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The first investigation of borane-unsaturated nucleoside reaction system

Joanna Niziol[1], Wojciech Rode[2] and Tomasz Ruman[1*]

[1]*Rzeszów University of Technology, Faculty of Chemistry, Bioorganic Chemistry Laboratory, 6 Powstańców Warszawy Ave. 35-959 Rzeszów, Poland*

[2]*Nencki Institute of Experimental Biology, 3 Pasteur Street, 02-093 Warsaw, Poland*

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Abstract: A novel synthetic approach is presented, involving unsaturated nucleoside hydroboration, with protected stavudine catalytically boronated with pinacolborane to several pinacolborane derivatives of stavudine or 2',3'-dideoxythymidine. The products were converted to much more stable trifluoroborate derivatives that may be considered trifluoroboron analogues of nucleoside phosphates. The post-reaction mixture contained four isomers, being products of catalytic hydroboration, and two isomers, resulting from dehydrogenative borylation, each containing unsaturated 2',3'-moiety. The new compounds were analyzed with NMR and LDI-HRMS methods.

Keywords: BNCT; boron nucleoside; boron nucleotide; dehydrogenative borylation; hydroboration; NMR; nucleoside trifluoroborate.

1. Introduction

Boron analogues/derivatives of biologically active compounds are gaining rising attention in the last years. Compared to the parent, carbon-based, isosteric and often isoelectronic natural compounds, they show unique properties, including a capability to form tetrahedral sp^3 hybridized boron ate complexes resulting from the nucleophilic attack of a biomolecule electron pair onto the boron. The ate complexes with enzymes are often stable, causing effective inhibition.[1-3] Additionally, boron-containing compounds may be useful in boron-neutron capture therapy (BNCT).[4-7]

The field of boron derivatives/analogues of nucleosides and nucleotides has been recently overviewed.[8-9] A few boron derivatives are known with boron atom substituting 2'-, 3'- or 5'-position of the sugar moiety. To this group belong the 3'-boramide derivatives synthesized by Burnham et al.[10] and Yan et al.[11] A series of bononucleotides was recently presented, encompassing thymidine derivatives with boron-containing C(5')-CH_2-$B(OH)_2$ moiety.[12] Other complexes are also known, e.g. cyanoborane adducts of 2'-deoxyinosine, 2'-deoxyguanosine, 2'-deoxyadenosine and 2'-deoxycytidine, each containing the N-BH_2CN moiety, where N is nucleic base nitrogen atom.[13] Similar compounds, containing CN or COOMe groups at boron atom, were presented by Vyakaranam et. al.[14] An important achievement in the boron nucleoside field was synthesis of 5-dihydroxyboryl (C(5)-$B(OH)_2$) derivatives of uracil and uridine, presented for the first time by Schinazi et al.[15] Stavudine boron modifications could be considered the most important in boron nucleoside field. This compound (2',3'-didehydro-3'-deoxythymidine; D4T) is a synthetic thymidine nucleoside analogue with a double bond between the 2'- and 3'-carbon atoms of the pentose ring. Stavudine is an HIV virus nucleoside reverse

*Corresponding author: E-mail: tomruman@prz.edu.pl; Tel: +48178651896, Fax: +48178543655

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transcriptase inhibitor (NRTI),[16-18] approved to be used in combination with other antiretroviral agents in the treatment of HIV infections in USA and EU. So far only a few 5'-boron derivatives of anti-HIV/anti-AIDS compounds have been described.[19]

Seeking new borononucleotide analogues, a pioneer synthetic approach was tested by catalytic boronating of protected stavudine with pinacolborane. The products that may be considered trifluoroboron analogues of nucleoside phosphates, underwent detailed NMR and LDI HRMS (Laser Desorption/Ionization High-Resolution Mass Spectrometry) analyses.

