Synthesis of 2,3,4-Trideoxy-4,4-difluoro-\(\text{\textit{d}-ribo}\)-hexopyranose Adenosines

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Abstract: A novel synthetic route to 2,3,4-trideoxy-4,4-difluoro-\(\text{\textit{d}-ribo}\)-hexopyranose adenosine and 2,3,4-trideoxy-2,3-didehydro-4,4-difluoro-\(\text{\textit{d}-ribo}\)-hexopyranose adenosine has been developed. The approach highlights the highly regio- and stereoselective palladium-catalyzed glycosylation of Boc-protected pyranose, which was prepared from the oxidation–cyclization of a difluorinated diol. The diol was provided through ozonization and Lindlar reduction of optically pure enynic alcohol.

Key words: nucleosides, fluorinated compounds, palladium-catalyzed glycosylation

The discovery of a large and varied class of natural bioactive hexopyranosyl nucleoside-containing products, such as blasticidin,1 gougerotin,2 hikizimycin,3 and mildiomyycin,4 has inspired many efforts on the synthesis of hexopyranosyl nucleosides as potential anticancer and antiviral agents.5 Among these hexopyranosyl nucleosides, 2,3-dideoxyxyranosyl nucleosides and 2,3-unsaturated hexopyranosyl nucleosides constitute a distinct class of bioactive compounds. They have been demonstrated to show anticancer and antiviral activities. For example, 2,3-dideoxy-\(\text{\textit{d}-ribo}\)-hexopyranose adenosine (5) and 2,3-didehydro-\(\text{\textit{d}-ribo}\)-hexopyranose adenosine (6) were synthesized as a selective inhibitor of protein synthesis and several transplantable animal tumors (Figure 1). Inter- estingly, the presence of a double bond at C2–C3 of pyranose rings in 6 can make it adopt a twisted half-chair conformation that is similar to the furanose rings of the naturally occurring nucleosides.6a,8 Based on this fact, many furanose ring mimic nucleosides bearing a 2,3-didehydroxyranose ring have been used in various biological systems.9 Thus, there has been a great demand for efficient synthetic methods to access these valuable compounds. On the other hand, special attention has also been paid to the \(\text{\textit{gem}-difluoromethylene}\) group (CF\(_2\)) because the introduction of this group into organic compounds can bring about remarkable changes in physical, chemical, and biological properties.10 The well-known example is Gemcitabine,11 a \(\text{\textit{gem}-difluoromethylenated}\) nucleoside, which has been used for treatment of lung, ovarian, renal, pancreatic, head, and neck cancers. However, to the best of our knowledge, the \(\text{\textit{gem}-difluorinated}\) hexopyranosyl nucleosides have never been reported. As part of our continuous study to develop new antiviral and anticancer agents, we designed \(\text{\textit{gem}-difluorinated}\) hexopyranosyl nucleosides 1 and 3, in which the hydroxy groups at C4 in 5 and 6 were replaced with a CF\(_2\) group based on the idea that the \(\text{\textit{gem}-difluoromethylene}\) group (CF\(_2\)) is the chemical isostere for hydroxy group.12 Herein, we describe an efficient synthesis of target molecules 1 and 3 from a fluorinated building block.

Figure 1  Hexopyranosyl nucleosides 5, 6 and design of 2,3,4-trideoxy-4,4-difluoro-\(\text{\textit{d}-ribo}\)-hexopyranose adenosines

Very recently, our group has reported the preparation of \(\text{\textit{gem}-difluorinated}\) 1,2-disubstituted carbocyclic nucleosides via palladium-catalyzed glycosylation. We found that the nitrogen nucleophilic bases can specifically attack the more electrophilic carbon of intermediate 9 resulting only in \(\gamma\)-substituted product 8 (Scheme 1).13 Interestingly, O’Doherty’s group reported that palladium-catalyzed glycosylation of hexopyranosyl substrates with various alcohol nucleophiles proceeded smoothly with excellent stereocentrol and the more electrophilic Pd-\(\sigma\)-allyl intermediate 1 (Scheme 1) is essential to the reaction.14 Employing this strategy, they successfully synthesized hexopyranosyl nucleosides.15 Thus, taking all these results together, we planned to install the base moiety of target molecule 1 by palladium-catalyzed N-glycosylation (Scheme 2). We envisaged that the presence of an electron-withdrawing CF\(_2\) group in intermediate 11 would direct bases regioselectively and stereoselectively to attack the carbon far away from the CF\(_2\) group. Therefore, the palladium-catalyzed glycosylation of the difluorinated pyranose 12 with base would give nucleoside 10, a precursor of 1. Compound 12 could be prepared from diol 13 by oxidation of the primary hydroxyl to aldehyde followed by the simultaneous cyclization. Diol 13 could be easily obtained via ozonization and Lindlar reduction of our reported optically pure alcohol (R)-14 (Scheme 2).15
Thus, the synthesis of the target molecules was started from \((R)-14\). Treatment of \((R)-14\) with \(\text{O}_3\) followed by NaBH₄-mediated reduction gave diol 15 in 75% yield. Hydrogenation of diol 15 in the presence of Lindlar catalyst gave (Z)-diol 16 in 83% yield. Selective benzylation of the primary hydroxy group of diol 16 and subsequent removal of TBS group with TBAF provided the gem-difluorinated alcohol 13 in 70% yield (Scheme 3).

