Pergamon

Tetrahedron 58 (2002) 1005–1010

TETRAHEDRON

Synthesis of pyrazole C-nucleosides via Tin(IV) chloride-promoted reactions of β-D-ribofuranosyl cyanide with β-dicarbonyl compounds

Monica Manferdini,[a] Carlo F. Morelli[b] and Augusto C. Veronese[a,*]

[a]*Dipartimento di Scienze Farmaceutiche, Via Fossato di Mortara 17, I-44100 Ferrara, Italy*
[b]*Dipartimento di Chimica Organica e Industriale, via Venezian 21, I-20133 Milano, Italy*

Received 25 August 2001; revised 5 November 2001; accepted 29 November 2001

Abstract—2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl cyanide reacts with methyl acetoacetate and diethyl malonate in the presence of stoichiometric amounts of $SnCl_4$ to give a β-D-ribofuranosyl-enaminoketoester and a β-D-ribofuranosyl-enaminodiester, respectively. The β-D-ribofuranosyl-enaminoketoester was debenzoylated, treated with 2,2-dimethoxypropane and *tert*-butyl-dimethylsilyl chloride to give the methyl 3-amino-3-(5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-2-acetyl propanoate obtained in good yield together with small amounts of its α-anomer. The reactions of the β-anomer with hydrazine, methyl- and phenylhydrazine, carried out under controlled experimental conditions, afforded the pyrazole C-nucleosides in good yields as β-anomers.

1. Introduction

The metal promoted reactions of β-dicarbonyl compounds with nitriles afford β-enaminodicarbonyl derivatives through a C–C bond formation between the methylene and the cyano groups.[1] We have recently reported that this reaction can be applied to the synthesis of heterocyclic C-nucleosides. β-D-ribofuranosyl ketoesters react with alkylcyanoformates in the presence of a transition metal catalyst to give β-D-ribofuranosyl enaminoketoesters. The reactions of these compounds with hydrazines and amidines afford pyrazole and pyrimidine C-nucleosides as β-anomers in good yields.[2]

In this paper we report on an alternative route to the synthesis of pyrazole C-nucleosides involving as a key step the metal promoted reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylcyanide (**1**) with β-dicarbonyl compounds.

2. Results and discussion

The ribofuranosyl cyanide (**1**) can be easily prepared from 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl acetate.[3] The reactions of cyano derivative **1** with β-dicarbonyl compounds were carried out in dichloroethane at room temperature in the presence of a stoichiometric amount of tin(IV) chloride. The reaction of **1** with methyl acetoacetate afforded the β-D-ribofuranosyl enaminoketoester **2** in good yield. A similar reaction of **1** with diethylmalonate gave the enaminodiester **3** in lower yield (Scheme 1).

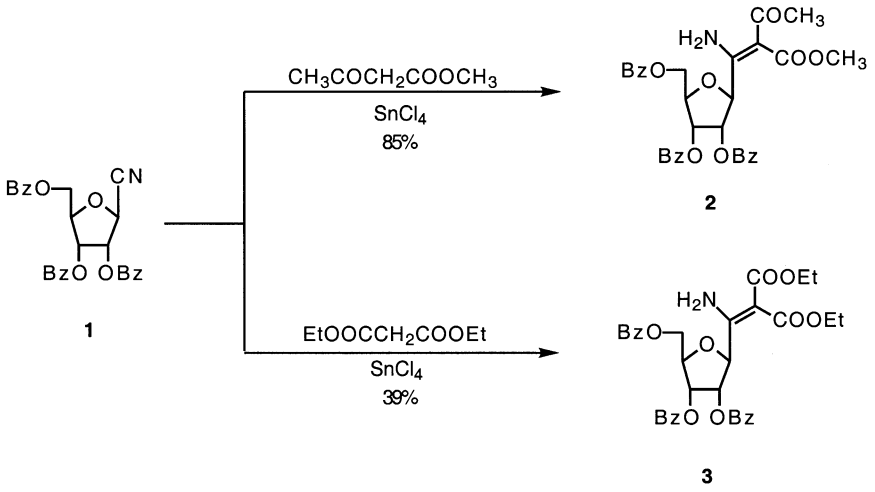
On the basis of results recently reported on the synthesis of pyrazole derivatives from enaminoketoesters,[4] we decided to investigate the possibility of utilizing compound **2**, obtained in good yield, as an intermediate in the synthesis of pyrazole C-nucleosides, analogous to pyrazofurine, a natural pyrazole C-nucleoside showing antiviral and antitumour activities.[5]

When we reacted compound **2** with hydrazine hydrate, we obtained only complex reaction mixtures possibly because of the deprotection of the ribofuranosyl moiety and decomposition of the obtained compounds.[6] So we decided to modify the protection of ribose hydroxy groups in order to obtain analogues of compound **2** suitable for the treatment with hydrazines.

