$Er(OTf)_3$ as a Valuable Catalyst in a Short Synthesis of 2′,3′-Dideoxy Pyranosyl Nucleosides via Ferrier Rearrangement

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Abstract: $Er(OTf)_3$ is a useful catalyst for the Ferrier rearrangement furnishing 2′,3′-dideoxy pyranosyl nucleosides easily by means of cleaner reaction profiles, short reaction times, mild reaction conditions, good stereoselectivity, and good recoverability of the commercially available catalyst.

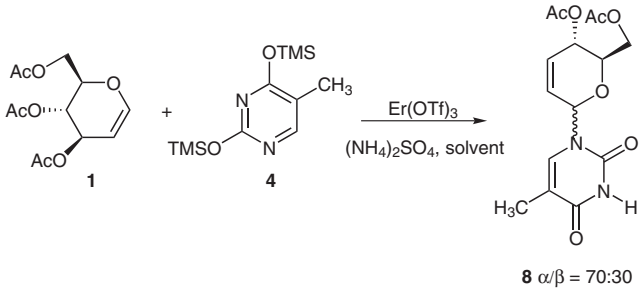
Key words: Ferrier rearrangement, erbium(III) triflate, Lewis acid catalyst, nucleosides, glycals

Over recent decades, there has been considerable interest in nucleoside analogues as a consequence of their potential use as antiviral, antineoplastic,[1] and antibiotic therapeutic agents.[2] Therefore, many structural modifications of natural nucleosides have been made to find molecules showing enhanced biological activities.[1b,d,3] Most nucleoside modifications have focused around five-membered ring systems, but few examples have been published on the corresponding pyranosides,[1b,4] especially regarding the 2,3-dideoxy pyranoside nucleoside analogues,[2,4a,4e,5] which resemble the potent antiviral modified nucleosides ddNs.

Very few methodologies exist to prepare *N*-glycosides by means of a Ferrier rearrangement, and often they have limitations in terms of drastic reaction conditions, work-up, reaction time, and amount of catalyst; some others were tested in only limited examples. Herdewijn and co-workers proposed,[6] about ten years ago, a 'no-acid-added' Ferrier rearrangement of the glycal 3,4-bis-*O*-(*p*-nitrobenzoyl)-D-xylal and pyridine/pyrimidine derivatives to provide acceptable yields of α,β-2′,3′-unsaturated pentopyranosyl nucleosides on a preparative scale.

Herein we report the synthesis of 2′,3′-pyranosyl nucleosides via Ferrier rearrangement catalyzed by erbium(III) triflate.

Over the last few years, we have developed the use of new catalytic reagents for several strategic steps in organic synthesis with the aim of lowering the environmental impact.[7] More recently, we described the use of erbium(III) trifluoromethanesulfonate, as a Lewis acid catalyst, for the synthesis of 2,3-unsaturated *C*-glycosides via Ferrier rearrangement using silylated nucleophiles.[8] In order to expand the applicability of $Er(OTf)_3$ as a Lewis acid catalyst in the Ferrier rearrangement we looked at N-glycosidation. We first tested the reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with transient protected trimethylsilyl thymine **4** generate in situ using HMDS (Scheme 1).[9]



Scheme 1

The reaction conditions were explored performing the process in several solvents at different temperatures with different amounts of catalyst (Table 1).

The best result was obtained when the reaction was carried out in anhydrous acetonitrile with 10 mol% $Er(OTf)_3$ at 50 °C (Table 1, entry 3). A similar result was obtained in anhydrous THF, but the reaction time almost doubled (Table 1, entry 5). All the other solvents were shown to be considerably less appropriate for the reported reaction and in the absence of anhydrous conditions no product was recovered.