The preparation of lactol 17 was initially carried out by the Giacomelli’s procedure for the selective oxidation of primary alcohol to aldehyde in the presence of trichloroisocyanuric acid (TCCA) and catalytic TEMPO (Table 1). However, when diol 13 was treated with 1.0 equivalent of TCCA and catalytic TEMPO at room temperature, only a trace amount of the desired lactol 17 was produced and lactone 18 was formed as the major product (42%) (Table 1, entry 1). The oxidation of diol 13 with bis(acetoxyiodo)benzene (BAIB) afforded the desired lactol 17 in 21% yield \((\text{anti/syn} = 4:1)\), but lactone 18 was still produced in 32% yield (entry 3). To prepare lactol 17 efficiently, the complete conversion of diol 13 to lactone 18 and then reduction of 18 to lactol 17 were investigated.

The peroxidation of diol 13 with 3.0 equivalents of TCCA provided lactone 18 in 47% yield (entry 2). We were pleased to find that lactone 18 was isolated in 76% yield when BAIB was used instead of TCCA (entry 4).

**Table 1 Oxidation of Diol 13**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Equiv</th>
<th>Yield (%) of 17</th>
<th>Yield (%) of 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TCCA</td>
<td>1.0</td>
<td>trace</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>TCCA</td>
<td>3.0</td>
<td>–</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>BAIB</td>
<td>1.0</td>
<td>21*</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>BAIB</td>
<td>3.0</td>
<td>–</td>
<td>76</td>
</tr>
</tbody>
</table>

* Ratio of \(\text{anti/syn} = 4:1\), determined by \(^{19}\text{F}\) NMR spectroscopy.

Reduction of lactone 18 with DIBAL-H afforded diol 19 in 70% yield with anti-isomer as the major product \((\text{anti}
Synthesis of 2,3,4-trideoxy-4,4-difluoro-β-D-ribo-hexopyranose adenosines 1–4 using palladium-catalyzed glycosylation as a key step. The high regio- and stereoselectivities of such palladium-catalyzed glycosylation could be used as an efficient and practical strategy for the synthesis of other gem-difluorinated hexopyranosyl substrates. Antiviral and cytotoxicity evaluations of 1–4 are currently in progress and will be reported soon.
THF and benzene were distilled from sodium metal. CH2Cl2 was distilled from CaH2. Melting points are uncorrected. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C.

1H and 13C NMR spectra were recorded on a Bruker AM300 spectrometer. 19F NMR spectra were recorded on a Bruker AM300 spectrometer (CFCl3 as external standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz.

(R)-6-(tert-Butyldimethylsilyloxy)-3,3-difluorohex-4-yne-1,2-diol (15)
Ozone was bubbled through a solution of (R)-14 (4.45 g, 12.6 mmol) in MeOH–CH2Cl2 (70 mL–70 mL) for 45 min at −78 °C till a blue color persisted. Then, N2 was bubbled through the solution until the blue color disappeared and NaBH4 (2.35 g, 63.5 mmol) was added. After warming to r.t. and stirring for 1 h, the reaction was quenched with sat. aq NH4Cl (30 mL). The layers were separated and the aqeous phase was exchanged with CH2Cl2(3 x 30 mL). The combined organic layers were washed with brine (50 mL). The organic layer was dried (Na2SO4) and concentrated under vacuo to give the crude product. Purification by flash silica gel column chromatography (PE–EtOAc, 1:1) yielded 15 (2.66 g, 75%) as a clear oil; [α]D26 +4.8 (c 0.65, CHCl3).

IR (film): 3400, 2933, 2861, 1755, 1726, 1453, 1230, 1070, 711 cm–1.

HRMS (MALDI): m/z = 273.1 [M + H]+.