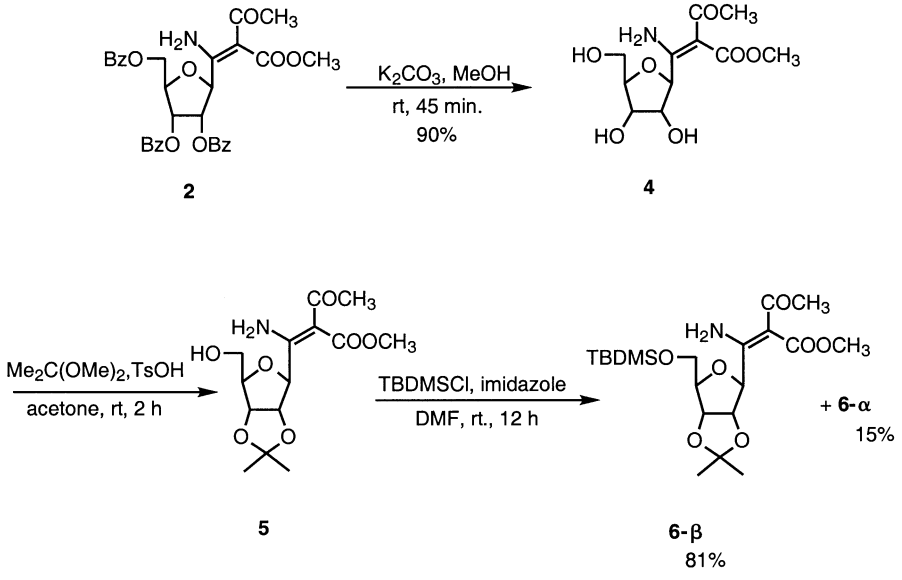
The tri *O*-benzoyl enaminoketoester **2** was deprotected by treatment with K_2CO_3 in methanol at room temperature for 45 min to give the β-ribofuranosyl enaminoketoester **4**. This compound was treated with 2,2-dimethoxypropane in acetone to afford the isopropylidene derivative **5**. The reaction of **5** with *tert*-butyl-dimethylsilyl chloride in DMF in the presence of imidazole afforded two compounds in 81 and 15% yields, respectively. On the basis of their NMR spectra, according to the results reported by

Keywords: pyrazole C-nucleosides; β-D-ribofuranosyl cyanide; β-dicarbonyl compounds.
* Corresponding author. Tel.: +39-532-291287; fax: +39-532-291296; e-mail: vra@dns.unife.it

0040–4020/02/$ - see front matter
PII: S0040-4020(01)01194-2



Scheme 1.



Scheme 2.

Moffat et al.,[7] the structure of anomer **6**-β was attributed to the main compound while the structure of anomer **6**-α was attributed to the compound obtained in lower yield.

The anomer **6**-β was then reacted with hydrazine hydrate in refluxing methanol. In this reaction two products were obtained: the expected pyrazolyl C-nucleoside **7a** in ca. 30% yield together with the anomer **6**-α obtained in 70% yield. This result demonstrated that in these experimental conditions **6**-β epimerises easily to anomer **6**-α.[8]

Attempts to react **6**-α with hydrazine hydrate under many experimental conditions did not afford any reaction product leading to the complete recovery of the starting material (Scheme 2).

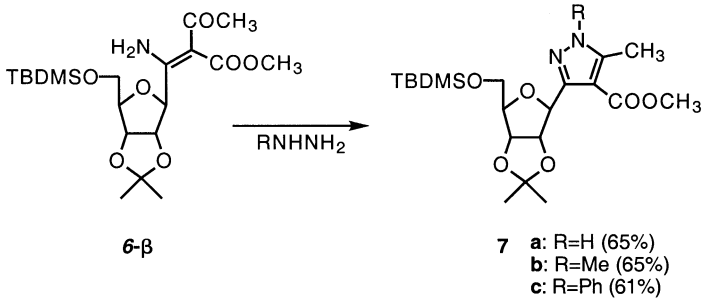
In order to find experimental conditions suitable for the synthesis in good yield of pyrazole C-nucleosides we studied the stability of anomer **6**-β in different solvents at their reflux temperature.

The results obtained heating at reflux for 2 h a solution of anomer **6**-β in different solvents are reported in Table 1. The percentage of epimerisation is strongly dependent on solvent, ethanol being the solvent in which least epimerisation was found.

