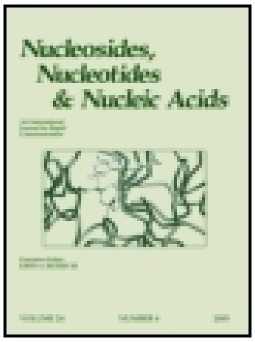

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CHEMOSELECTIVE *N*-DEACETYLATION OF PROTECTED NUCLEOSIDES AND NUCLEOTIDES PROMOTED BY SCHWARTZ'S REAGENT

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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 organozircocene emerging as one of the most useful classes of transition metal derivatives for use in organic synthesis.[1] One important reagent belonging to this class of organometallic compounds is the chlorobis(cyclopentadienyl)hydrido-zirconium **1**, also called zirconocene hydrochloride but better known as Schwartz's reagent.[2] Wailes and Weigold[3] were the first to prepare **1** and, subsequently, Schwartz[2a] and many other scientists exploited its potential in the functionalization of organic compounds.[4] 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,

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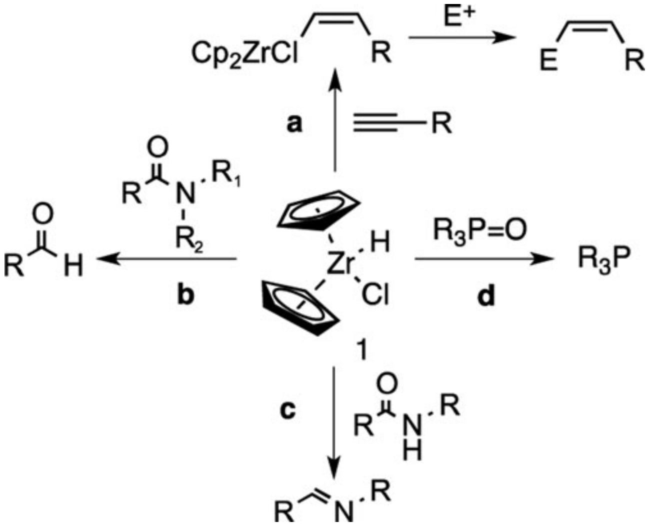


FIGURE 1 Selected organic transformations involving the Schwartz's reagent.

Reaction a).[5] 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.[2b]

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**),[6] and the reduction of secondary amides to *N*-substituted imines (Figure 1, **Reaction c**).[7] 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**).[4d] Recently, Bhat and co-workers reported a very mild and useful deacetylation procedure of acetamides involving reagent **1**.[8] 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.

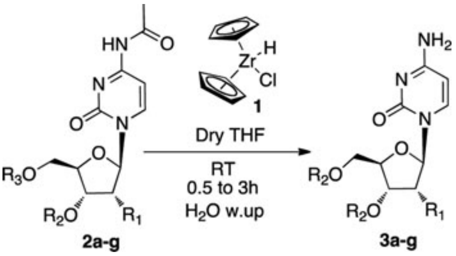
The amine functionality is present in many compounds of biological interest,[9] for instance natural products and pharmaceuticals. Nucleoside and nucleotide chemistry frequently involves protecting procedures at the amine and hydroxyl groups and benefit of selective deprotection methods, in order to 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[10] 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[11] and hydrazine hydrate[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[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



Entry	Cpd	*R*1	*R*2	*R*3	**1** (eq)	Temp (°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	Ac	3	rt	3	**3e**	70	23
6	**2f**	OBz	Bz	Bz	3	rt	3	**3f**	53	41
7	**2g**	CMe_2		H	3	rt	3	**3g**	55	38
8	**2a**	H	Ac	Ac	6	rt	3	**3a**	55	42
9	**2a**	H	Ac	Ac	3	70	12	**3a**	48	39