2. Results and discussion

The method of choice to obtain boron nucleosides is the well-known hydroboration process, using transition metal catalysts and described as fast, easy and resulting in good yields of products. With reference to nucleoside-type compounds hydroboration suffers certain drawbacks, as nucleosides and nucleotides (i) are rather fragile compounds, (ii) contain many groups of different reactivity, (iii) often must be used in a protected form. Sterical demands are the main problem considering synthesis of 2' and 3'-boron derivatives of nucleosides by hydroboration of 2',3'-unsaturated moiety. It should be noted that the use of small borane complexes such as BH_3:SMe_2, BH_3:THF or BH_3:py may not be recommended, because of a potential risk of the cross-coupling and reductive cleavage of nucleoside structure.[22] Furthermore, a small borane group attached to a nucleoside molecule undergoes rather easily undesired reactions with oxygen or moisture. Although, in view of the foregoing, it is better to use sterically bigger, mono-hydride borane species, such as catecholborane or pinacolborane, their molecules, due to their sterical demands, are much less reactive in hydroboration reactions and virtually do not react with the 2',3'-unsaturated region of a protected or unprotected nucleoside. These boranes, however, may be used, provided the reaction is properly catalyzed. The catalysts active in olefin hydroboration include for example Wilkinson's catalyst (chlorotris(triphenylphosphine)-rhodium(I)) and bis(1,5-cyclooctadiene)diiridium(I) dichloride/dppp (1,3-bis(diphenylphosphino)-propane) catalytic system.[23-25]

Seeking a boron-nucleoside synthetic route, we prepared protected stavudine, i.e. 3,5'-dibenzoylstavudine (**1**), and performed catalytic hydroboration of this compound. The reaction was carried out in a septa-sealed NMR tube, with the use of dehydrated and deoxygenated reagents and solvents. At room temperature no reaction was apparent with either catalyst. The same amount (3 mol% calculated for monometallic form of catalyst) of each of the two catalysts was used. Even at 50^{o}C it had to run for 200 hours. Following the pinacolborane catalytic hydroboration step, the post-reaction mixture was analyzed with NMR and MS methods (Supplementary Materials), revealing the presence of pinacolborane derivatives of protected stavudine, with Bpin group at 2' and 3' positions of the unsaturated ring, and also of 2'- and 3'-pinacolborane hydroboration products. After analysis, KHF_2 was used to transform the pinacolborane derivatives to much more stable trifluoroborate forms[26] and the reaction mixture analyzed again by the NMR (also with high-resolution COSY) and LDI HRMS methods.

Figure 1 presents molecular structures of the products documented by the analyses to be present in the post-reaction mixture, including four isomers resulting from catalytic hydroboration (**2**-**5**), two isomers with unsaturated 2',3'-moiety, being products of dehydrogenative borylation (**7**,**8**), and a product (**6**) of benzoyl cleavage from compound **7**. Figure 2 presents an example of ^{1}H NMR spectrum of the post-reaction mixture, collected following the rhodium complex-catalyzed process, with assignment of the resonances. The detailed NMR data for compounds **1**-**8** are presented in Table 1. It should be noted that detailed analysis of NMR data shown in Table 1 was based on larger quantity of 1D and especially 2D spectra such as HSQC, HMBC, COSY, NOESY, DEPT or HETCOR. Mentioned spectra are not presented for the sake simplicity of present work.