The reaction of **6**-β with hydrazine was then carried out using absolute ethanol as solvent (1–2 mL vs 1 mmol of **6**-β). To this solution hydrazine hydrate in a large excess

Table 1. Solvent and temperature effect on the stability of anomer **6**-β

Solvent	Reflux temperature (°C)	**6**-β/**6**-α (%)
Absolute ethanol	78	80/20
Benzene	80	65/45
1,2-Dichloroethane	84	42/58
2,2-Dimethoxyethane	81	65/35
Dichloromethane	40	52/48
Methanol	65	40/60
Chloroform	61	30/70



6-β

7 **a**: R=H (65%)
b: R=Me (65%)
c: R=Ph (61%)

Scheme 3.

(molar ratio **6**-β/hydrazine 1:5) was added at room temperature and the reaction mixture was heated slowly (1 h) until reflux temperature (78°C) and further heated under reflux for 1 h. Under these conditions the β-D-ribofuranosyl pyrazole **7a** was obtained in 65% yield together with a small amount of anomer **6**-α (yield less than 20%). Under similar experimental conditions **6**-β reacted with methyl and phenyl hydrazines to afford derivatives **7b**,**c** in ca. 65% yield (Scheme 3).

The structures of compounds **7a**–**c** were assigned on the basis of the NMR spectra. In particular the ^{13}C NMR spectra of compounds **7b**,**c** show resonances at ca. 152 and 144 ppm attributable, respectively, to the C-3 and C-5 of the pyrazole ring. The resonances at ca. 152 ppm were singlets while the absorptions at ca. 144 ppm were detected as a quartet (^2J=6.5 Hz) due to the long range coupling between the C-5 carbon atom and the hydrogens of methyl group linked to the C-5 and this confirms the proposed structures.[4]

3. Conclusion

The results obtained demonstrated that compound **6**-β can be transformed, under controlled experimental conditions, into β-D-ribofuranosyl pyrazole C-nucleosides so opening a new route to the synthesis of derivatives analogous to pyrazofurine.

4. Experimental

4.1. General

Mps were determined on a 'Kofler' apparatus and are uncorrected. IR spectra were recorded on FT-IR Perkin–Elmer Paragon 500 spectrometer. NMR spectra were recorded on Bruker AC (200 MHz) spectrometer. Chemical shifts are given in ppm (δ) with respect to tetramethylsilane and coupling constants (J) are in Hz. Glass plates 'Merk Kieselgel 60' F 245 were used for thin layer chromatography. Silica gel 'ICN Silica 32–60, 60 Å' was used for column chromatography.

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**1**) was prepared according to procedures previously described.[2,3]

4.1.1. Methyl 3-amino-3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-acetyl propenoate (2). To a stirred solution of 1 M $SnCl_4$ in CH_2Cl_2 (3 mL) a solution of ribofuranosyl cyanide (**1**) (1.177 g, 2.5 mmol) and methyl acetoacetate (0.32 mL, 3 mol) in CH_3Cl_2 (5 mL) was added. The reaction mixture was stirred at room temperature for 10 min, diluted with ethyl acetate (10 mL), treated under stirring for 30 min with an aqueous saturated solution of $NaHCO_3$ and filtered on celite. The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by column chromatography (flash chromatography, SiO_2, ethyl acetate/light petroleum 1:3) to give colourless crystals (1.3 g, yield 85%), mp 55–58°C, $[\alpha]_D$=+62 (c=1.5, $CHCl_3$); FT-IR (KBr): 3420 (br), 1720, 1600, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.38 (s, 3H, Me), 3.56 (s, 3H, OMe), 4.6–4.8 (m, 3H, OCH_2, H-4′), 5.63 (dd, 1H, J=8.5, 4.7 Hz, H-3′), 5.73 (d, J=1.6 Hz, H-1′), 5.87 (dd, J=4.7, 1.6 Hz, H-2′), 7.1–8.2 (m, 16H, Ph, NH), 11.70 (br, NH); ^{13}C NMR ($CDCl_3$) δ: 31.21 (q, J=127.1 Hz, Me), 51.08 (q, J=146.4 Hz, OMe), 62.65 (t, J=148.6 Hz, OCH_2), 69.94 (d, J=152.0 Hz, CH), 76.74 (d, J=163.3 Hz, CH), 78.16 (d, J=156.0 Hz, CH), 80.22 (d, J=170.5 Hz, CH), 99.94 (s, C-2), 128.37 (d, Ph), 128.58 (d, Ph), 128.77 (d, Ph), 129.28 (s, Ph), 129.62 (d, Ph), 129.76 (d, Ph), 129.85 (d, Ph), 133.54 (d, Ph), 133.70 (d, Ph), 164.84 (s, C–NH_2), 165.07 (s, COO), 166.41 (s, COO), 166.96 (s, COO), 168.34 (s, COO), 198.91 (s, CO). Found: C, 65.50; H, 4.80; N, 2.20. $C_{32}H_{29}NO_{10}$ requires C, 65.41; H, 4.97; N, 2.38.

