Synthesis of trans-Configurated Spacered Nucleoside Analogues Comprising a Difluorocyclopropane Moiety

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A novel class of trans-configurated difluorinated cyclopropanoic nucleoside analogues containing a methylene spacer between the cyclopropane ring and the heterocycle has been prepared. Some of these compounds showed weak anti-HIV activity in preliminary screenings.

Key words: Nucleoside Analogues, Cycloproanes

Introduction

Fluorinated carbocyclic nucleoside analogues are regarded as most promising candidates for a successful therapy against viruses. During our own efforts towards the development of cyclopropanoic nucleoside analogues, we became interested in the synthesis of compounds showing a trans relationship between the hydroxymethyl moiety and the methylene spaced heterocycle.

Thus, a difluorinated, trans configurated and suitably substituted cyclopropane seemed to be the best suited starting material for such an approach. Geminal difluorinated cyclopropanes have previously been prepared by the addition of difluorocarbenes to nucleophilic olefins using either phenyl(trifluoromethyl)mercury [1 – 3] or bromodifluoromethylphosphonium bromide in the presence of cesium or potassium fluoride [4 – 6] or by the thermal decomposition of sodium chlorodifluoroacetate [7 – 10].

Results and Discussion

A suitable precursor has previously been synthesized by Taguchi et al. [10] by a sequence of reactions starting from [(E)-4-(benzylxoy)-2-butenyl]oxy(tert-butyl)dimethylsilane whose thermal reaction with sodium chlorodifluoroacetate yielded the corresponding difluorocyclopropane that was subsequently subjected to a de-silylation reaction. The yields of this approach were only moderate and thus another approach to a suitable starting material was called for.

Thus, commercially available (E)-1,4-dibromo-but-2-ene (1) was acetylated using anhydrous potassium acetate in glacial acetic acid [11] to afford 2. Since the mono-deacetylation with potassium carbonate in methanol [12] failed to give excellent yields especially for large scale preparations, a different route had to be established. Chemoenzymatic routes have been used in the past very successfully for different hydrolyses reactions. Several lipases, esterases, amidases and proteases were screened on a small scale; among these the esterase from porcine liver (PLE) showed a high selectivity and an excellent reaction rate. Using pH-stat-conditions at pH = 7 the chemoenzymatic mono-deacetylation of 2 yielded 83% of the monoacetate (E)-4-hydroxy-2-butenyl acetate (3). Reaction of 3 with benzyl bromide / sodium hydride [13] gave the benzyl ether 4. Reaction of 4 with sodium chlorodifluoroacetate in dry diglyme at 190 – 200 °C gave the racemic difluorocyclopropane 5 together with unreacted starting material 4. The chromatographic separation of these two compounds failed under many different conditions. Thus, a different strategy had to be applied: Treatment of the mixture 4/5 under Zemplén conditions with a catalytic amount of sodium methoxide in methanol led to a deacetylation reaction affording a mixture of 6 and 7 that was easily separated by column chromatography. Re-acetylation of 6 gave 4.

The trans-configurated difluorocyclopropane 6 is well characterized by its $^{19}$F NMR spectrum. Whereas for the corresponding cis-analogue 8 the difference in the chemical shifts of the two fluorine substituents $|\Delta F_{1, F-2}| = 25.4$ ppm is rather large, for the trans-
Scheme 1. Reactions: a) KOAc/Ac₂O; b) PLE, pH = 7.0; c) BnBr, NaH; d) ClF₂CO₂Na, 190–200 °C, diglyme; e) NaOMe (cat.) in MeOH; f) H₂, Pd/C, MeOH; g) pyridine/Ac₂O; h) DEAD, TPP, N₃-benzoyl-thymine; i) KOH/MeOH; j) DEAD, TPP, N₃-benzoyl-uracil; k) DIAD, TPP, N₃-benzoyl-5-fluoro-uracil; l) NH₃, MeOH; m) Pearlman’s catalyst, MeOH, cyclohexene; n) 6-chloro-purine, DEAD, TPP; o) NH₃, 75 °C, 3.6 Mpa.