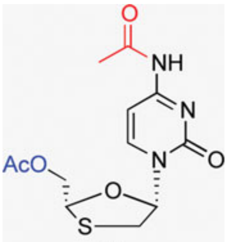
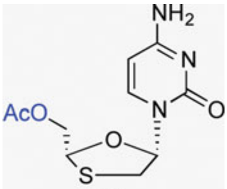
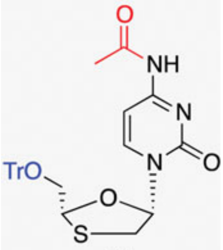
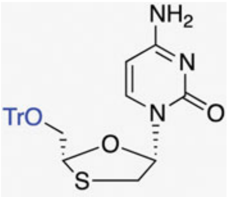
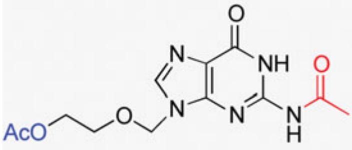
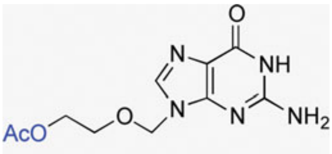
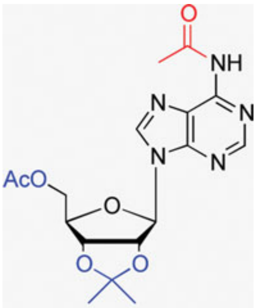
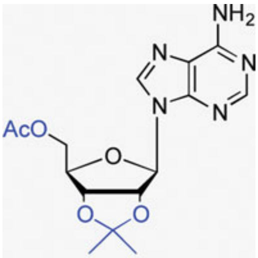
(Table 1, Entry 8). Incrementing the temperature up to 70°C did not enhance the yield (Table 1, Entry 9). Subsequently, we decided to broaden the scope of the methodology by testing it on examples of other pyrimidine and purine nucleoside derivatives bearing different PGs (Table 2). Lamivudine was acetylated 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).

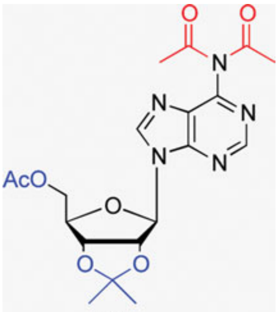
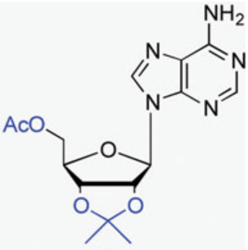
Finally, *N,N*-diacetyl-2′,3′-isopropylidene adenosine **2l** was submitted to the optimized protocol. In this case Schwartz's reagent was able to remove both *N*-acetyl groups, affording compound **3k** in 53% yield, with only traces of mono-*N*-acetylated derivative **2k**.

TABLE 2 *N*-deacetylation of protected pyrimidine and purine nucleosides, promoted by Schwartz's reagent

Entry	Compound	Product	Yield (%)
1	 **2h**	 **3h**	56
2	 **2i**	 **3i**	25
3	 **2j**	 **3j**	47
4	 **2k**	 **3k**	76

(Continued on next page)

TABLE 2 *N*-deacetylation of protected pyrimidine and purine nucleosides, promoted by Schwartz's reagent *(Continued)*

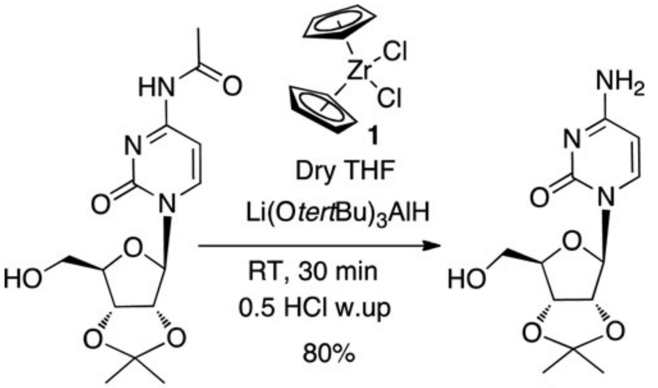
Entry	Compound	Product	Yield (%)
5	 **2l**	 **3K**	53

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.*[6c] reported a practical method to generate Schwartz's reagent in situ using Li(O*t*-Bu)$_3$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 **2g** 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 **2g** and 1.5 equivalents of Cp_2ZrCl_2 in THF, solid Li(O*t*-Bu)$_3$AlH was added in one portion and the mixture was stirred for 40 minutes. Aqueous workup, followed by column chromatography, afforded compound **3g** 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. [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.[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.[15] Among different nucleoside monophosphate prodrug strategies is

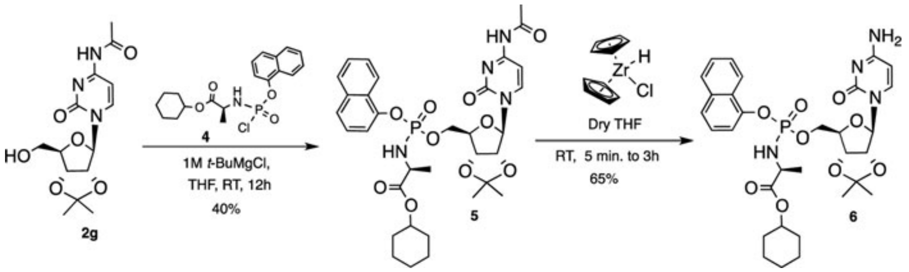


2g

3g

SCHEME 1 *N*-deacetylation of *N*-acetyl-2′,3′-*O*-isopropylidene cytidine 2 g with in situ generated Schwartz's reagent 1.

the phosphoroamidate prodrug approach (ProTide), consisting of an amino acid ester promoiety 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 phosphoramidate motif and whether this protocol can be used at later stage in the synthesis of this class of prodrugs.