4.1.2. Ethyl 3-amino-3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-ethoxycarbonyl propenoate (3). To a stirred solution of 1 M $SnCl_4$ in CH_2Cl_2 (2 mL, 2 mmol) a solution of ribofuranosyl cyanide (**1**) (0.707 g, 1.5 mmol) and diethylmalonate (0.3 mL, 2 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred at room temperature for 24 h, diluted with ethyl acetate (10 mL), treated under stirring for 30 min with an aqueous saturated solution of $NaHCO_3$ and filtered on celite. The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by column chromatography (flash chromatography, SiO_2, ethyl acetate/light petroleum 1:4): colourless oil (0.37 g, yield 39%), $[\alpha]_D$=+41 (c=1.2, $CHCl_3$); FT-IR (neat): 3400 (br), 1740, 1720, 1610, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.13 (t, 3H, J=7.0 Hz, Me), 1.27 (t, J=7.0 Hz, 3H, Me), 3.90–4.10 (m, 2H, OCH_2), 4.10–4.20 (m, 2H, OCH_2), 4.60–4.70 (m, 3H, OCH_2 and H-4), 5.70 (m, 1H, H-2 or H-3), 5.73 (d, J=2.9 Hz, H-1), 5.85 (m, 1H, H-2 or H-3), 6.90 (br, 1H, NH), 7.20–7.60 (m, 9H, Ph), 7.75–7.85 (m, 2H, Ph), 8.01–8.09 (m, 4H, Ph), 9.10 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 10.51 (q, J=129.5 Hz, Me), 61.34 (t,

J=147.1 Hz, OCH_2), 64.15 (t, J=145.1 Hz, OCH_2), 70.15 (d, J=149.4 Hz, CH), 75.20 (d, J=158.7 Hz, CH), 77.23 (d, J=157.2 Hz, CH), 79.54 (d, J=164.3 Hz, CH), 103.56 (s, C-2), 127.18 (d, Ph), 127.78 (d, Ph), 128.12 (d, Ph), 128.68 (s, Ph), 128.96 (d, Ph), 129.05 (d, Ph), 129.54 (d, Ph), 132.16 (d, Ph), 132.60 (d, Ph), 162.52 (s, C–NH_2), 166.21 (s, COO), 166.64 (s, COO), 167.54 (s, COO), 169.12 (s, COO), 169.56 (s, COO). Found: C, 64.50; H, 5.40; N, 2.15. $C_{34}H_{33}NO_{11}$ requires C, 64.65; H, 5.27; N, 2.22.

4.1.3. Methyl-3-amino-3-β-D-ribofuranosyl-2-acetyl-propenoate (4). To a solution of enaminoketoester (**2**) (147 mg, 0.25 mmol) in methanol (5 mL) K_2CO_3 (11 mg, 0.083 mmol) was added. The obtained solution was stirred at room temperature for 45 min, and concentrated under reduced pressure to give a residue which was purified by column chromatography (flash chromatography, SiO_2, methylene chloride/methanol 9:1): colourless crystals, mp 68–71°C, 62 mg (yield 90%); $[\alpha]_D$=−39.1 (c=11.6, MeOH); FT-IR (KBr): 3367 (br), 1674, 1601, 1099 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.16 (s, 3H, Me), 3.66 (s, 3H, OMe), 3.50–3.60 (m, 1H, CH_2O), 3.70–3.80 (m, 4H, CH_2O, H-2, H-3), 4.91 (s, 1H, H-1), 4.97 (d, 1H, J= 6.0 Hz, exchanges with D_2O, OH), 5.25 (d, 1H, J=4.5 Hz, exchanges with D_2O, OH), 5.46 (t, 1H, J=4.5 Hz, exchanges with D_2O, OH), 8.60 (br, 1H, exchanges with D_2O, NH), 11.30 (br, 1H, exchanges with D_2O, NH); ^{13}C NMR (DMSO-d_6) δ: 30.04 (q, J=127.3 Hz, Me), 51.03 (q, J=147.6 Hz, OMe), 58.93 (t, J=140.3 Hz, CH_2O), 68.81 (d, J=144.4 Hz, CH), 76.91 (d, J=148.5 Hz, CH), 81.51 (d, J=146.2 Hz, CH), 81.69 (d, J=160.1 Hz, CH), 98.89 (s, C-2), 168.76 (s, C–NH_2), 169.78 (s, COO), 195.82 (s, CO). Found: C, 48.15; H, 6.15; N, 5.15. $C_{11}H_{17}NO_7$ requires C, 48.00; H, 6.23; N, 5.09.