Table 1. Characteristic NMR data for compounds 8 (cis) and 6 (trans)

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>δ(ppm) 8</th>
<th>δ(ppm) 6</th>
<th>Δ(δ₈ - δ₆)</th>
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<tr>
<td>C-1</td>
<td>28.35</td>
<td>28.79</td>
<td>0.44</td>
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<tr>
<td>C-2</td>
<td>113.78</td>
<td>114.23</td>
<td>0.45</td>
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<tr>
<td>C-3</td>
<td>24.83</td>
<td>26.44</td>
<td>1.61</td>
</tr>
<tr>
<td>C-4</td>
<td>55.58</td>
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<td>3.48</td>
</tr>
<tr>
<td>C-5</td>
<td>62.58</td>
<td>65.97</td>
<td>3.39</td>
</tr>
<tr>
<td>F-1</td>
<td>-124.0</td>
<td>-138.90</td>
<td>14.9</td>
</tr>
<tr>
<td>F-2</td>
<td>-149.60</td>
<td>-140.53</td>
<td>9.07</td>
</tr>
<tr>
<td></td>
<td>25.6</td>
<td>1.63</td>
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</tbody>
</table>

analogue 6 | δ(F⁻₁,F⁻₂) = 1.5 ppm is small. In the ¹³C NMR spectrum of 6 the signal for the carbon bearing the geminal fluoro substituents is found as a doublet of doublet with ¹JC,F = 286.7 and ¹JC,F = 285.9 Hz. Characteristic NMR parameters for 8 and 6 are compiled in Table 1.


Reaction of 6 with 6-chloro-purine/TPP/DEAD in 1,4-dioxane gave 73% of 17 whose ammonolysis (75 °C, 3.6 MPa) in an autoclave gave 71% of the corresponding 6-amino-purine 18. Transfer-hydrogenolysis of 18 with cyclohexene and Pearlman’s catalyst afforded 78% of the adenosine analogue 19.

Again, ¹⁹F NMR spectroscopy can be used quite efficiently to distinguish between cis and trans-configured difluorocyclopropanes as exemplified for the cis- and trans-adenosine analogues 19 and 20, respectively. Thus, whereas for cis-20 the signals of the two difluoro substituents are found at δ = -124.38 and δ = -151.45 ppm, for the trans-configurated 19 an AB-spin system is observed (δ = -136.92 and δ = -138.56 ppm, J_AB = 164.5 Hz).

Compounds 11, 13, 16 and 19 have been tested for anti-HIV activity but only weak to moderate activity was observed.

Experimental Section

General: Melting points are uncorrected (Leica hot stage microscope), optical rotations were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell), NMR spectra (internal Me₄Si) were recorded using the Varian spectrometers.
Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me$_2$Si for $^1$H and $^{13}$C NMR spectra, internal CDCl$_3$ for $^{19}$F NMR spectra, C) correspond to the atoms of the heterocycle, IR spectra (film or KBr pel- let) on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. MS spectra were taken on a Integra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 instru- ment (electrospray, voltage 4.5 kV, sheath gas nitrogen); for MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 instru- ment (electrospray, voltage 4.5 kV, sheath gas nitrogen); for mass analysis (electrospray, voltage 4.5 kV, sheath gas nitrogen); for mass analysis (electrospray, voltage 4.5 kV, sheath gas nitrogen); for elemental analysis a Foss-Heraeus Vario EL instrument was used; tlc was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium(IV)) sulfate followed by gentle heating.

(E)-Butene-1,4-diol monooacetate (3)

In a pH-stat equipment a mixture of 2 (146.0 g, 0.85 mol) in water (2000 ml) was stirred at pH = 7 in the presence of PLE (Boehringer-Mannheim, 10 × 200 µl) for 5 days keep- ing the pH constant at 7.0 by the addition of 1 N sodium hydroxide (amount: 855 ml). The reaction mixture was ex- tracted with ethyl acetate (7 × 400 ml), the combined organic phases were dried and the solvent evaporated. The crude product was purified by chromatography (silica gel, hexane/ethyl acetate 4:1) to afford pure 3 (91.8 g, 83.1%) as a colorless liquid. – $n_D^20$ = 1.4523. – RF (ethyl acetate/hexane 1:4) 0.14. – IR (film): ν = 3410s, 3015w, 2945m, 2875m, 2360w, 1740s, 1450m, 1385s, 1365s, 1240s, 1090s, 1025s cm$^{-1}$. – $^1$H NMR (400 MHz, CDCl$_3$): δ = 5.80 (dtt, $J_{CH} = 15.6, 5.8, 1.2$ Hz, 1 H, –CH=C), 5.35 (m, 2 H, CH$_2$-OAc), 4.15 (dq, $J_{CH} = 5.0, 1.2$ Hz, 2 H, CH$_2$O, 2.16 (br s, 1 H, OH), 2.05 (s, 3 H, CH$_3$). – $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 172.10 (s, CO), 138.03 (s, C q-phenyl), 130.83 (s, CH$_3$-phenyl), 128.31 (d, Cortho-phenyl), 127.84 (d, Cmeta-phenyl), 127.67 (d, Cpara-phenyl), 113.78 (dd, 1 H, CH$_2$-phenyl), 25.39 (virt dt, 2 H, CH$_2$-OAc). – MS (EI, 70 eV): m/z (%) = 374 (100). – Analysis for C$_{13}$H$_{16}$O$_3$ (220.27): calcd. C 70.89, H 7.32; found C 70.85, H 7.38.