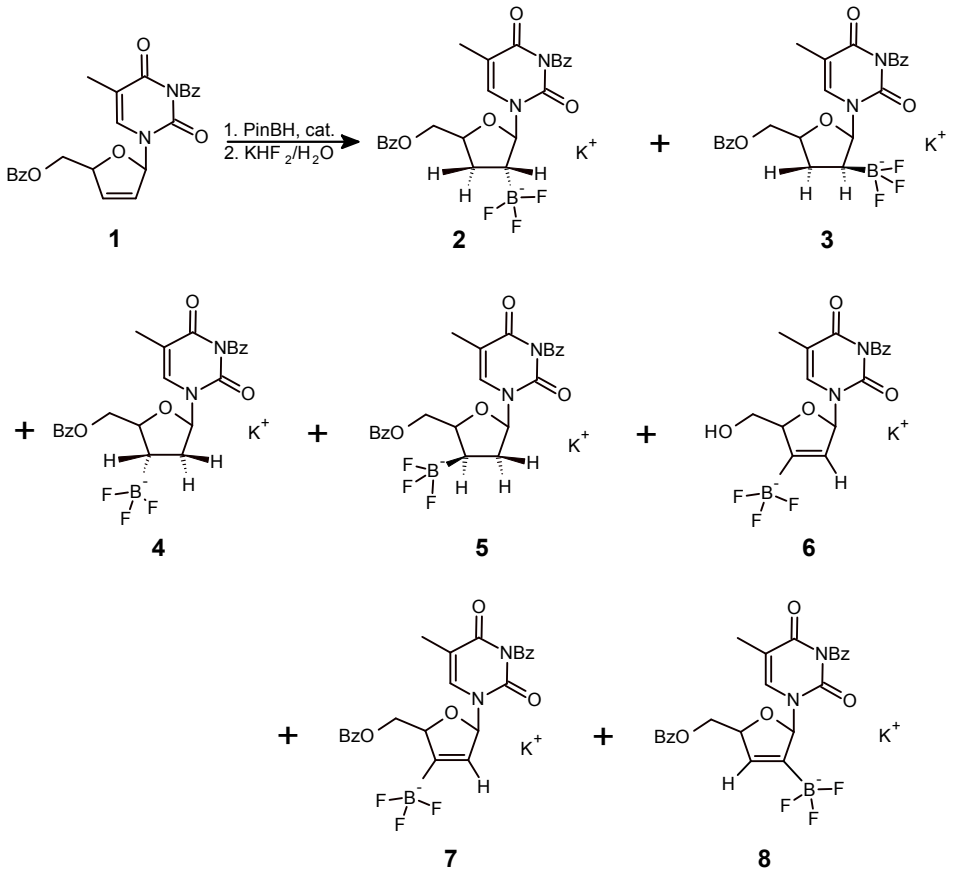

Figure 1. Nucleoside trifluoroborates obtained in the unsaturated nucleoside hydroboration (**2-5**) and dehydrogenative borylation (**6-8**) processes.

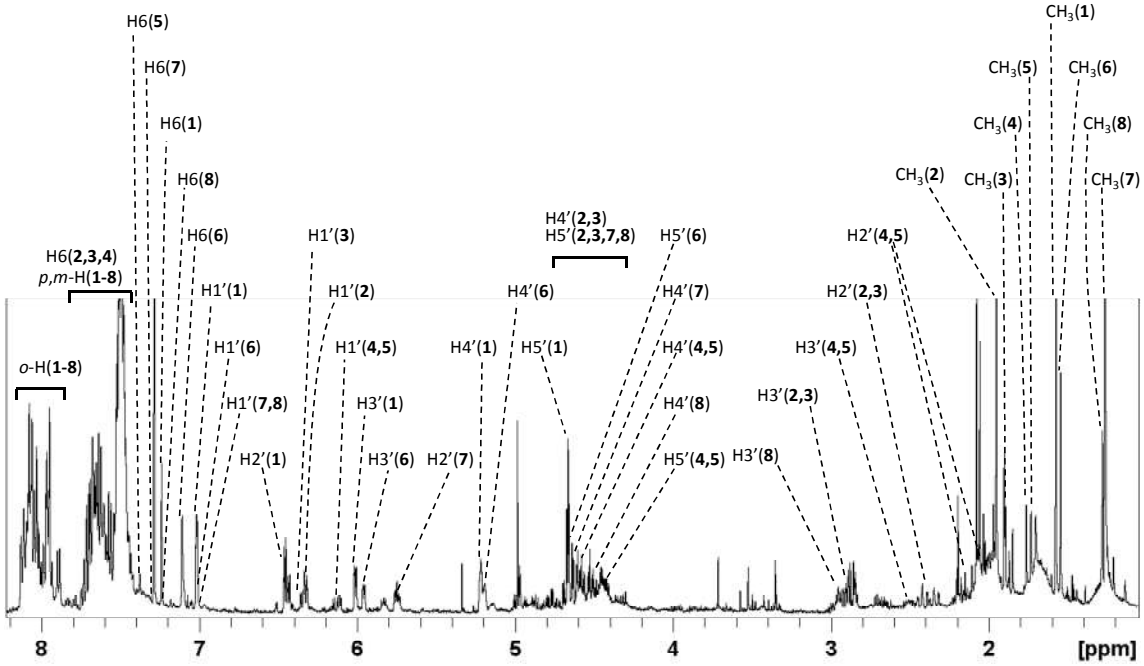

Figure 2. ^{1}H NMR spectrum of the post-reaction mixture of **1** boronation, catalyzed by tris(triphenylphosphine)rhodium(I) chloride.