2g

5

6

SCHEME 2 Synthesis and deacetylation of *N*-acetyl-2′,3′-*O*-isopropylidene- cytidine-5′-*O*-[napthyl (cyclohexyl-L-alanyl)] phosphate (5) promoted by Schwartz reagent.

Phosphoroamidate **5** was synthesized from **2g** and (2*S*)-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 phosphoramidate 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[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_3OD (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_3PO_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.[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_2Cl_2 (2 × 5 mL). The combined organic layer is washed with brine solution and dried over anhydrous Na_2SO_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.[6c] To a solution of *N*-acetyl nucleoside (100 mg) and Cp_2ZrCl_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 CH_2Cl_2 (2 × 5 mL). The combined organic layer is washed with brine solution and dried over anhydrous Na_2SO_4, 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**[19a,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_2Cl_2/MeOH from 98/2 to 95/5 to give **3a**[19c] as a white solid (0.050 g, 57% yield). ^{1}H NMR (500 MHz) $CDCl_3$ δ_H 2.08 (3H, s, $OCOCH_3$), 2.09 (3H, s, $OCOCH_3$), 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). ^{13}C NMR (125 MHz) $CDCl_3$ δ_C 20.90, 20.98 (CH_3), 38.24 (CH_2-2′), 63.82 (CH_2-5′), 74.12 (C-3′), 82.63 (C-4′), 88.18 (C-1′), 95.87 (C-5), 140.21 (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 $C_{13}H_{18}N_3O_6^+$ $(M+H)^+$ 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 CH_2Cl_2/MeOH from 98/2 to 95/5 to give **3b**[20c] as a white solid (0.044 g, 49%). ^{1}H NMR (500 MHz) $CDCl_3$ δ_H 0.12 (6H, s, 2 × CH_3), 0.15 (6H, s, 2 × CH_3), 0.91 (9H, s, $C(CH_3)_3$), 0.98 (9H, s, $C(CH_3)_3$), 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); ^{13}C NMR (125 MHz) $CDCl_3$ δ_C –4.92, –4.58 ($SiCH_3$), 17.93, 18.94 ($C(CH_3)_3$) 26.04, 26.22 ($C(CH_3)_3$), 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 $C_{21}H_{42}N_3O_4Si_2^+$ $(M+H)^+$ 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 CH_2Cl_2/MeOH from 98/2 to 95/5 to give **3c** as a white solid (0.061 mg, 68%). ^{1}H NMR (500 MHz) CD_3OD δ_H 1.44–1.48 (8H, m, CH_2 Py), 1.61–1.76 (4H, m, CH_2 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, CH_2O 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, CH_2O 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); ^{13}C NMR (125 MHz) CD_3OD δ_C 20.47, 20.50, 20.68, 20.77 (CH_2 Py), 26.51, 26.55 (CH_2 Py), 31.69, 31.75, 31.94, 32.01 (CH_2 Py), 39.54, 39.71, 40.82, 40.98 (C-2′), 63.69, 63.73, 63.75, 63.92 (CH_2O), 68.30, 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 $C_{19}H_{30}N_3O_6^+$ $(M+H)^+$ 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 CH_2Cl_2/MeOH from 98/2 to 95/5 to give **3d** as a white solid (0.035 g, 39% yield). ^{1}H NMR (500 MHz) CD_3OD δ_H 1.47 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$), 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, d, 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); ^{13}C NMR (125 MHz) CD_3OD δ_C 27.96, 28.02 ($C(CH_3)_3$), 31.70 ($C(CH_3)_3$), 61.96 (C-5′), 74.17 (C-3′), 77.25 (C-2′), 83.93 (C-4′), 89.94 (C-1′), 96.64 (C-5), 143.07 (C-6), 153.61, 153.89 ($COC(CH_3)_3$), 158.01(C-2), 167.56 (C-4); MS (ES+) m/z = 444 [M+1]. HRMS (ES$^+$) m/z found 444.1973 [calcd for $C_{19}H_{30}N_3O_9^+$ $(M+H)^+$ 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 CH_2Cl_2/MeOH from 98/2 to 95/5 to give **3e**[10b] as a white solid (0.063 g, 70% yield). ^{1}H NMR (500 MHz) CD_3OD δ_H 2.10 (3H, s, $COCH_3$), 2.11 (3H, s, $COCH_3$), 2.12 (3H, s, $COCH_3$), 4.34–4.40 (3H, m, H4′, H5′), 5.41 (dd, J = 5.0, 5.9 Hz, 1H, 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); ^{13}C NMR (125 MHz) CD_3OD δ_C 20.40 ($COCH_3$), 20.45 ($COCH_3$), 20.69 ($COCH_3$), 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 ($COCH_3$), 171.39 ($COCH_3$), 172.19 ($COCH_3$); MS (ES+) m/z (370) [M+1]. HRMS (ES$^+$) m/z found 370.1243 [calcd for $C_{15}H_{20}N_3O_8^+$ $(M+H)^+$ 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 CH_2Cl_2/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_3Cl δ_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_3Cl δ_c 63.92 (C5′), 71.20 (C3′), 74.45 (C2′), 80.15 (C4′), 89.25 (C1′), 95.45 (C5), 128.46 (CH Ar), 128.49 (CH-Ar), 128.68 (CH-Ar), 128.75 (C-Ar), 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 (ES+) *m/z* (556) [M+1]; HRMS (ES$^+$) *m/z* found 556.1711 [calcd for $C_{30}H_{26}N_3O_8{}^+$ (M+H)$^+$ 556.1714].