(E)-4-(benzyloxy)-2-butenyl acetate (4)

To a suspension of sodium hydride (24.0 g, 60%) in dry diglyme (5 ml) at room temperature and usual work- up followed by chromatography (silica gel, hexane/ethyl acetate 8:1 → 3:2) 4 (91.72 g, 87.4%) was obtained as an oil. – $n_D^20$ = 1.5083. – RF (ethyl acetate/hexane 1:3) 0.40. – IR (film): ν = 3090w, 3065w, 3030w, 2940w, 2855m, 2360w, 2340w, 1740s, 1605w, 1495w, 1455m, 1380m, 1365s, 1235s, 1105s, 1025s cm$^{-1}$. – $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.30 (m, 5 H, phenyl), 5.87 (m, 2 H, CH$_2$=), 4.60 (d, J = 4.7 Hz, CH$_2$OAc), 4.52 (s, 2 H, CH$_2$-Ph), 4.02 (d, J = 4.7 Hz, CH$_2$Obn), 2.07 (s, 3 H, CH$_3$). – $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 170.5 (s, CO), 138.03 (s, C meta-phenyl), 130.83 (d, CH$_3$), 128.31 (d, phenyl), 127.55 (d, CH$_3$), 72.30 (t, CH$_2$-ph), 69.66 (t, OCH$_2$), 64.12 (t, CH$_2$-OAc), 20.78 (q, CH$_3$). – MS (EL, 70 eV): m/z (%) = 221 (6), 220 (13), 160 (6), 105 (46), 92 (20), 91 (100). – Analysis for C$_{13}$H$_{16}$O$_2$ (220.27): calcd. C 70.89, H 7.32; found C 70.85, H 7.38.

(+)-(1 SR, 3 SR)-trans-[3-Benzylxoxymethyl-2,2-difluoro- cyclopropyl)methylacetate (±-5)

A solution of 4 (3.6 g, 16.4 mmol) in dry diglyme (5 ml) was heated to 190°C. A solution of sodium chlorodifluoro- acetate (27.3 g, 179 mmol) in dry diglyme (47 ml) was added at this temperature over a period of 60 minutes. Af- ter keeping the reaction at 190°C for an additional 15 minutes it was cooled to room temperature, poured into ice water and the aqueous solution was extracted with hexane (4 × 100 ml). The combined organic layers were washed with brine, dried (MgSO$_4$), the solvents evaporated under re- duced pressure and the remaining brown oil was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:8) to afford 5 (2.97 g, 67%) as a colorless oil contami- nated with some starting material that was easily separated in the next reaction step; an analytical pure sample of com- pound 5 was prepared by deacetylation (vide infra), chroma- tography (silica gel, ethyl acetate/hexane 1:2 → 1:1 and re-acetylation (pyridine, acetic anhydride). – RF (ethyl acetate/hexane 1:8) 0.18. – IR (film): ν = 3030w, 2865m, 1745s, 1670w, 1485s, 1455s, 1390s, 1370s, 1325m, 1230s, 1195s, 1100s, 1025s cm$^{-1}$. – $^1$H NMR (200 MHz, CDCl$_3$): δ = 7.35 – 7.24 (m, 5 H, phenyl), 4.35 and 4.47 (AB system, $J_{AB} = 11.9$ Hz, 2 H, CH$_2$-phenyl), 4.25 – 4.02 (m, 2 H, CH$_2$-OAc). 3.65 (dd, $^3J_{HF} = 5.7$, 5.1 Hz, 2 H, CH$_2$-Obn), 2.03 (s, 3 H, CH$_3$), 1.86 – 1.73 (m, 3 H, CH$_3$-phenyl), 1.54 – 1.43 (m, 1 H, CH$_2$-phenyl). – Analysis for C$_{13}$H$_{16}$O$_3$F$_2$ (270.28): calcd. C 62.21, H 7.59; found C 61.88, H 7.43.

