz, H5'), 4.43–4.38 (1H, m, H4'). 4.99 (1H, dd, \( J = 3.4 \) Hz, 6.3 Hz, H3'), 5.41 (1H, dd, \( J = 2.0 \) Hz, 6.3 Hz, H2'), 5.94 (2H, br s, NH\textsubscript{2}), 6.04 (1H, d, \( J = 2.0 \) Hz, H1'), 7.82 (1H, s, H8), 8.28 (1H, s, H2'); \textsuperscript{13}C NMR (125 MHz) CDCl\textsubscript{3} \( \delta \)C 20.68 (COCH\textsubscript{3}), 25.41 (CCH\textsubscript{3}), 27.14 (CCH\textsubscript{3}), 64.09 (C5'), 81.73 (C4'), 84.23 (C3'), 85.04 (C2'), 91.06 (C1'), 114.59 (C5), 120.35 (CCH\textsubscript{3}), 139.71 (C8), 149.27 (C4), 153.22 (C2), 155.71 (C6), 170.41 (COCH\textsubscript{3}). MS (ES\textsuperscript{+}) m/z (350) [M+1]; HRMS (ES\textsuperscript{+}) m/z found 350.1451 [calcd for C\textsubscript{15}H\textsubscript{20}N\textsubscript{5}O\textsubscript{5} \textsuperscript{+} (M+H)\textsuperscript{+} 350.1459].

N-acetyl-2',3'-O-isopropylidene-5'-O-[naphthyl (cyclohexyl-L-alamyl)] phosphate cytidine (5). To a solution of 2g\textsuperscript{[12a,b]} (0.5 g, 1.53 mmol) and (2S)-cyclohexyl 2-((chloro(naphthalen-1-yloxy)phosphoryl)amino)propanoate (4\textsuperscript{[16,18a]}), 1.02g, 3.073 mmol) in anhydrous THF (10mL), 1M tBuMgCl (3.08 mL, 3.073 mmol) is added dropwise and the reaction mixture is stirred
at room temperature overnight. After this period, the solvent is removed under reduced pressure. The crude is purified by column chromato-ography on silica gel gradient elution of CH$_2$Cl$_2$/MeOH from 98/2 to 95/5. The compound 5 is recovered as a white solid$^{[16,18a]}$ (0.420, 40% yield). $^1$H NMR (500 MHz) CD$_3$OD $\delta$H 1.28–1.40 (11H, m, CHCH$_3$, CH$_3$, 2 $\times$ CH$_2$-cHex), 1.52–1.58 (4H, m, CH$_3$, CH$_2$-cHex), 1.69–1.78 (4H, m, 2 $\times$ CH$_2$-cHex), 2.15, 2.18 (3H, s, COCH$_3$), 3.99–4.02 (1H, m, CHCH$_3$), 4.40–4.52 (3.5H, m, CH-2', H-4', H-5'), 4.68–4.72 (2H, m, H-2', H-3'), 4.90 (0.5H, m, H-3'), 5.80 (1H, d, $J = 2.5$ Hz, H1'), 7.25 (0.5H, d, $J = 7.5$ Hz, H-5), 7.35 (0.5H, d, $J = 7.5$ Hz, H-6), 7.39–7.42 (1H, m, Naph), 7.47–7.49 (1H, m, Naph), 7.52–7.58 (2H, m, Naph), 7.70–7.72 (1H, m, Naph), 7.87–7.89 (1.5H, m, Naph, H-5), 7.96 (0.5H, d, $J = 7.5$ Hz, H-5), 8.08–8.10 (0.5H, m, Naph), 8.13–8.15 (0.5H, m, Naph); $^{13}$C NMR (125 MHz) CD$_3$OD $\delta$C 20.45 (d, $J_{CP} = 7.5$ Hz, CHCH$_3$), 20.60 (d, $J_{CP} = 7.5$ Hz, CH$_3$), 24.51 (CH$_2$-cHex), 25.50, 25.56, (CH$_3$), 26.39 (CH$_2$-cHex), 27.45, 27.47 (CH$_3$), 32.36, 32.45 (CH$_2$-cHex), 51.89, 51.97 (CHCH$_3$), 68.01, 68.02 (d, $J_{CP} = 7.5$ Hz, C-5'), 75.00 (CHO), 82.22, 82.24 (CH$_3$), 86.57 (CH$_2$), 87.51 (d, $J_{CP} = 2.5$ Hz, C-4'), 87.57 (d, $J_{CP} = 2.5$ Hz, C-4'), 96.58, 96.65 (C-1'), 98.02, 98.12 (C-6), 115.06, 115.21 (C-Naph), 116.22 (d, $J_{CP} = 3.7$ Hz, CH-Naph), 116.49 (d, $J_{CP} = 3.7$ Hz, CH-Naph), 122.60, 122.68, 126.15, 126.53 (CH-Naph), 126.59, 127.60, 127.70, 127.80, 127.85, 127.93, 128.97 (CH-Naph), 136.28 (C-Naph), 147.20, 147.35 (C5), 147.85 (d, $J_{CP} = 7.5$ Hz, ipso-Naph), 148.00 (d, $J_{CP} = 7.5$ Hz, ipso-Naph), 157.55, 157.59 (C-2'), 164.57 (C-4), 172.85, 172.91 (COCH$_3$), 174.32 (d, $J_{CP} = 3.7$ Hz, CO$_2$), 174.63 (d, $J_{CP} = 3.7$ Hz, CO$_2$); $^{31}$P NMR (500 MHz) MeOD $\delta$P 3.92, 4.15. MS (ESI+) $m/z$ = 685 [M+1]. HRMS (ES+) $m/z$ found 685.2631 [calcd for C$_{33}$H$_{42}$N$_4$O$_{10}$P$^+$ (M+H)$^+$ 685.2633].