Table 1 N-Glycosidation of 3,4,6-Tri-*O*-acetyl-D-glucal (**1**) in Various Reaction Conditions

Entry	Solvent	$Er(OTf)_3$ (mol%)	Time (h)	Temp (°C)	Yield (%)
1	CH_2Cl_2 (anhyd)	5	24	25	20
2	CH_2Cl_2 (anhyd)	10	15	50	30
3	CH_3CN (anhyd)	10	7	50	64
4	CH_3NO_2 (anhyd)	10	15	50	10
5	THF (anhyd)	10	15	50	40
6	Et_2O (anhyd)	10	15	50	10
7	$CHCl_3$ (anhyd)	10	10	50	30

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Table 2 N-Glycosidation of Glycal Derivatives Using $Er(OTf)_3$[a]

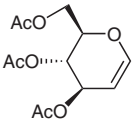
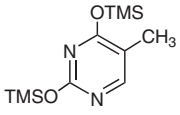
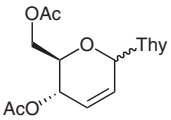
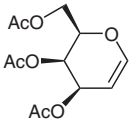
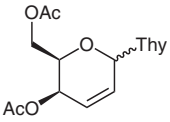
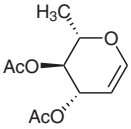
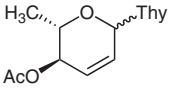
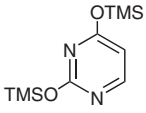
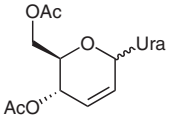
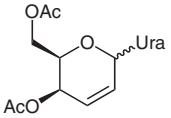
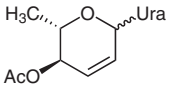
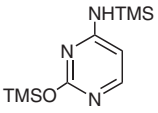
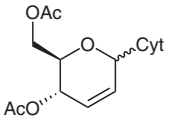
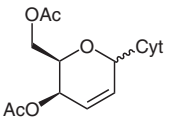
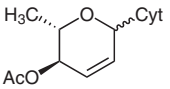
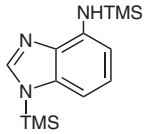
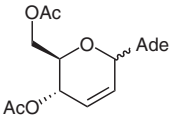
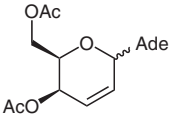
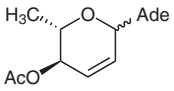
Entry	Glycal	Silyl nucleobase	Product	Time (h)	Yield (%)	α/β ratio
1	 **1**	 **4**	 **8**	7[b]	64	70:30
2	 **2**	**4**	 **9**	16	43	65:35
3	 **3**	**4**	 **10**	14	51	27:73
4	**1**	 **5**	 **11**	10[b]	55	75:25
5	**2**	**5**	 **12**	8	42	65:35
6	**3**	**5**	 **13**	12	70	37:63
7	**1**	 **6**	 **14**	10	45	71:29
8	**2**	**6**	 **15**	15	42	73:27
9	**3**	**6**	 **16**	16	36	38:62
10	**1**	 **7**	 **17**	8	60	65:35
11	**2**	**7**	 **18**	13	45	72:28

Table 2 N-Glycosidation of Glycal Derivatives Using $Er(OTf)_3$[a] (continued)

Entry	Glycal	Silyl nucleobase	Product	Time (h)	Yield (%)	α/β ratio
12	**3**	**7**	 **19**	15	46	40:60

[a] $Er(OTf)_3$ (10 mol%) in anhyd MeCN at reflux.
[b] The reaction was carried out at 50 °C.

In addition, the yield of the reaction did not exceed 64%; nevertheless, it is much higher than the yields in the previously reported examples.[2,6]

Noteworthy, after work-up, the aqueous phase can be concentrated under reduced pressure to furnish the Er(III) salt[10] as a pale pink solid (85–90% recovered), which can be recycled after drying overnight over P_2O_5. The recovered catalyst was used five times in the above reported reaction without significant loss of activity.

Based on the results reported in Table 1, we adopted a simple experimental procedure and tested the four nucleobases **4**–**7** with glucal **1**, galactal **2**, and 6-deoxyglucal **3**. A solution of the substrate in anhydrous acetonitrile was stirred in the presence of 10 mol% catalyst for about five minutes, then the silyl nucleic base (2.0 equiv) was added under reflux and the course of reaction was followed by TLC (Table 2).