(+)-(1 SR, 3 SR)-trans-[3-Benzylxoxymethyl-2,2-difluoro- cyclopropyl)methylacetate (±-6)

A solution of 5 (2.97 g, 11.0 mmol) in methanol (7 ml) was treated with catalytic amounts of sodium methoxide.
After 90 minutes the reaction was complete and the reaction mixture was neutralized by the addition of 10% aqueous hydrochloric acid. The solvent was evaporated and the residue suspended in water (10 ml). The resulting suspension was extracted with ethyl acetate (4 × 50 ml), the combined organic layers were washed with brine, dried (MgSO₄), and the solvents were evaporated. The remaining crude oil was purified by column chromatography (silica gel, ethyl acetate/hexane 1:2 → 1:1) to afford 6 (2.16 g, 58% yield from 4) as a colorless oil. – RF (ethyl acetate/hexane 1:1) 0.40. – UV/Vis (methanol): λmax (lg ε) = 263 nm (2.21). – IR (film): ν = 3400s, 3065w, 3030m, 2875s, 1485s, 1455s, 1365s, 1320w, 1265s, 1185s, 1015s cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 7.40–7.24 (m, 5 H, H-phenyl), 4.55 and 4.48 (AB system, JAB = 11.9 Hz, 2 H, CH₂-phenyl), 3.67–3.60 (m, 2 H, CH₂-OH), 3.59–3.48 (m, 2 H, CH₂-OBn), 2.30 (br s, 1 H, OH), 2.08 (br s, 1 H, OH), 2.05 (s, 3 H, CH₃), 1.81–1.74 (m, 2 H, cyclopentyl). – ¹³C NMR (50 MHz, CDCl₃): δ = 137.67 (s, Cq-phenyl), 128.46 (d, Cmeta-phenyl), 118.00 (d, Cpara-phenyl), 114.23 (dd, 1JC,F = 286.7, 285.9 Hz, CF₂), 72.72 (t, CH₂-phenyl), 65.97 (dt, 1JC,F = 3.9 Hz, CH₂-OBn), 59.06 (dt, 1JC,F = 5.4 Hz, CH₂-OH), 28.79 (vijt, 1JC,F = 10.0 Hz, C-1), 26.44 (vijt, 1JC,F = 10.8 Hz, C-3). – ¹⁹F NMR (188 MHz, CDCl₃): δ = –138.99 and –140.53 (AB system, JAB = 165.6 Hz, FA and FB). – MS (EI, 70 eV): m/z (%) = 228 (6), 107 (14), 91 (100), 79 (4), 65 (5). – Analysis for C₁₂H₁₄O₂F₂ (228.24): calcd. C 63.14, H 6.13; found C 63.35, H 6.31.