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_2Cl_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_2Cl_2/MeOH from 98/2 to 95/5 to give **3g** as a white solid (0.070 g, 80% yield). ^{1}H NMR (500 MHz) CD_3OD δ_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 = 7.5Hz, H-6); ^{13}C NMR (125 MHz) CD_3OD δ_C 25.55 ($C\mathit{C}H_3)_2$), 27.55 ($C\mathit{C}H_3)_2$), 63.19 (C5′), 82.25 (C3′), 86.40 (C2′), 88.69 (C4′), 95.45 (C1′), 96.20 (C5), 115.03 ($\mathit{C}CH_3)_2$), 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 $C_{12}H_{18}N_3O_5{}^+$ (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_2Cl_2/MeOH from 98/2 to 95/5 to give **3h**[25] as a white solid (0.048 g, 56% yield). ^{1}H NMR (500 MHz) CD_3OD δ_H 1.90 (3H, s, $COCH_3$), 2.95 (1H, dd, J = 3.0, 12.5 Hz, H-4′), 3.35 (1H, dd, J = 5.5, 12.5 Hz, H-4′), 4.20 (1H, dd, J = 3.0, 12.5 Hz, CH_2OH), 4.35 (1H, dd, J = 5.0, 12.5 Hz, CH_2OH), 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_3OD δ_C 20.62 (CH_3), 38.15 (C-4′), 65.64 (CH_2OH), 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 ($\mathit{C}OCH_3$); MS (ESI+) *m/z* = 272 [M+1]. HRMS (ES$^+$) *m/z* found 272.0701 [calcd for $C_{10}H_{14}N_3O_4S^+$ (M+H)$^+$ 272.0700].

***O*-Trityl-lamivudine (3i).** Prepared from **2i**[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_2Cl_2/MeOH from 98/2 to 95/5 to give **3i** as a white solid (0.023 g, 25% yield). ^1H NMR (500 MHz) $CDCl_3$ δ_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_2OH), 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); ^{13}C NMR (125 MHz) $CDCl_3$ δ_C 36.72 (C-4′), 61.31 (CH_2OH), 83.90 (C-2′), 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 (ES+) *m/z* found 472.1685 [calcd for $C_{27}H_{26}N_3O_3S^+$ $(M+H)^+$ 472.1689].

***O*-Acetyl-acyclovir (3j).** Prepared from **2j**[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_2Cl_2/MeOH from 98/2 to 95/5 to give **3j**[27b] as a white solid (0.041 g, 47%). ^1H NMR (500 MHz) $(CD_3)_2SO$ δ_H 1.95 (3H, s, $COCH_3$), 3.65 (2H, dd, $J = 7.0, 7.5$ Hz, CH_2O), 4.10 (2H, dd, $J = 5.0, 6.0$ Hz, CH_2O), 6.55 (2H, s, NCH_2O), 7.80 (1H, s, H-8), 10.65 (1H, brs, NH); ^{13}C NMR (125 MHz) $(CD_3)_2SO$ δ_C 20.53 (CH_3), 62.70 (NCH_2), 66.48 (CH_2O), 71.80 (NCH_2O), 116.45 (C-5), 137.62 (C-8), 151.39 (C-4), 153.92 (C-2), 156.71(C-6), 170.22 (*C*OCH_3); MS (ESI+) *m/z* = 268 [M+1]. HRMS (ES^+) *m/z* found 268.1044 [calcd for $C_{10}H_{14}N_5O_4^+$ $(M+H)^+$ 268.1040].