All reactions gave satisfactory yields, comparable or higher than reported examples. Particularly, the tri-*O*-acetyl-D-glucal **1** always gave higher yields than the galactal analogue **2** as previously reported.[8,11d,13]

In every case, the anomeric ratio was determined from the crude mixture by means of ^1H and ^{13}C NMR spectroscopy in accordance with earlier studies.[8,11] Then the major anomer was fully characterized by ^1H and ^{13}C NMR after purification by flash column chromatography. The configuration was assigned on the basis of NOE experiments (Figure 1) and on the assertion that, in the ^{13}C NMR spectra, the C-5 chemical shift is always less than 75 ppm as reported for the γ-gauche effect on 1,5-*trans* isomers (α for D-gluco and galacto-series and β for L-deoxygluco series).[12]

The stereoselectivity of this reaction is good, giving mostly the α-anomers for the glucal- and galactal-derivatives. It is easily explained considering the key step of the reaction where all cationic intermediates should take a conformation with C-6 in a pseudo-equatorial orientation, independently from the 4-AcO-group position as was reported in our previous publications.[8] Then the less hindered face of the C1–O π-orbital of the D-gluco and galacto series orients the incoming nucleophile to form a bond always in the α-axial position. On the other hand, in L-deoxy glucal, the less hindered face of the π-orbital allows the nucleophile to find a major orbital overlapping, approaching from the β-side of the ion, so that the β-anomer was the predominant product.

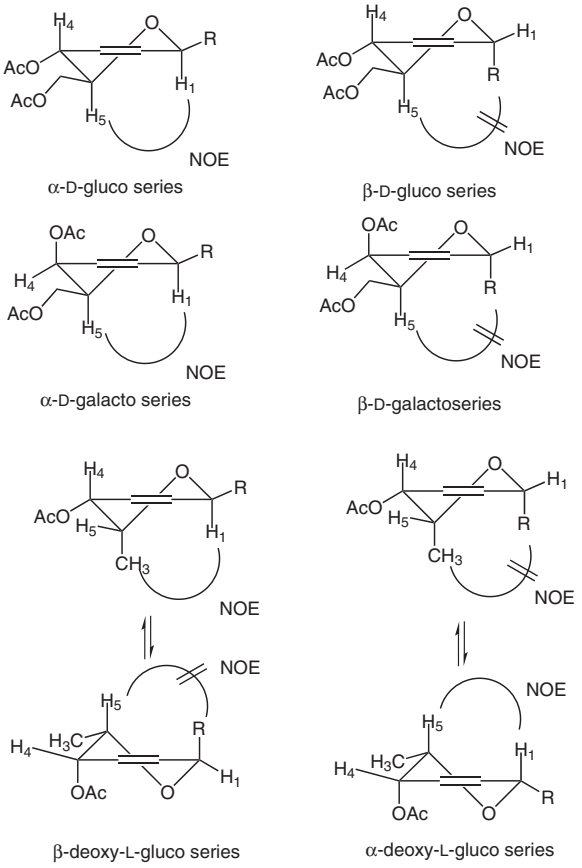


Figure 1 NOE interactions in glycals

In conclusion, the use of $Er(OTf)_3$ presents several advantages which include acceptable yields of products, cleaner reaction profiles, mild reaction conditions [a solution 0.1 M of $Er(OTf)_3$ in water is only weakly acidic with pH ca. 5.9], good stereoselectivity, wide applicability, and recoverability of the catalyst, which is also commercially available.

^1H and ^{13}C NMR spectra were recorded with a Bruker WM 300 instrument, at 300 MHz and 75 MHz respectively in $CDCl_3$ solution, with TMS as the internal standard. Elemental analyses were performed on a Perkin Elmer 2400 analyzer.

Preparation of Silylated Nucleobases

The appropriate nucleobase (4.4 mmol) was heated at 140–150 °C with HMDS (2.62 g, 16.2 mmol), TMSCl (217 mg, 2.0 mmol), and a trace of $(NH_4)_2SO_4$ until a clear solution formed. Then, the solution was concentrated in vacuo giving the product as a white solid which is pure enough to be used in the next step.