The reaction was performed using the same conditions as described for 17 using 9 (0.28 g, 1.56 mmol), triphenylphosphine (0.8 g, 3.04 mmol), N₂-benzoylthymine (0.60 g, 2.61 mmol), 1,4-dioxane (7 ml) and DEAD (0.49 ml, 3.02 mmol) in 1,4-dioxane (20 ml). Evaporation of the solvents and purification by column chromatography (silica gel, ethyl acetate/hexane 1:2) gave 10 (0.50 g, 82%) as an oil. – RF (ethyl acetate) 0.63. – UV/Vis (MeOH): λmax₁ (lg ε) = 254 nm (4.26), λmax₂ (lg ε) = 283 nm (3.91). – IR (film): ν = 3340w, 3070w, 2960w, 1705m, 1700m, 1650s, 1600s, 1485m, 1440m, 1365m, 1230m, 1245m, 1200m, 1180m, 1120w, 1040m, 1015m cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): δ = 7.94–7.89 (m, 2 H, Hortho), 7.67–7.61 (m, 1 H, Hpara), 7.53–7.27 (m, 2 H, Hmeta), 7.10 (s, 1 H, H₂'-H'), 4.23–4.03 (m, 3 H, CH₂-OAC H-CH'N), 3.56 (dd, 2JC,H = –14.5 Hz, 1JFH = 6.9 Hz, 1 JHH = 1.1 Hz, H'-CH'N), 2.09–1.84 (m, 7 H, 1H, 3H, 2H, C₂H₅). – ¹³C NMR (50 MHz, CDCl₃): δ = 170.68 (s, C=O (Ac)), 168.71 (s, C=O (Bz)), 162.87 (s, C-2), 149.79 (s, C-4'), 139.47 (d, C-6'), 135.07 (s, Cq-phenyl), 131.44 (d, Cpara-phenyl), 130.33 (d, Cortho-phenyl), 129.12 (d, Cmeta-phenyl), 113.29 (dd, 1JC,F = 289.0, 289.0 Hz, CF₂), 111.28 (s, C-5'). 59.82 (dt, 1JC,F = 4.6 Hz, CH₂-OAC), 45.52 (dt, 1JC,F = 3.8 Hz, CH₂-N), 26.21 (vijt, 1JC,F = 10.8 Hz, C-3), 25.80 (vijt, 1JC,F = 10.4 Hz, C-1), 20.56 (q, CH₃ (Ac)), 12.30 (q, 5'-CH₃). – ¹⁹F NMR (188 MHz, CDCl₃): δ = –138.30 and –139.85 (AB system, JAB = 164.4 Hz, FA and FB). – MS (EI, 70 eV): m/z (%) = 392 (30), 364 (12), 333 (5), 322 (11), 305 (13), 277 (10), 262 (15), 183 (8), 105 (100), 77 (36). – Analysis for C₁₉H₁₈N₂O₅F₂ (440.15): calcd. C 57.16, H 5.02, N 6.76; found C 57.35, H 4.97, N 6.67.

A solution of 10 (0.44 g, 1.12 mmol) and potassium hydroxide (0.18 g, 3.2 mmol) in methanol (25 ml) was stirred at room temperature for 3 hours. After neutralization by hydrochloric acid (10%) all volatiles were removed in vacuo and the remaining oil was subjected to column chromatography (silica gel, ethyl acetate) to afford 11 (0.18 g, 63%) as a white solid. – M.p.: 157–161 °C. – RF (ethyl acetate) 0.25. – UV/Vis (methanol): λmax₁ (lg ε) = 271 nm, 3.92. – IR (KBr): ν = 3500m, 3156w, 3030m, 2830w, 1710s, 1665s, 1480m, 1420m, 1360m, 1315w, 1265m, 1240m, 1225m, 87.00m, 86.00m, 82.00m, 74.00m, 73.00m, 55.00m, 43.00m, 35.00m, 31.00m, 28.00m, 21.00m, 20.00m, 16.00m, 14.00m, 13.00m, 12.00m, 10.00m, 9.00m, 8.00m, 7.00m, 6.00m, 5.00m, 4.00m, 3.00m, 2.00m, 1.00m. – MS (EI, 70 eV): m/z (%) = 263 (1), 149 (1), 100 (2), 91 (5), 90 (16), 77 (13), 64 (4), 51 (9), 43 (100). – Analysis for C₇H₁₀O₃F₂ (170.10): calcd. C 46.67, H 5.59; found C 46.66, H 5.61.
120m, 1160m, 1130w, 1054m cm⁻¹. 1H NMR (400 MHz, CD₂OD): δ = 7.41 (d, 2JHH = 1.2 Hz, 1 H, 6'-H), 3.99 – 3.94 (m, 1 H, H-CH'N), 3.76 (dd, 2JHH = −15.4 Hz, 3JHH = 7.4, 1 H, H'-CHN), 3.59 (virts, 2JHH = 6.8 Hz, 2 H, CH₂-OH), 1.98 – 1.89 (m, 2 H, 1-H, 3-H), 1.86 (d, 2JHH = 1.2, 3 H, CH₃). 13C NMR (100 MHz, CD₂OD): δ = 167.03 (s, C-2'), 153.16 (s, C-4'), 144.74 (d, C-6'), 140.55 (s, C-1), 141.61 (d, C-3), 126.20 (s, C-5'), 119.20 (s, C-3'), 115.54 (s, C-6'), 115.11 (s, C-2'), 107.46 (s, C-1'), 96.75 (s, C-2'), 87.66 (s, C-4'), 76.96 (s, OAc), 30.04 (s, CH₃), 26.44 (s, CH₂-N), 25.80 (s, CH₂-OAc), 23.89 (s, CH₃). 19F NMR (188 MHz, CD₃OD): δ = 167.03 (s, C-2'), 153.16 (s, C-4'), 144.74 (d, C-6'), 140.55 (s, C-1), 141.61 (d, C-3), 126.20 (s, C-5'), 119.20 (s, C-3'), 115.54 (s, C-6'), 115.11 (s, C-2'), 107.46 (s, C-1'), 96.75 (s, C-2'), 87.66 (s, OAc), 30.04 (s, CH₃), 26.44 (s, CH₂-N), 25.80 (s, CH₂-OAc), 23.89 (s, CH₃).