Table 1. ^{1}H NMR data for compounds **1-8.**

Compound	Multiplicity, area, assignment	δ [ppm]	Coupling const. [Hz]
3,5'-Dibenzoylstavudine (**1**)	m; 2H, *o*-H; 5'-*O*-Bz	8.07	
	m; 2H, *o*-H, 3-*N*-Bz	7.96	
	m, 1H, *p*-H, 5'-*O*-Bz m, 1H, *p*-H, 3-*N*-Bz	7.74-7.49	
	m, 2H, *m*-H, 5'-*O*-Bz m, 2H, *m*-H, 3-*N*-Bz	7.55-7.44	
	q, 1H, H-6	7.24	1.2
	m, 1H, H-1'	7.03-7.00	1.8, 6.1
	dt, 1H, H-2'	6.44	6.1, 1.8
	m, 1H, H-3'	6.01	6.1, 1.8
	m, 1H, H-4'	5.22	
	m, 2H, H-5'	4.66	
	d, 3H, CH_3	1.57	1.2
Potassium *(R)*-2'-(3,5'-dibenzoyl-2'-deoxythymidinyl)trifluoroborate (**2**)	m, 2H, *o*-H, 5'-*O*-Bz m, 2H, *o*-H, 3-*N*-Bz	8.14-7.86	
	m, 2H, *m*-H, 5'-*O*-Bz m, 2H, *m*-H, 3-*N*-Bz m, 2H, *p*-H, 5'-*O*-Bz m, 2H, *p*-H, 3-*N*-Bz	7.76-7.41	
	q, 1H, H-6	7.73	
	m, 1H, H-1'	6.34-6.31	7.9, 1.8
	dt, 1H, H-2'	2.46-2.30	
	m, 2H, H-3'	2.88-3.01	
	m, 1H, H-4'	4.70-4.30	
	m, 2H, H-5'	4.70-4.30	
	d, 3H, CH_3	1.95	
Potassium *(S)*-2'-(3,5'-dibenzoyl-2'-deoxythymidinyl)trifluoroborate (**3**)	m, 2H, *o*-H, 5'-*O*-Bz m, 2H, *o*-H, 3-*N*-Bz	8.14-7.86	
	m, 2H, *m*-H, 5'-*O*-Bz m, 2H, *m*-H, 3-*N*-Bz m, 1H, *p*-H, 5'-*O*-Bz m, 1H, *p*-H, 3-*N*-Bz	7.76-7.41	
	q, 1H, H-6	7.60	
	m, 1H, H-1'	6.37-6.32	
	dt, 2H, H-2'	2.46-2.30	
	m, 1H, H-3'	2.88-3.01	
	m, 1H, H-4'	4.70-4.30	
	m, 2H, H-5'	4.70-4.30	
	d, 3H, CH_3	1.90	
Potassium *(S)*-3'-(3,5'-dibenzoyl-2'-deoxythymidinyl)trifluoroborate (**4**)	m, 2H, *o*-H, 5'-*O*-Bz m, 2H, *o*-H, 3-*N*-Bz	8.14-7.86	
	m, 2H, *p*-H, 3-*N*-Bz m, 2H, *p*-H, 3-*O*-Bz m, 2H, *m*-H, 5'-*O*-Bz m, 2H, *m*-H, 3-*N*-Bz	7.76-7.41	
	q, 1H, H-6	7.50	
	m, 1H, H-1'	6.13-6.10	
	m, 2H, H-2'	2.20-2.15 2.14-2.03	
	m, 1H, H-3'	2.55-2.46	
	m, 1H, H-4'	4.53-4.41	
	m, 2H, H-5'	4.41-4.38	
	d, 3H, CH_3	1.76	1.2
Potassium *(R)*-3'-(3,5'-dibenzoyl-2'-deoxythymidinyl)trifluoroborate (**5**)	m, 1H, *o*-H, 5'-*O*-Bz m, 1H, *o*-H, 3-*N*-Bz	8.14-7.86	
	m, 2H, *p*-H, 3-*N*-Bz m, 2H, *p*-H, 3-*O*-Bz m, 2H, *m*-H, 5'-*O*-Bz m, 2H, *m*-H, 3-*N*-Bz	7.76-7.41	
	q, 1H, H-6	7.38	1.2
	m, 1H, H-1'	6.13-6.10	
	m, 2H, H-2'	2.20-2.15 2.14-2.03	