N-Glycosidation; Typical Procedure

The 3,4,6-tri-*O*-acetyl-D-glucal (**1**; 0.5 g, 1.84 mmol) was added to a solution of Er(OTf)$_3$ (0.11 g, 0.184 mmol, 10 mol%) in dry MeCN (3.0 mL) and the resulting solution was stirred at r.t. for 5 min. Then, silylated thymine **4** (0.13 g, 1.103 mmol) was added and the reaction was stirred under reflux for 7 h, until almost complete conversion of substrate **1** was achieved (TLC, $CHCl_3$–MeOH, 9:1). The organic solution was washed with H_2O (5.0 mL), dried, and concentrated to give the crude product, which was purified by flash chromatography ($CHCl_3$–MeOH, 9:1); yield: 0.398 g (1.18 mmol).

1-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)thymidine (8)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.94 (d, *J* = 1.24 Hz, 3 H, CH_3), 2.09 (s, 3 H, CH_3COO), 2.14 (s, 3 H, CH_3COO), 3.98–4.09 (m, 1 H, H-5′), 4.18 (dd, *J* = 12.21, 3.46 Hz, 1 H, H-6′), 4.29 (dd, *J* = 12.21, 5.63 Hz, 1 H, H-6′), 5.21–5.32 (m, 1 H, H-4′), 5.86–5.96 (m, 1 H, H-2′), 6.28–6.37 (m, 1 H, H-3′), 6.44 (dd, *J* = 4.40, 2.06 Hz, 1 H, H-1′), 7.28 (d, *J* = 1.24 Hz, 1 H, H-6), 9.92 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 12.4, 20.6, 62.2, 64.00, 70.0, 110.7, 126.1, 131.1, 136.2, 150.8, 164.0, 170.0, 170.5.

Anal. Calcd for $C_{15}H_{18}N_2O_7$: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.21; H, 5.39; N, 8.11.

1-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*threo*-hex-2-enopyranosyl)thymidine (9)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.93 (d, *J* = 1.32 Hz, 3 H, CH_3), 2.10 (s, 3 H, CH_3COO), 2.13 (s, 3 H, CH_3COO), 3.95–4.26 (m, 3 H, H-5′, H-6′), 4.60–4.70 (m, 1 H, H-2′), 4.80–4.90 (m, 1 H, H-4′), 5.10–5.25 (m, 1 H, H-3′), 6.85 (dd, *J* = 6.27, 1.62 Hz, 1 H, H-1′), 7.29 (d, *J* = 1.32 Hz, 1 H, H-6), 9.10 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 12.4, 20.7, 50.3, 62.0, 66.6, 71.0, 95.1, 110.7, 136.4, 150.7, 163.8, 169.1, 170.3.

Anal. Calcd for $C_{15}H_{18}N_2O_7$: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.18; H, 5.30; N, 8.21.

1-(4′-*O*-Acetyl-2′,3′,6′-trideoxy-β-L-*erythro*-hex-2-enopyranosyl)thymidine (10)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.20 (d, *J* = 6.13 Hz, 3 H, CH_3), 1.95 (d, *J* = 1.07 Hz, 3 H, CH_3), 2.12 (s, 3 H, CH_3COO), 4.02–4.19 (m, 1 H, H-5′), 4.60–4.67 (m, 1 H, H-4′), 4.77–4.88 (m, 1 H, H-2′), 5.38–5.57 (m, 1 H, H-3′), 6.65 (dd, *J* = 6.01, 2.27 Hz, 1 H, H-1′), 7.29 (d, *J* = 1.07 Hz, 1 H, H-6), 9.76 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.2, 21.4, 23.6, 68.8, 71.1, 110.9, 123.1, 132.9, 134.3, 149.8, 164.0, 169.6, 170.1.

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.61; H, 5.69; N, 9.85.