A solution of 12 (0.45 g, 1.19 mmol) and potassium hydroxide (0.47 g, 8.4 mmol) in methanol (20 ml) was stirred at room temperature overnight. After neutralization by diluted hydrochloric acid (10%) and filtration the filtrate was evaporated under reduced pressure and the remaining oil was subjected to column chromatography (silica gel, ethyl acetate → ethyl acetate/methanol 9:1) to afford 13 (0.17 g, 62%) as a white solid. – M. p.: 192 – 199 °C. – Rp (ethyl acetate) 0.20. – UV/vis (methanol): λmax (lg e) = 265 nm (3.96). – IR (KBr): ν = 3410s, 3155s, 3015s, 2970s, 2980m, 2825m, 2530s, 2270s, 1760m, 1680s, 1480s, 1430s, 1405s, 1375s, 1360m, 1270s, 1255s, 1245s, 1195m, 1104s, 1105m, 1070s, 1040s, 1025s, 1000s cm⁻¹. 1H NMR (200 MHz, CDCl₃): δ = 7.56 (d, 2JHH = 7.8 Hz, 1 H, 6'-H), 5.66 (d, 2JHH = 7.8 Hz, 1 H, 5'-H), 4.11 – 3.97 (m, 1 H, H-CH'N), 3.83 – 3.66 (m, 1 H, H'-CHN), 3.61 – 3.58 (m, 2 H, CH₂-OAc), 2.03 – 1.82 (m, 2 H, 1-H, 3-H). 13C NMR (100 MHz, CDCl₃): δ = 166.43 (s, C-2'), 152.55 (s, C-4'), 146.49 (d, C-6'), 115.54 (d, 2JCC = 287.9, 287.9 Hz, C-2'), 102.22 (d, C-5'), 58.43 (d, 2JCF = 4.9 Hz, CH₂-OAc), 46.00 (dt, 3JCF = 4.9 Hz, CH₂-N), 30.24 (virts, 2JCC = 9.6 Hz, C-3), 25.90 (virts, 2JCF = 10.8 Hz, C-1). 19F NMR (188 MHz, CDCl₃): δ = −136.12 and −138.55 (AB system, JAB = 164.5 Hz, FA and FB) – HRMS calcd. for C₂H₄O₂N₂O₃F₂: 232.0659; found: 232.0659. – Analysis for C₉H₁₀N₂O₃F₂ (232.18): C 46.56, H 4.34, N 12.07; found C 46.41, H 4.43, N 12.12.
3.43 (m, 3 H, H'-CHN, CH₂-OBn), 1.96–1.76 (m, 2 H, H-1', 3-H'), 13C NMR (50 MHz, CDCl₃): δ = 167.18 (s, C=O (Bz)), 156.20 (d, J₈C₁₆ = 26.9 Hz, C-4'), 148.56 (s, C-2'), 140.34 (d, J₈C₁₆ = 241.6 Hz, C-5'), 137.55 (s, CₚH₆ phenyl, Bn)), 135.55 (s, CₚH₆ phenyl, Bz), 131.07 (d, J₇C₁₆ = 214 Hz, C-phenyl, Bz), 129.36 (d, CₚH₆ phenyl, Bz), 128.65 (d, CₚH₆ phenyl, Bn), 128.07 (d, CₚH₆ phenyl, Bn), 127.86 (dd, J₈C₁₆ = 33.6 Hz, C-6'), 127.73 (d, J₇C₁₆ = 290.9, 285.5 Hz, CF₂), 73.04 (t, CH₂-phenyl), 65.19 (dt, J₈C₁₆ = 3.7 Hz, CH₂-OBn), 46.01 (dt, J₈C₁₆ = 5.0 Hz, CH₂-N), 27.55 (virt dt, J₂C₁₆ = 10.6 Hz, C-3), 25.05 (virt dt, J₂C₁₆ = 11.0 Hz, C-1). − 19F NMR (188 