	m, 1H, H-3’	2.55-2.46	
	m, 1H, H-4’	4.53-4.41	
	m, 2H, H-5’	4.41-4.38	
	d, 3H, CH_3	1.73	1.2
Potassium 2’-(3-benzoylstavudinyl)-trifluoroborate (**6**)	m, 1H, *o*-H, 5’-O-Bz	8.14-7.86	
	m, 1H, *o*-H, 3-N-Bz		
	m, 2H, *p*-H, 3-N-Bz	7.76-7.41	
	m, 2H, *p*-H, 3-O-Bz		
	m, 2H, *m*-H, 5’-O-Bz		
	m, 2H, *m*-H, 3-N-Bz		
	q, 1H, H-6	7.11	1.2
	dd, 1H, H-1’	7.03-7.00	1.8
	m, 1H, H-2’	-	
	m, 1H, H-3’	5.96	5.8
	m, 1H, H-4’	5.19	
	m, 2H, H-5’	4.71-4.56	
	d, 3H, CH_3	1.54	1.2
Potassium 3’-(3,5’-dibenzoyl-stavudinyl)trifluoroborate (**7**)	m, 1H, *o*-H, 5’-O-Bz	8.14-7.86	
	m, 1H, *o*-H, 3-N-Bz		
	m, 2H, *p*-H, 3-N-Bz	7.76-7.41	
	m, 2H, *p*-H, 3-O-Bz		
	m, 2H, *m*-H, 5’-O-Bz		
	m, 2H, *m*-H, 3-N-Bz		
	q, 1H, H-6	7.29	
	m, 1H, H-1’	7.07-7.00	
	m, 1H, H-2’	5.78-5.71	
	m, 1H, H-3’	-	
	m, 1H, H-4’	4.62-4.53	
	m, 2H, H-5’	5.03-4.23	
	d, 3H, -CH_3	1.26	
Potassium 2’-(3,5’-dibenzoyl-stavudinyl)trifluoroborate (**8**)	m, 1H, *o*-H, 5’-O-Bz	8.14-7.86	
	m, 1H, *o*-H, 3-N-Bz		
	m, 2H, *p*-H, 3-N-Bz	7.76-7.41	
	m, 2H, *p*-H, 3-O-Bz		
	m, 2H, *m*-H, 5’-O-Bz		
	m, 2H, *m*-H, 3-N-Bz		
	q, 1H, H-6	7.24	
	m, 1H, H-1’	7.07-7.00	
	m, 1H, H-2’	-	
	m, 1H, H-3’	5.86-5.80	
	m, 1H, H-4’	4.48-4.39	
	m, 2H, H-5’	5.03-4.23	
	d, 3H, -CH_3	1.28	

The quantitative analysis of the post-reaction mixture showed in the case of rhodium catalyst certain percentage of unreacted **1** to be recovered. Integration of resonances observed after boronation with the Wilkinson catalyst process showed ratios of the areas of relative resonances (H1’) for **1**-**2**-**3**-**4**-**5**-**6**-**7**-**8** to be 100:84:37:36:11:61:85:44. Apart from a rather large amount of unreacted substrate **1**, this catalyst allowed 0.9:1 ratio of products of hydroboration:dehydrogenative borylation. The ratio of the hydrogenation products with the boron group under the theoretical ribose plane (on the opposite side than nucleic base) to those with the boron group above this plane was 2.5:1, in a very good agreement with well-known boron preference to attach to sterically less crowded positions. However, a detailed explanation of the reactivity would require an advanced molecular modeling. The preference for dehydrogenative borylation at positions 2’- 3’ was 1:2.