1-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)uracil (11)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.12 (s, 3 H, CH_3COO), 2.14 (s, 3 H, CH_3COO), 4.07–3.98 (m, 1 H, H-5′), 4.13–4.34 (m, 2 H, H-6′), 5.23–5.30 (m, 1 H, H-4′), 5.86–5.93 (m, 1 H, H-2′), 6.35–6.28 (m, 1 H, H-3′), 6.46 (dd, *J* = 4.40, 2.05 Hz, 1 H, H-1′), 7.21 (d, *J* = 8.07 Hz, 1 H, H-5), 7.47 (d, *J* = 8.07 Hz, 1 H, H-6), 9.68 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 16.9, 18.5, 66.9, 73.2, 74.3, 79.7, 101.5, 127.7, 143.6, 130.2, 151.9, 163.8, 170.8, 171.0.

Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64; O, 34.54. Found: C, 51.78; H, 4.89; N, 8.51.

1-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*threo*-hex-2-enopyranosyl)uracil (12)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.09 (s, 3 H, CH_3COO), 2.13 (s, 3 H, CH_3COO), 4.09–4.13 (m, 1 H, H-5′), 4.14–4.29 (m, 2 H, H-6′), 4.70–4.79 (m, 1 H, H-2′), 4.90–4.98 (m, 1 H, H-4′), 5.27–5.34 (m, 1 H, H-3′), 5.75 (d, *J* = 8.13 Hz, 1 H, H-5), 6.82 (dd, *J* = 6.14, 1.34 Hz, 1 H, H-1′), 7.52 (d, *J* = 8.13 Hz, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 20.7, 50.6, 62.1, 66.4, 70.9, 94.4, 102.3, 140.8, 149.3, 150.6, 163.3, 169.2, 170.4.

Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.93; H, 4.90; N, 8.74.

1-(4′-*O*-Acetyl-2′,3′,6′-trideoxy-β-L-erythro-hex-2-enopyranosyl)uracil (13)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.29 (d, 3 H, CH_3, *J* = 6.27 Hz), 2.10 (s, 3 H, CH_3COO), 4.05–4.21 (m, 1 H, H-5′), 4.53–4.62 (m, 1 H, H-4′), 4.76–4.90 (m, 1 H, H-2′), 5.57–5.70 (m, 1 H, H-3′), 5.80 (d, *J* = 8.13 Hz, 1 H, H-5), 6.65 (dd, *J* = 5.87, 2.1 Hz, 1 H, H-1′), 7.25 (d, *J* = 8.13 Hz, 1 H, H-6), 9.76 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 20.2, 20.4, 69.3, 78.0, 102.9, 126.9, 131.9, 139.9, 150.2, 163.4, 169.7, 170.2.

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.08; H, 5.39; N, 10.41.

1-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)cytosine (14)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.73 (br s, 2 H, NH_2), 2.08 (s, 3 H, CH_3COO), 2.11 (s, 3 H, CH_3COO), 3.98–4.06 (m, 1 H, H-5′), 4.17–4.26 (m, 2 H, H-6′), 5.33–5.41 (m, 1 H, H-4′), 5.73–5.85 (m, 2 H, H-2′, H-5), 6.06–6.13 (m, 1 H, H-3′), 6.72 (dd, *J* = 4.0, 2.54 Hz, 1 H, H-1′), 7.30 (d, *J* = 7.47 Hz, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 20.7, 21.1, 60.1, 66.4, 68.3, 79.9, 95.8, 124.2, 126.1, 140.1, 152.3, 168.3, 171.3, 172.4.

Anal. Calcd for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30; N, 13.00. Found: C, 51.93; H, 5.39; N, 12.91.

1-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*thero*-hex-2-enopyranosyl)cytosine (15)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.70 (br s, 2 H, NH_2), 2.10 (s, 3 H, CH_3COO), 2.14 (s, 3 H, CH_3COO), 4.08–4.16 (m, 1 H, H-5′), 4.18–4.40 (m, 2 H, H-6′), 5.32–5.43 (m, 1 H, H-4′), 5.63–5.78 (m, 2 H, H-2′, H-5), 6.01–6.10 (m, 1 H, H-3′), 6.77 (dd, *J* = 1.74, 6.27 Hz, 1 H, H-1′), 7.28 (d, *J* = 7.33 Hz, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 20.4, 20.7, 58.3, 66.1, 65.3, 77.4, 100.0, 123.2, 125.2, 139.1, 150.2, 167.3, 169.8, 171.2.