4.1.4. Methyl-3-amino-3-(2′,3′-*O*-isopropilydene-β-D-ribofuranosyl)-2-acetyl-propenoate (5). A solution of compound (**4**) (180 mg, 0.65 mmol), 2,2-dimethoxypropane (0.2 mL, 1.6 mmol) and *p*-toluensulfonic acid (5 mg) in dry acetone (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate (20 mL). The solution was washed with a saturated aqueous solution of $NaHCO_3$, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a yellow oil which was purified by column chromatography (flash chromatography, SiO_2, ethyl acetate/light petroleum 2:1): pale yellow oil, 177 mg (yield 86%); $[\alpha]_D$=−27.0 (c=10.5, MeOH); FT-IR (neat): 3350 (br), 1699, 1605, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.34 (s, 3H, Me), 1.57 (s, 3H, Me), 2.34 (s, 3H, Me), 3.77 (s, 3H, OMe), 3.83 (dd, J=11.5, 2.5 Hz, 1H, CH_2O), 4.03 (dd, J=11.5, 2.3 Hz, 1H, CH_2O), 3.94 (br, 1H, OH), 4.10–4.20 (m, 1H, H-4′), 4.63 (dd, J=5.7, 1.8 Hz, 1H, H-2′), 4.72 (dd, J=5.7 Hz, 1H, H-3′), 5.31 (d, J=1.8 Hz, 1H, H-1′), 8.00 (br, 1H, NH), 11.40 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 25.71 (q, J=124.4 Hz, Me), 27.53 (q, J=117.5 Hz, Me), 30.16 (q, J=127.8 Hz, Me), 51.38 (q, J=146.1 Hz, OMe), 61.53 (t, J=140.9 Hz, CH_2O), 72.15 (d, J=154.2 Hz, CH), 81.17 (d, J=156.3 Hz, CH), 83.36 (d, J=156.9 Hz, CH), 86.32 (d, J=160.0 Hz, CH), 98.76 (s, C-2), 112.16 (s, CMe_2), 167.31 (s, C–NH_2), 169.96 (s, COO), 197.52 (s, CO). Found: C, 53.20; H, 6.60; N, 4.35. $C_{14}H_{21}NO_7$ requires C, 53.33; H, 6.71; N, 4.44.

4.1.5. Methyl 3-amino-3-(5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-2-acetyl-propenoate (6). A solution of compound (**5**) (300 mg, 1 mmol), *tert*-butyldimethylsilylchloride (180 mg, 1.12 mmol) and imidazole (170 mg, 2.5 mmol) in DMF (2 mL) was stirred at room temperature for 12 h. To the reaction mixture ethyl acetate (20 mL) was added and the solution was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by column chromatography (flash chromatography, SiO_2, ethyl ether/light petroleum 3:7). Two anomeric compounds were obtained.

6-β: R_f=0.35 (ethyl ether/light petroleum 3:7): colourless oil, 349 mg (yield 81%); $[\alpha]_D$=−17.3 (c=1.13, $CHCl_3$); FT-IR (neat): 3350, 1700, 1610, 1255, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.06 (s, 6H, $SiMe_2$), 0.85 (s, 9H, *t*-Bu), 1.25 (s, 3H, Me), 1.50 (s, 3H, Me), 2.30 (s, 3H, Me), 3.75 (s, 3H, OMe), 3.70–3.80 (m, 1H, CH_2O), 4.10 (dd, 1H, J=11.4, 2.3 Hz, 1H, CH_2O), 4.07–4.14 (m, 1H, H-4′), 4.60–4.69 (m, 2H, H-2′, H-3′), 5.27 (s, 1H, H-1′), 8.1 (br, 1H, NH), 11.60 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: −5.40 (q, J=118.3 Hz, $SiMe_2$), 18.22 (s, C–Si), 25.77 (q, J=124.4 Hz, Me), 25.81 (q, 126.5 Hz, *t*-Bu), 27.65 (q, J=119.0 Hz, Me), 30.50 (q, J=127.4 Hz, Me), 51.12 (q, J=144.3 Hz, OMe), 62.17 (t, J=143.5 Hz, CH_2O), 77.73 (d, J=165.0 Hz, CH), 82.09 (d, J=163.5 Hz, CH), 85.65 (d, J=148.3 Hz, CH), 87.05 (d, J=162.2 Hz, CH), 99.50 (s, C-2), 113.56 (s, CMe_2), 168.80 (s, C–NH_2), 169.32 (s, COO), 201.10 (s, CO). Found: C, 55.80; H, 8.30; N, 3.20. $C_{20}H_{35}NO_7Si$ requires C, 55.92; H, 8.21; N, 3.26.