Surprisingly, lack of the substrate resonances indicated nearly 100% substrate transformation with the iridium catalytic system. Moreover, there was no 5’-benzoyl cleavage product (**6**) resonances in the ^{1}H NMR spectrum (Supplementary Materials). As for the products found in the spectrum, the ratios of the relative areas of resonances for **2**-**3**-**4**-**5**-**7**-**8** were 100:41:141:61:87:51 reflecting. The hydroboration to dehydrogenative borylation ratio, calculated based on the area of H1’ resonances, was 2.5:1.

The detailed analysis of those resonances near boron atom, for example H at 2' carbon atom in **2** and **3**, being in a 2-bond distance from boron atom, shows an interesting coupling constant and coupling pattern. The resonance is a complicated multiplet with a rather distinct feature of four similar parts with identical distances between them. Each distance is 16.2 Hz and its origin must be connected with coupling with boron atom because typical hydrogen systems are not capable of this kind of coupling pattern formation. The four parts of peak are an effect of ^{1}H-^{11}B coupling, as boron-11 has its nuclear spin number 3/2. Another isotope, ^{10}B, should give coupling pattern visually constructed of seven peaks or seven multiplets (nuclear spin 3) but due to its much lower natural abundance, and a low peak area due to sevenfold coupling pattern, ^{10}B-couplings are rarely seen in complicated spectra. Similar ^{11}B-^{1}H coupling system was noticed also for H3' of 4 and 5 whose $^{2}J_{B,H}$ is 6.8 Hz. The differences found in the latter case result from an average B-C(3')-H angle and are difficult to anticipate based on experimental or theoretical methods.

The anionic trifluoroborate moiety, found in all the new compounds has quite interesting properties from the point of view of NMR analyses. The electronic, through-bond effects have, compared to thymidine hydroxyl, a rather upfield-shifting effect, surely due to the negative charge of this group. The 3'-hydrogen atom of thymidine has its chemical shift at 5.3 (DMSO-*d6*), while 3'H near trifluoroborate anion in **4** and **5** as low as at 2.5 ppm.

HRMS LDI MS spectra of post reaction mixtures (Supplementary materials) prove the existence of hydroboration products **2-5** as peaks of ions derived from these compounds have been found. The mentioned ions are adducts of the formula $[C_{24}H_{21}BF_3N_2O_6+H+Na]^+$ and $[C_{24}H_{21}BF_3N_2O_6+Na_2]^+$ which have their experimental *m/z* values of 525.1502 and 547.1116 respectively. Calculated monoisotopic *m/z* for these two compounds are 525.1425 and 547.1244 respectively, giving differential $\Delta m/z$ values of 0.0077 and 0.0128. Negative reflectron mode mass spectra contain also peak at *m/z* 501.1402 which is in very good agreement with calculated 501.1449 ($\Delta m/z$ = 0.0047) and belongs to discussed hydroboration products in anionic form without potassium cation $[C_{24}H_{21}BF_3N_2O_6]^-$. Reflectron negative mode spectra contain also peaks of dehydrogenative borylation products **7** and **8** (**(**$[C_{24}H_{19}BF_3N_2O_6]^-$) at *m/z* 499.1280, a value that is in very good agreement with calculated *m/z* value of 499.1293 ($\Delta m/z$ = 0.0013). Positive reflectron mode spectra contains also peak at *m/z* 545.1130 corresponding with sodium adduct of **7** and **8** of general formula $[C_{24}H_{19}BF_3N_2O_6+Na_2]^+$ for which calculated *m/z* is 545.1088 ($\Delta m/z$ = 0.0042). Dehydrogenative borylation and 5'-benzoyl cleavage product (**6**) was also found in positive mode LDI MS spectra as dihydrogen adduct peak at *m/z* 397.1193 shows perfect correlation with calculated value of 397.1186 ($\Delta m/z$ = 0.0007).