5′-*O*-Acetyl-2′,3′-*O*-isopropylidene-adenosine (3k). Prepared from **2k**[19a,28] or **2l**[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_2Cl_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 **2l**). ^1H NMR (500 MHz) CD_3Cl δ_H 1.33 (3H, s, CH_3).1.55 (3H, s, CH_3), 1.92 (3H, s, $COCH_3$), 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_2), 6.04 (1H, d, $J = 2.0$ Hz, H1′), 7.82 (1H, s, H8), 8.28 (1H, s, H2); ^{13}C NMR (125 MHz) $CDCl_3$ δ_C 20.68 ($COCH_3$), 25.41 (CCH_3), 27.14 (CCH_3), 64.09 (C5′), 81.73 (C4′), 84.23 (C3′), 85.04 (C2′), 91.06 (C1′), 114.59 (C5), 120.35 (*C*CH_3), 139.71 (C8), 149.27 (C4), 153.22 (C2), 155.71 (C6), 170.41 ($COCH_3$). MS (ES+) *m/z* (350) [M+1]; HRMS (ES^+) *m/z* found 350.1451 [calcd for $C_{15}H_{20}N_5O_5^+$ $(M+H)^+$ 350.1459].

***N*-acetyl-2′,3′-*O*-isopropylidene-5′-*O*-[napthyl (cyclohexyl-L-alanyl)] phosphate cytidine (5).** To a solution of **2g**[24a,b] (0.5 g, 1.53 mmoL) and (2*S*)-cyclohexyl 2-((chloro(naphthalen-1-yloxy)phosphoryl)amino)propanoate (**4**[16,18a], 1.02g, 3.073 mmoL) in anhydrous THF (10mL), 1M ^{t}BuMgCl (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 chromatography on silica gel gradient elution of CH_2Cl_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_3OD δH 1.28–1.40 (11H, m, $CHCH_3$, CH_3, 2 × CH_2-cHex), 1.52–1.58 (4H, m, CH_3, CH_2-cHex), 1.69–1.78 (4H, m, 2 × 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_3OD δC 20.45 (d, J_{CP} = 7.5 Hz, $CHCH_3$), 20.62 (d, J_{CP} = 7.5 Hz, $CHCH_3$), 24.57 ($COCH_3$), 24.60, 24.62 (CH_2-cHex), 25.42, 25.52, (CH_3), 26.38 (CH_2-cHex), 27.37, 27.43 (CH_3), 32.35, 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, ipsoC-Naph), 148.00 (d, J_{CP} = 7.5 Hz, ipsoC-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 δP 3.92, 4.15. MS (ESI+) *m/z* = 685 [M+1]. HRMS (ES+) *m/z* found 685.2631 [calcd for $C_{33}H_{42}N_4O_{10}P^+$ $(M+H)^+$ 685.2633].

2′,3′-*O*-isopropylidene-5′-*O*-[napthyl (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_2Cl_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_3OD δ_H 1.32–1.41 (12H, m, $CHC\mathit{H}_3$, CH_3, 3 × CH_2-*c*Hex), 1.54 (3H, s, CH_3), 1.55–1.84 (4H, m, CH_2-cHexyl), 4.00–4.05 (1H, m, $C\mathit{H}CH_3$), 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_3OD δ_C 20.45 (d, J_{CP} = 7.5 Hz, $CH\mathit{C}H_3$), 20.60 (d, J_{CP} = 7.5 Hz, $\mathit{C}H_3$), 24.61 (CH_2-*c*Hex), 25.50, 25.56, (CH_3), 26.39 (CH_2-*c*Hex), 27.45, 27.47 (CH_3), 32.36, 32.45 (CH_2-*c*Hex), 51.91, 51.96 ($\mathit{C}HCH_3$), 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′), 95.65 (C-1′), 96.24 (C-6), 115.24, 115.31 (C-Naph), 116.31 (d, J_{CP} = 3.7 Hz, CH-Naph), 116.

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_3OD δ_P 3.96, 4.11; MS (ES+) *m/z* = 643 [M+1]. HRMS (ES+) *m/z* found 643.2521 [calcd for $C_{31}H_{40}N_4O_9P^+$ $(M+H)^+$ 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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