2',3'-O-isopropylidene-5'-O-[naphthyl (cyclohexyl-L-alanyl)] phosphate cytidine (6). Prepared from 5$^{[16,18a]}$ according to standard procedure for the N-deacetylation reaction. The crude compound is purified by flash chromatography on silica gel gradient elution of CH$_2$Cl$_2$/MeOH from 98/2 to 95/5 to give 6 as a white solid (0.061g, 65% yield). $^1$H NMR (500 MHz) CD$_3$OD $\delta$H 1.32–1.41 (12H, m, CHCH$_3$, CH$_3$, 3 $\times$ CH$_2$-cHex), 1.54 (3H, s, CH$_3$), 1.55–1.84 (4H, m, CH$_2$-cHexyl), 4.00–4.05 (1H, m, CHCH$_3$), 4.34–4.44 (3H, m, H-4', H-5'), 4.64–4.77 (2H, m, H-2', H-3'), 4.81–4.84 (m, 1H, CHO), 5.74 (0.5H, d, $J = 7.5$ Hz, H-6), 5.78–5.81 (1.5H, m, H-1', H-6), 7.43–7.48 (1.5H, m, CH-Naph.), 7.50–7.53 (1.5H, m, CH-Naph), 7.55–7.59 (2H, m, CH-Naph, H-5), 7.73 (1H, d, $J = 5.0$ Hz, CH-Naph), 7.90–7.92 (1H, m, CH-Naph), 8.16–8.20 (1H, m, Naph); $^{13}$C NMR (125 MHz) CD$_3$OD $\delta$C 20.45 (d, $J_{CP} = 7.5$ Hz, CHCH$_3$), 20.60 (d, $J_{CP} = 7.5$ Hz, CH$_3$), 24.61 (CH$_2$-cHex), 25.50, 25.56, (CH$_3$), 26.39 (CH$_2$-cHex), 27.45, 27.47 (CH$_3$), 32.36, 32.45 (CH$_2$-cHex), 51.91, 51.96 (CHCH$_3$), 68.11, 68.13 (d, $J_{CP} = 5.0$ Hz, C-5'), 74.98 (CHO), 82.23, 82.27 (C-3'), 86.04, 86.09 (C-2'), 86.63 (d, $J_{CP} = 2.5$ Hz, C-4'), 86.70 (d, $J_{CP} = 2.5$ Hz, C-4'), 96.24 (C-6), 115.24, 115.31 (C-Naph), 116.31 (d, $J_{CP} = 3.7$ Hz, CH-Naph), 116.
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48 (d, $J_{CP} = 3.7$ Hz, CH-Naph), 122.74, 126.08, 126.54, 126.58, 127.55, 127.60, 127.84 127.87, 128.93 (CH-Naph), 136.33 (C-Naph), 144.19 (C-5), 147.85 (d, $J_{CP} = 7.5$ Hz, ipso C-Naph), 148.00 (d, $J_{CP} = 7.5$ Hz, ipso C-Naph), 157.84 (C-2), 167.84 (C-4), 174.32 (d, $J_{CP} = 3.7$ Hz, CO$_2$), 174.63 (d, $J_{CP} = 3.7$ Hz, CO$_2$); $^{31}$P NMR (500 MHz) CD$_3$OD $\delta$P 3.96, 4.11; MS (ES$^+$) $m/z$ = 643 [M$^+$ + 1]. HRMS (ES$^+$) $m/z$ found 643.2521 [calcd for C$_{31}$H$_{40}$N$_4$O$_9$P$^+$ (M$^+$ + H)$^+$ 643.2527].

SUPPLEMENTARY MATERIALS

Supplementary file includes experimental procedures for the synthesis of protected nucleosides and analytical data for all new compounds. Supplementary materials are available for this article. Go to the publisher’s online edition of Nucleosides, Nucleotides and Nucleic Acids to view the free supplementary files.

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