The new compounds may be considered boron or fluoroboron analogues of nucleoside 3'- or 2'-phosphates. Each of those newly attached groups is almost isosteric with phosphate group and has an identical mono-negative charge. The compounds **6-8**, fluoroboron derivatives of the anti-HIV drug stavudine, are also potential HIV reverse transcriptase inhibitors.

4. Experimental Section:

^{1}H NMR spectra were obtained with the Bruker Avance II spectrometer, operating in the quadrature mode at 500MHz. All ^{11}B spectra were performed using 5 mm pure quartz NMR tube. The residual peaks of deuterated solvents were used as internal standards. Reagents and deuterated solvents of the highest commercially available grade were purchased from Aldrich. All procedures, including preparation of samples for the NMR measurements, were carried out under nitrogen. All reagents, with the exception of boranes, were dried by triple aseotropic distillation from deuterated chloroform. Pinacolborane was distilled under high vacuum (vacuum pump of 1.5 mbar maximum vacuum pressure) and the middle 1/3 of total reagent volume was collected (50-51^{o}C fraction) and used in experiments. The catalytic hydroboration step was performed in a sealed NMR tube, filled with dry nitrogen and shaken three times to remove traces of oxygen. 3,5'-Dibenzoylstavudine (**1**) was prepared by the method used in thymidine benzoylation.[20] High-resolution COSY spectra were prepared using 4096x4096 measurement points.

Mass spectrometry measurements were performed with the use of the Bruker Autoflex Speed II LDI-MS instrument. Sample ionization was brought about using the monoisotopic ^{109}AgNPET

target, prepared as previously described[21] but with the use of a gold-plated target. Silver and gold ions were used for the 5 to 15-point (typically 10) spectrum calibration. All the presented spectra were recorded in the reflectron mode.

*4.1. Boronation of 3,5'-dibenzoylstavudine (**1**) with tris(triphenylphosphine)rhodium(I) chloride catalyst:*

The nucleoside substrate, 3,5'-dibenzoylstavudine (**1**, 9 mg) in anhydrous $CDCl_3$ (0.5 ml), was mixed with tris(triphenylphosphine)rhodium(I) chloride solution (0.1 ml of 1.9 mg/ml $CDCl_3$ solution) in a NMR tube, followed by vigorous shaking in dry nitrogen atmosphere (three times) for oxygen removal. Pinacolborane (19 µl) was added to the resulting solution and the reaction mixture incubated for 200h at 50°C. Then both NMR and MS spectra were collected (discussed in Results and Discussion) and potassium hydrogen difluoride solution (1 ml of 1M water solution) added to the sample. Following 48h reaction, the mixture was vacuum-dried, extracted to $CDCl_3$ (0.7 ml) and the organic solution directly analyzed with the use of the NMR and MS methods.

*4.2. Boronation of 3,5'-dibenzoylstavudine (**1**) with bis(1,5-cyclooctadiene)diiridium(I) dichloride catalyst:*

The reaction was run similarly to the one presented above (point 4.2) but for a different catalyst, bis(1,5-cyclooctadiene)diiridium(I) dichloride (0.1 ml of 4.2 mg/ml $CDCl_3$ solution added to reaction sample) and an additional ligand, 1,3-bis(diphenylphosphino)propane (10 µl of 5.2 mg/ml $CDCl_3$ solution was added), used. The NMR data for compounds **2**-**8** are presented in Table 1, and LDI HRMS spectra in *Supplementary Materials*.

5. Conclusion

We have synthesized a series of novel boron nucleotide analogues using iridium-catalyzed hydroboration process. The hydroboration process of nucleoside structure is presented for the first time in literature. The products were converted to much more stable trifluoroborate derivatives that may be considered trifluoroboron analogues of nucleoside phosphates. Catalysed reaction of unsaturated nucleoside with borane yielded products of hydroboration and also of dehydrogenative borylation. The new compounds were analyzed with 1D and 2D NMR and also with monoisotopic silver-nanoparticle-based LDI-HRMS methods.

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