(R)-3,3-Difluoro-6-oxo-3,6-dihydro-2H-pyran-2-ylmethyl Benzoate (18)
To a solution of benzoate 13 (106 mg, 0.39 mmol) in anhyd CH2Cl2 (3 mL) were added DIAB (376 mg, 1.20 mmol) and TEMPO (12 mg, 20 mmol%) at 0 °C. After stirring the mixture for 3 h at r.t., the reaction was quenched with sat. aq NaHCO3 (30 mL). The organic-layer was washed sequentially with sat. aq NaHCO3 (30 mL), H2O (10 mL) was added and the mixture was stirred for 30 min. The mixture was washed sequentially with aq 1 N HCl (50 mL), sat. aq NaHCO3 (30 mL), and brine (30 mL). The organic layer was dried (Na2SO4), filtered, and the solvent was removed in vacuo. The residue was purified by flash silica gel column chromatography (PE–EtOAc, 1:1) to give 18 (79 mg, 76%) as a clear oil; [α]D26 +2.3 (c 1.25, CHCl3).

IR (film): 1755, 1726, 1453, 1230, 1070, 711 cm–1.

1H NMR (300 MHz, CDCl3): δ = 8.03 (d, J = 1.5 Hz, 2 H), 7.61 (t, J = 1.2 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 6.89–6.82 (m, 1 H), 6.37 (d, J = 10.2 Hz, 1 H), 5.04–4.92 (m, 1 H), 4.82 (dd, J = 12.6, 3.6 Hz, 1 H), 4.68 (q, J = 6.9 Hz, 1 H).

13C NMR (75.5 MHz, CDCl3): δ = 165.8, 159.4, 137.1 (dd, J = 26.3, 19.6 Hz), 133.5, 129.7, 129.3, 128.5, 126.7 (t, J = 19.6 Hz), 111.9 (t, J = 183.8 Hz), 60.4 (t, J = 262.0, 11.8 Hz, 1 F), –108.75 (dd, J = 271.3, 19.5 Hz, 1 F). MS (MALDI): m/z = 291.0 [M + Na]+.


(6R)-5,5-Difluoro-6-(hydroxymethyl)-5,6-dihydro-2H-pyran-2-yl (19)
To a solution of lactone 18 (122 mg, 0.46 mmol) in anhyd CH2Cl2 (5 mL) were added DIAB (172 mg, 0.50 mmol) and TEMPO (5 mg, 0.02 mmol) at 0 °C. After stirring the mixture for 3 h at r.t., the reaction was quenched with sat. aq NaHCO3 (30 mL), H2O (10 mL) was added and the mixture was stirred for 30 min. The mixture was washed sequentially with aq 1 N HCl (50 mL), sat. aq NaHCO3 (30 mL), and brine (30 mL). The organic layer was dried (Na2SO4), filtered, and the solvent was removed in vacuo. The residue was purified by flash silica gel column chromatography (PE–EtOAc, 1:1) to give 19 (70 mg, 70%) as a white solid.
IR (film): 3204, 1387, 1158, 1103, 1073, 1053, 1025, 937, 868, 789, 754 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 6.17 (dd, J = 9.9, 2.7 Hz, 1 H), 5.89 (t, J = 9.0 Hz, 1 H), 5.34–5.28 (m, 1 H), 4.21 (d, J = 7.2, 3.9 Hz, 1 H), 3.83 (dd, J = 12.0, 3.3 Hz, 1 H), 3.70–3.59 (m, 1 H).

¹³C NMR (75.5 MHz, CDCl₃): δ (major product) = 135.2 (t, J = 23.1 Hz, 1 H), 128.6, 128.3, 125.8 (dd, J = 23.2, 19.0 Hz, 1 H), 90.9, 83.5, 70.0 (dd, J = 23.2, 18.3 Hz, 1 H), 60.6 (d, J = 5.2 Hz); δ (minor product) = 166.0, 133.1, 132.8 (t, J = 7.0 Hz, 1 H), 129.8, 129.7, 129.6, 125.1 (t, J = 21.4 Hz, 1 H), 90.0, 83.6, 73.4 (d, J = 23.2, 19.3 Hz), 61.7 (d, J = 5.2 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ (major product) = –109.99 (ddd, J = 260.9, 21.6, 2.3 Hz, 1 F), –114.27 (dd, J = 273.0, 8.5 Hz, 1 F); δ (minor product) = –98.24 (dm, J = 265.9 Hz, 1 F), –109.45 (dm, J = 273.8 Hz, 1 F).