MHz, CDCl₃): δ = −137.65 and −139.60 (AB system, J₈F = 14.7, 0.2 Hz, 3 J₂F = 10.2 Hz, C-3), 26.30 (virt dt, J₂F = 26.5 Hz, C-4'), 137.58 and 137.65 and 137.84 and 137.90 (s, CₚH₆ phenyl, Bn), 130.55 (s, CₚH₆ phenyl, Bz), 129.00 (d, J₇C₁₆ = 233.8 Hz, C-5'), 120.10 (d, J₇C₁₆ = 33.6 Hz, C-6'), 115.97 (dd, J₁C₁₆ = 288.4, 285.5 Hz, CF₂), 58.86 (dt, J₈C₁₆ = 4.9 Hz, CH₂-OH), 46.56 (dt, J₂C₁₆ = 5.4 Hz, CH₂-N), 30.76 (virt dt, J₂C₁₆ = 10.2 Hz, C-3), 26.30 (virt dt, J₂C₁₆ = 10.7 Hz, C-1). − 13C NMR (100 MHz, CD₃OD): δ = 167.68 (s, 5'-(F = -12.1 Hz, 3 J₂F = 290.5, 290.9 Hz, CF₂), 58.86 (dt, J₈C₁₆ = 4.9 Hz, CH₂-OH), 46.56 (dt, J₂C₁₆ = 5.4 Hz, CH₂-N), 30.76 (virt dt, J₂C₁₆ = 10.2 Hz, C-3), 26.30 (virt dt, J₂C₁₆ = 10.7 Hz, C-1). − 19F NMR (188 MHz, CD₃OD): δ = −135.90 and −138.40 (AB system, J₈F = 116.5 Hz, Fₙ and Fₘ), −167.68 (s, 5'-(F = -12.1 Hz, 3 J₂F = 290.5, 290.9 Hz, CF₂), 58.86 (dt, J₈C₁₆ = 4.9 Hz, CH₂-OH), 46.56 (dt, J₂C₁₆ = 5.4 Hz, CH₂-N), 30.76 (virt dt, J₂C₁₆ = 10.2 Hz, C-3), 26.30 (virt dt, J₂C₁₆ = 10.7 Hz, C-1). − 13C NMR (100 MHz, CD₃OD): δ = 167.68 (s, 5'-(F = -12.1 Hz, 3 J₂F = 290.5, 290.9 Hz, CF₂), 58.86 (dt, J₈C₁₆ = 4.9 Hz, CH₂-OH), 46.56 (dt, J₂C₁₆ = 5.4 Hz, CH₂-N), 30.76 (virt dt, J₂C₁₆ = 10.2 Hz, C-3), 26.30 (virt dt, J₂C₁₆ = 10.7 Hz, C-1). − 19F NMR (188 MHz, CD₃OD): δ = −135.90 and −138.40 (AB system, J₈F = 116.5 Hz, Fₙ and Fₘ), −167.68 (s, 5'-(F = -12.1 Hz, 3 J₂F = 290.5, 290.9 Hz, CF₂), 58.86 (dt, J₈C₁₆ = 4.9 Hz, CH₂-OH), 46.56 (dt, J₂C₁₆ = 5.4 Hz, CH₂-N), 30.76 (virt dt, J₂C₁₆ = 10.2 Hz, C-3), 26.30 (virt dt, J₂C₁₆ = 10.7 Hz, C-1). − 19F NMR (188 MHz, CD₃OD): δ = −135.90 and −138.40 (AB system, J₈F = 116.5 Hz, Fₙ and Fₘ), −167.68 (s, 5'-(F = -12.1 Hz, 3 J₂F = 290.5, 290.9 Hz, CF₂), 58.86 (dt, J₈C₁₆ = 4.9 Hz, CH₂-OH), 46.56 (dt, J₂C₁₆ = 5.4 Hz, CH₂-N), 30.76 (virt dt, J₂C₁₆ = 10.2 Hz, C-3), 26.30 (virt dt, J₂C₁₆ = 10.7 Hz, C-1).
\[ 1^H \text{NMR} (400 \text{ MHz, CDCl}_3): \delta = 8.70 \ (s, 1 \ H, 2'-H), 8.22 \ (s, 1 \ H, 8''-H), 7.31 - 7.15 \ (m, 5 \ H, H-phenyl), 4.48 - 4.29 \ (m, 4 \ H, CH_2-phenyl, CH_2-N), 3.58 \ (\text{ddd, } 3J_{HF} = 10.4, 3J_{HH} = 7.0, \text{ppm, CDCl}_3) \].