Anal. Calcd for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30; N, 13.00. Found: C, 52.11; H, 5.23; N, 12.89.

1-(4′-*O*-Acetyl-2′,3′,6′-trideoxy-β-L-erythro-hex-2-enopyranosyl)cytosine (16)

Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.21–1.30 (m, 3 H, CH_3), 2.04 (m, 3 H, CH_3COO), 3.98–4.18 (m, 1 H, H-5′), 5.15–5.27 (m, 1 H, H-4′), 5.60–5.90 (m, 2 H, H-5, H-2′), 6.00–6.12 (m, 1 H, H-3′), 6.65–6.76 (m, 1 H, H-1′), 7.17 (d, *J* = 7.35 Hz, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 14.2, 20.3, 68.8, 74.8, 78.3, 95.4, 127.8, 128.5, 140.7, 155.9, 165.3, 169.2.

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.46; H, 5.59; N, 15.91.

7-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)adenine (17)
Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 3 H, CH_3COO), 2.46 (s, 3 H, CH_3COO), 4.41–4.48 (m, 1 H, H-5′), 4.55–4.58 (m, 2 H, H-6′), 5.77–5.87 (m, 1 H, H-4′), 6.32–6.39 (m, 1 H, H-2′), 6.52–6.58 (m, 1 H, H-3′), 6.97 (dd, *J* = 4.0, 2.4 Hz, 1 H, H-1′), 8.01 (s, 1 H, H-2), 8.38 (s, 1 H, H-8).

^{13}C NMR ($CDCl_3$): δ = 17.5, 17.9, 67.0, 71.1, 75.8, 83.9, 132.2, 143.6, 149.1, 153.6, 156.2, 170.9, 171.3.

Anal. Calcd for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found: C, 51.95; H, 4.89; N, 20.09.

7-(4′,6′-*O*-Diacetyl-2′,3′-dideoxy-α-D-*thero*-hex-2-enopyranosyl)adenine (18)
Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.68 (br s, 2 H, NH_2), 2.09 (s, 3 H, CH_3COO), 2.13 (s, 3 H, CH_3COO), 4.18–4.34 (m, 3 H, H-5′, H-6′), 4.70–4.76 (m, 1 H, H-2′), 5.40–5.45 (m, 1 H, H-4′), 5.53–5.60 (m, 1 H, H-3′), 6.43–6.50 (dd, *J* = 6.27, 1.74 Hz, 1 H, H-1′), 7.94 (s, 1 H, H-2), 8.40 (s, 1 H, H-8).

^{13}C NMR ($CDCl_3$): δ = 20.9, 21.7, 62.9, 68.9, 69.7, 82.0, 120.1, 127.3, 140.8, 150.3, 152.7, 156.6, 170.3, 171.0.

Anal. Calcd for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found: C, 51.75; H, 4.99; N, 20.29.

7-(4′-*O*-Acetyl-2′,3′,6′-trideoxy-β-L-erythro-hex-2-enopyranosyl)adenine (19)
Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3COO), 4.16–4.22 (m, 1 H, H-5′), 4.57–4.68 (m, 1 H, H-4′), 5.07–5.18 (m, 1 H, H-2′), 5.54–5.70 (m, 1 H, H-3′), 6.62–6.75 (m, 1 H, H-1′), 7.83 (s, 1 H, H-2), 8.43 (s, 1 H, H-8).

^{13}C NMR ($CDCl_3$): δ = 13.4, 20.5, 67.4, 72.3, 80.9, 119.4, 125.3, 127.9, 139.3, 148.3, 152.8, 156.1, 170.3.

Anal. Calcd for $C_{13}H_{15}N_5O_3$: C, 53.97; H, 5.23; N, 24.21. Found: C, 53.83; H, 5.32; N, 24.11.

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