MS (MALDI): m/z = 288.2 [M + Na]⁺.


[(2R,6R)-6-(6-Chloro-7H-purin-7-yl)-3,3-difluoro-3,6-dihydro-2H-pyran-2-yl]methyl Benzoate (21)
To a solution of compound 20 (130 mg, 0.35 mmol) and 5-chloro-purine (105 mg, 0.68 mmol) in THF (10 mL) was added Pd(PPh₃)₄ (20 mg, 5 mmol%) and PPh₃ (9 mg, 10 mmol%). The mixture was stirred at 60 °C for 5 h and then cooled to rt. After concentration, the crude product was purified by flash silica gel column chromatography (PE–EtOAc, 1:1) to give 21 (55 mg, 39%) and 10 (14 mg, 10%) as foams.

IR (film): 3116, 1724, 1590, 1564, 1397, 1337, 1272, 1158, 1093, 1052, 948, 831, 711, 636, 566 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 8.76 (s, 1 H), 8.24 (s, 1 H), 8.02 (d, J = 8.1 Hz, 2 H), 7.57 (t, J = 8.1 Hz, 1 H), 7.43 (t, J = 7.2 Hz, 2 H), 6.76 (t, J = 4.8 Hz, 1 H), 6.45–6.37 (m, 2 H), 4.82–4.79 (m, 1 H), 4.59–4.47 (m, 2 H).

¹³C NMR (75.5 MHz, CDCl₃): δ = 171.3, 157.7, 156.6 (d, J = 39.9 Hz), 148.0, 138.6, 137.5 (t, J = 6.7 Hz), 136.7, 134.9, 135.4, 133.6, 132.8 (dd, J = 23.6, 20.2 Hz), 117.2 (d, J = 184.3, 179.2 Hz), 81.9, 80.6 (d, J = 23.6, 19.6 Hz), 65.8 (d, J = 4.5 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ (major product) = –106.14 (ddd, J = 282.8, 18.0, 7.9 Hz, 1 F), –107.90 (dd, J = 283.1, 4.5 Hz, 1 F).

MS (MALDI): m/z = 407.0 [M⁺ + H]⁺.

HRMS (MALDI): m/z [M⁺ + H]⁺ calcd For C₁₈H₁₉ClF₂O₂: 407.0717; found: 407.0727.

IR (film): 2926, 1724, 1591, 1565, 1338, 1276, 1197, 1160, 1096, 1053, 947, 832, 711, 636, 565 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 8.72 (s, 1 H), 8.21 (s, 1 H), 8.06 (d, J = 6.0 Hz, 2 H), 7.70 (t, J = 7.2 Hz, 1 H), 7.45 (t, J = 7.8 Hz, 2 H), 6.71–6.51 (m, 3 H), 4.70–4.56 (m, 2 H), 4.40–4.30 (m, 1 H).

¹³C NMR (75.5 MHz, CDCl₃): δ = 165.7, 152.6, 151.5 (d, J = 11.0 Hz, 1 H), 143.2, 133.3, 131.9, 129.6 (t, J = 6.9 Hz, 1 H), 129.3, 129.0, 128.3, 128.0 (d, J = 3.2 Hz), 127.8, 112.0 (d, J = 184.8, 178.1 Hz), 76.0, 70.9 (d, J = 23.5, 18.9 Hz), 60.1 (d, J = 4.6 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ = –109.42 (dd, J = 268.7, 16.1 Hz, 1 F), –111.89 (dd, J = 272.7, 7.3, 3.4 Hz, 1 F).

MS (MALDI): m/z = 407.0 [M⁺ + H]⁺.

HRMS (MALDI): m/z [M⁺ + H]⁺ calcd For C₁₈H₁₉ClF₂O₂: 407.0717; found: 407.0717.
12.3, 4.2 Hz, 1 H).

J = 1 H), 4.28–4.19 (m, 1 H), 3.95 (dd, s, 1 H), 3.94–3.75 (m, 3 H), 2.85–2.76 (m, 1 H), 2.35–2.28 (m, 1 H).

IR (film): 1650, 1601, 1475, 1172, 1151, 1094, 1036, 836 cm⁻¹.

1H NMR (300 MHz, CD3OD): δ = 8.23 (s, 1 H), 8.20 (s, 1 H), 6.65–6.38 (m, 3 H), 4.19–4.07 (m, 1 H), 3.97–3.68 (m, 1 H), 2.85–2.76 (m, 1 H), 2.35–2.28 (m, 1 H).

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References


(17) Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition No. 694847).