6-α: R_f=0.40 (ethyl ether/light petroleum 3:7), colourless oil, 64 mg (yield 15%); $[\alpha]_D$=−10 (c=0.97, $CHCl_3$); FT-IR (neat): 3430, 1697, 1605, 1256, 1075 cm^{-1}; ^1H NMR: ($CDCl_3$) δ: −0.72 (s, 6H, $SiMe_2$), 0.92 (s, 9H, *t*-Bu), 1.31 (s, 3H, Me), 1.35 (s, 3H, Me), 2.38 (s, 3H, Me), 3.70 (s, 3H, OMe), 3.74–3.76 (m, 2H, CH_2O), 4.31–4.34 (m, 1H, H-4′), 4.77–4.80 (m, 1H, H-2′ or H-3′), 5.24–5.30 (m, 2H, H-1′, H-2′ or H-3′), 7.25 (br, 1H, NH), 11.85 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: −5.60 (Si–Me), −5.57 (Si–Me), 18.23 (C–Si), 18.23 (Me), 25.85 (*t*-Bu), 25.87 (Me), 31.24 (Me), 60.05 (OMe), 65.13 (CH_2O), 82.12 (CH), 82.65 (CH), 83.55 (CH), 83.94 (CH), 101.10 (C-2), 112.24 (CMe_2), 166.77 and 168.65 (C–NH_2 and COO), 199.04 (CO). Found: C, 55.80; H, 8.30; N, 3.20. $C_{20}H_{35}NO_7Si$ requires C, 55.92; H, 8.21; N, 3.26.

4.1.6. Methyl 5-methyl-3-(2′,3′-*O*-isopropylidene-5′-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-pyrazole-4-carboxylate (7a). A solution of **6**-β (334 mg, 0.78 mmol) and hydrazine hydrate (0.2 mL, 4.5 mmol) in absolute ethanol (1 mL) was stirred at room temperature for 1 h, heated slowly (1 h) till reflux (75°C) and heated at this temperature for 1 h. The obtained solution was concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate (20 mL). The organic solution was washed with 1N HCl (5 mL) and with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by column chromatography

(flash chromatography, SiO_2, ethyl ether/light petroleum 4:6): colourless oil, 212 mg (yield 65%); $[\alpha]_D=-7.6$ ($c=1.1$, MeOH); FT-IR (neat): 3280, 1715, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.13 (s, 3H, Si–Me), 0.15 (s, 3H, Si–Me), 0.92 (s, 9H, *t*-Bu), 1.34 (s, 3H, Me), 1.58 (s, 3H, Me), 2.43 (s, 3H, Me), 3.72 (dd, $J=11.4$, 3.5 Hz, 1H, CH_2O), 3.82 (s, 3H, OMe), 3.96 (dd, $J=11.4$ and 3.5 Hz, 1H, CH_2O), 4.23 (dd, $J=8.0$, 3.5 Hz, 1H, H-4′), 4.70 (dd, $J=8.0$, 5.8 Hz, 1H, H-3′), 4.75 (dd, $J=5.8$, 1.0 Hz, 1H, H-2′), 5.55 (d, $J=1.0$ Hz, 1H, H-1′), 9.30–12.30 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: −5.20 (q, $J=118.0$ Hz, $SiMe_2$), 13.51 (q, $J=125.9$ Hz, Me), 18.38 (s, C–Si), 25.8 (q, $J=124.5$ Hz, Me), 25.94 (q, $J=124.2$, *t*-Bu), 27.50 (q, $J=126.2$ Hz, Me), 51.15 (q, $J=146.7$ Hz, OMe), 63.30 (t, $J=140.5$ Hz, CH_2O), 79.92 (d, $J=156.3$ Hz, CH), 80.44 (d, $J=154.8$ Hz, CH), 85.47 (d, $J=147.6$ Hz, CH), 86.56 (d, $J=158.8$ Hz, CH), 107.80 (s, C-4), 113.35 (s, CMe_2), 148.25 (s, C-5), 150.26 (s, C-3), 164.0 (s, COO). Found: C, 56.20; H, 8.00; N, 6.50. $C_{20}H_{34}N2O_6Si$ requires C, 56.31; H, 8.03; N, 6.57.