- 13C NMR (100 MHz, CDCl_3): \( \delta_{C-3} = 26.63 \) (virt dt, \( \delta_{C-3} = 156.87 \) (s, C-6'), 152.85 (d, C-2'), 152.34 (s, C-4'), 145.78 (d, C-8'), 138.50 (s, Cq-phenyl), 129.58 (d, Cortho-phenyl), 129.00 (d, Cmeta-phenyl), 128.60 (d, Cpara-phenyl), 115.00 (s, C-5'), 114.32 (dd, \( \delta_{C-4} = 289.7, 286.3 \) Hz, CF_2), 73.84 (t, CH_2-phenyl), 66.07 (dt, \( \delta_{C-3} = 3.3 \) Hz, CH_2-OBn), 42.28 (dt, \( \delta_{C-3} = 5.0 \) Hz, CH_2-N), 28.85 (virt dt, \( \delta_{C-3} = 106.6 \) Hz, C-3), 26.63 (virt dt, \( \delta_{C-3} = 10.8 \) Hz, C-1).

- 19F NMR (188 MHz, CDCl_3): \( \delta_{CF} = -139.86 \) and \( -139.92 \) (AB system, \( J_{AF} = 164.5 \) Hz, F_A and F_B).

- MS (EI, 70 eV): \( m/z \) % = 364 (1), 277 (5), 258 (19), 238 (100), 223 (57), 203 (4), 181 (7), 167 (11), 155 (15), 91 (73). – HRMS calcld. for: \( C_{17}H_{12}N_4O_2F_2 \).

- Treatment of compound 17 (0.78 g, 2.14 mmol) with an excess of liquid ammonia in an autoclave at 75 °C and 40 bar resulted after evaporation of the volatiles and column chromatography (silica gel, ethyl acetate) in the formation of 18 (0.52 g, 71%) that was isolated as a white solid. – M. p. 148 – 149 °C. – \( R_F \) (ethyl acetate) 0.10. – UV/vis (methanol): \( \lambda_{max} \) (\( \lambda \) in nm) = 263 nm (4.22). – IR (KBr): \( \nu_{max} \) (cm\(^{-1}\)) = 3345nm, 1363, 1322, 1286, 1100, 821, 781, 741, 661, 641, 581, 561, 541, 511.

The reaction mixture was heated under reflux for 26 hours. After filtration and evaporation of \( 0.34 \) g, 20% \( \lambda_{max} \) (\( \lambda \) in nm) = 263 nm (4.22). – IR (KBr): \( \nu_{max} \) (cm\(^{-1}\)) = 3345, 1363, 1322, 1286, 1100, 821, 781, 741, 661, 641, 581, 561, 511.

To a solution of 17 (0.45 g, 1.3 mmol) in methanol (50 ml) were added cyclohexene (40 ml) and Pearlman's catalyst (0.34 g, 20%) and the reaction mixture was heated under reflux for 26 hours. After filtration and evaporation of \( 0.34 \) g, 20% \( \lambda_{max} \) (\( \lambda \) in nm) = 263 nm (4.22). – IR (KBr): \( \nu_{max} \) (cm\(^{-1}\)) = 3345, 1363, 1322, 1286, 1100, 821, 781, 741, 661, 641, 581, 561, 511.

- MS (EI, 70 eV): \( m/z \) % = 364 (1), 277 (5), 258 (19), 238 (100), 223 (57), 203 (4), 181 (7), 167 (11), 155 (15), 91 (73). – HRMS calcld. for: \( C_{17}H_{12}N_4O_2F_2 \).

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Synthesis of trans-Configurated Spacered Nucleoside Analogues