4.1.7. Methyl 1,5-dimethyl-3-(2′,3′-*O*-isopropylidene-5′-*O*-*tert*-butyl-dimethyl-silyl-β-D-ribofura-nosyl)-pirazole-4-carboxylate (7b). To a solution of **6**-β (176 mg, 0.41 mmol) in absolute ethanol (0.4 mL) methylhydrazine (0.11 mL, 2.25 mmol) and *p*-toluensulfonic acid (5 mg) were added. The reaction mixture was heated slowly (1 h) till reflux and further heated under reflux for 1.5 h. The obtained solution was concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate (20 mL). The organic solution was washed with saturated $NaHCO_3$, 1N HCl, brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (flash chromatography, SiO_2, ethyl acetate/light petroleum 1:4): colourless oil, 130 mg (yield 65%); $[\alpha]_D=-3.7$ ($c=0.9$, MeOH); FT-IR (neat): 1715, 1505, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.14 (s, 3H, Si–Me), 0.16 (s, 3H, Si–Me), 0.94 (s, 9H, *t*-Bu), 1.32 (s, 3H, Me), 1.65 (s, 3H, Me), 2.45 (s, 3H, Me), 3.75 (s, 3H, N–Me), 3.82 (dd, $J=11.3$, 3.2 Hz, CH_2O), 3.88 (s, 3H, OMe), 3.90 (dd, $J=11.3$, 3.2 Hz, CH_2O), 4.35 (dd, $J=6.4$, 3.5 Hz, 1H, H-4), 4.78 (dd, $J=6.49$, 3.06 Hz, 1H, H-3), 5.28 (dd, $J=6.5$, 3.7 Hz, 1H, H-2), 5.46 (d, $J=3.7$ Hz, 1H, H-1); ^{13}C NMR δ: −5.27 (q, $J=118.0$ Hz, $SiMe_2$), 11.03 (q, $J=127.9$ Hz, Me),16.52 (s, C–Si), 25.48 (q, $J=124.4$ Hz, Me), 25.85 (q, $J=126.8$ Hz, *t*-Bu), 27.35 (q, $J=125.4$ Hz, Me), 30.89 (q, $J=122.6$ Hz, Me), 51.20 (q, $J=146.6$ Hz, OMe), 63.32 (t, $J=140.6$ Hz, CH_2O), 81.36 (d, $J=156.0$ Hz, CH), 81.59 (d, $J=154.5$ Hz, CH), 86.86 (d, $J=146.5$ Hz, CH), 87.04 (d, $J=159.2$ Hz, CH), 108.8 (s, C-4), 112.92 (s, CMe_2), 144.73 (q, $^2J=6.5$ Hz, C-5), 153.05 (s, C-3,), 163.87 (s, COO). Found: C, 57.20; H, 8.10; N, 6.45. $C_{21}H_{36}N_2O_6Si$ requires C, 57.25; H, 8.24; N, 6.36.

4.1.8. Methyl 1-phenyl-5-methyl-3-(2′,3′-*O*-isopropylidene-5′-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-pyrazole-4-carboxylate(7c). To a solution of **6**-β (257 mg, 0.6 mmol) in absolute ethanol (0.5 mL) phenylhydrazine (0.32 mL, 3 mmol) and *p*-toluensulfonic acid (5 mg) were added. The reaction mixture was stirred at room temperature for 15 min, heated slowly till reflux (30 min) and heated under reflux for 1.5 h. The obtained solution was concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate (20 mL). The organic solution was washed with saturated aqueous solution of $NaHCO_3$, 1N HCl, brine and dried (Na_2SO_4). The solution was concentrated under reduced pressure and the residue was purified by column chromatography (flash chromatography, SiO_2, ethyl acetate/light petroleum 1:4): yellow oil, 110 mg (yield 61%); $[\alpha]_D=-5.3$ ($c=1.0$, MeOH); ^1H NMR ($CDCl_3$) δ: 0.16 (s, 3H, Si–Me), 0.18 (s, 3H, Si–Me), 1.10 (s, 9H, *t*-Bu), 1.45 (s, 3H, Me), 1.59 (s, 3H, Me), 2.60 (s, 3H, Me), 3.72 (dd, $J=11.3$, 3.20 Hz, 1H, CH_2O), 3.83 (s, 3H, OMe), 3.98 (dd, $J=11.2$, 3.0 Hz, 1H, CH_2O), 4.19 (dd, $J=6.4$, 3.5 Hz, 1H, H-4), 4.95 (dd, $J=6.5$, 3.1 Hz, 1H, H-3), 5.65 (dd, $J=6.5$, 3.7 Hz, 1H, H-2), 5.80 (d, $J=3.7$ Hz, 1H, H-1), 7.40–7.47 (m, 5H, Ph); ^{13}C NMR δ: −5.27 (q, $J=118.5$ Hz, $SiMe_2$), 12.60 (q, $J=127.9$ Hz, Me), 16.41 (s, C–Si), 25.65 (q, $J=124.8$ Hz, Me), 25.98 (q, $J=126.3$ Hz, *t*-Bu), 27.43 (q, $J=125.5$ Hz, Me), 51.37 (q, $J=146.6$ Hz, OMe), 63.66 (t, $J=140.3$ Hz, CH_2O), 79.77 (d, $J=156.3$ Hz, CH), 83.16 (d, $J=154.7$ Hz, CH), 83.69 (d, $J=146.3$ Hz, CH), 86.02 (d, $J=159.5$ Hz, CH), 110.2 (s, C-4), 113.43 (s, CMe_2), 125.60 (d, Ph), 129.25 (d, Ph), 129.57 (d, Ph), 138.73 (s, Ph), 145.16 (q, $^2J=6.7$ Hz, C-5), 151.70 (s, C-3), 164.24 (s, COO). Found: C, 62.20; H, 7.55; N, 5.50. $C_{26}H_{38}N_2O_6Si$ requires C, 62.12; H, 7.62; N, 5.57.

Acknowledgements

The authors are grateful to Dr A. Casolari and Mr P. Orlandini for recording NMR spectra.

References

1. Corain, B.; Basato, M.; Veronese, A. C. *J. Mol. Catal.* **1993**, *81*, 133.
2. (a) Veronese, A. C.; Morelli, C. F. *Tetrahedron Lett.* **1998**, *39*, 3853. (b) Morelli, C. F.; Manferdini, M.; Veronese, A. C. *Tetrahedron* **1999**, *55*, 10803.
3. (a) De las Heras, F. G.; Fernadez-Resa, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, *4*, 903. (b) Utimoto, K.; Horiie, T. *Tetrahedron Lett.* **1982**, *23*, 237.
4. Manferdini, M.; Morelli, C. F.; Veronese, A. C. *Heterocycles* **2000**, *53*, 2775.
5. (a) Daves, G. D.; Cheng, C. C. In *The Chemistry and Biochemistry of C-Nucleosides*; Ellis, G. P., West, G. B., Eds.; *Progress in Medicinal Chemistry*; North Holland: Amsterdam, 1976; Vol. 13, p 303. (b) Buchanan, J. G. The C-Nucleoside Antibiotics. *Progress in the Chemistry of Organic Natural Products*, Vol. 44; 1983; p 243. (c) Sweeney, M. S.; Davis, F. A.; Gutowski, G. E.; Hoffmann, D. H.; Poore, G. A. *Cancer Res.* **1973**, *33*, 2619.
6. Ishido, Y.; Nakazaki, N.; Sakairi, N. *J.Chem. Soc., Perkin Trans. 1* **1979**, 2088.
7. Ohrui, H.; Jones, G. H.; Moffat, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602 The attribution of the structure to the two anomers was made on the basis of NMR spectra: (i) in the ^1H NMR spectra of anomer obtained in higher yield no coupling constant was detected for the hydrogen linked to H-1 and this agrees with the structure of **6**-β; (ii) in the ^{13}C NMR spectra the resonances of two methyl groups of isopropylidene are significantly

different and agree with those reported by Moffat for similar anomers: 25.67 and 27.72 ppm for **6**-β (Moffat: 25.5±0.2 and 27.5±0.2 ppm for beta anomers); 24.9 and 26.3 ppm for **6**-α (Moffat: 24.9 and 26.3 ppm for alpha anomers); (iii) in the ^{1}H NMR spectra in $CDCl_3$ the difference of resonances of two methyl groups of isopropylidene is $\Delta\delta$=0.22 ppm (1.52−1.30 ppm) for the **6**-β and 0.05 ppm (1.36−1.31 ppm) for **6**-α and these differences agree with those reported by Moffat for similar compounds.

8. Moffat et al.[7] studying the relative stability of ribofuranosyl derivatives protected as 2′-3′-*O*-isopropylidene derivatives, demonstrated that in these oxygenated bicyclic systems the alpha anomer is thermodynamically more stable than the beta which is the kinetically favoured one. The interconversion of two anomers depends on the acidity of hydrogen linked to the carbon C-1′.