Efficient and β-Stereoselective Synthesis of Pyrazole *C*-Nucleosides

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Abstract: 3(5)-(β-D-Ribofuranosyl)pyrazole **1** and 3(5)-(2-deoxy-β-D-ribofuranosyl)pyrazole (**2**) were stereoselectively synthesized by cyclization of 1,2-diazafulvene intermediates obtained from 2,3,5-tri-*O*-benzyl-D-ribose (**5**) and 3,5-di-*O*-benzyl-2-deoxy-D-ribose (**10**), respectively.

Key words: pyrazole, *C*-nucleoside, β-anomer, stereoselective synthesis, diazafulvene

Pyrazofurin[1a] and formycin[1b,c] are two naturally occurring nucleosides possessing significant antitumor and antiviral activities (Figure 1).[2] These two nucleosides belong to the family of *C*-nucleosides in which the ribofuranosyl moiety is linked to the heterocyclic base by a carbon–carbon bond at the anomeric center.[1,2] With this *C*-glycosidic linkage, they are enzymatically stable to the action of nucleoside phosphorylase.[1] However, the high toxicity associated with these compounds has restricted development as potential therapeutic agents.[1a–c,2]

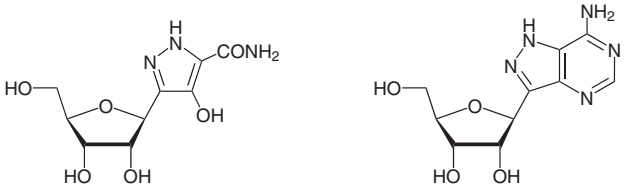


Figure 1 Pyrazofurin and formycin

Synthetic methods for *C*-nucleosides were classified into two major synthetic approaches:[3] (1) the introduction of a functional group at the anomeric position of a sugar derivative, followed by the construction of a heterocyclic base; and (2) direct attachment of a pre-formed aglycon unit to an appropriate carbohydrate moiety.[1,3] As the first approach involves many steps, it results in rather low yields and poor stereoselectivity. The second strategy was developed to overcome the drawbacks of the first approach.

Systematic studies on the synthetic methods of pyrazole *C*-nucleosides[4] and their conversion into pyrazofurin[5a–c] and formycin[5a,d] were continued for about two decades by Buchanan and Wightman et al. In this context, 3(5)-(β-D-ribofuranosyl)pyrazole **1** is used as a common precursor for pyrazofurin and formycin (Figure 2).[4] In 1995, Wightman et al. reported a stereoselective synthesis of **1** starting from 5-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone in 6 steps and about 20% overall yield.[4a] They used the first synthetic approach mentioned above, in which treatment of diol **3** (a 6:1 diastereomeric mixture) with TsCl afforded the desired β-alkyne **4β** (52%), together with α-anomer **4α** (10%) and β-L-lyxo isomer (7%) (Scheme 1).[4a] However, the yield and β-stereoselectivity in glycosylation reaction still remain to be optimized.

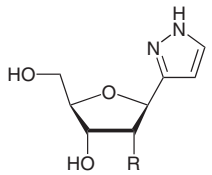
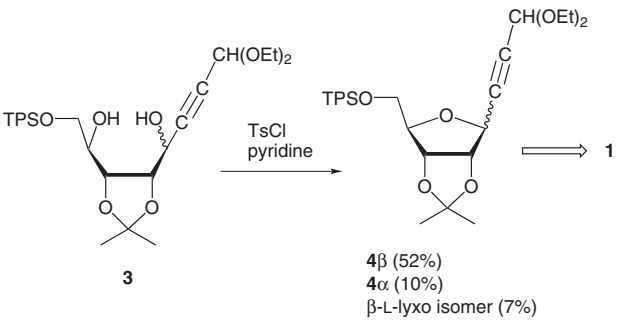


Figure 2 3(5)-(β-D-ribofuranosyl)pyrazole **1**



Scheme 1 Synthetic approach to **1** by Wightman et al.

We previously reported an efficient synthesis of 4(5)-β-D-ribofuranosylimidazoles with high stereoselectivity, using the cyclization of 1,3-diazafulvenes generated in situ.[6] This synthetic method belongs to the second approach in the current synthesis of *C*-nucleosides. The second strategy has not been done for the synthesis of β-D-ribofuranosylpyrazole to date.[3] Taking account of the analogies between imidazoles[7] and pyrazoles,[8] the synthesis of pyrazole *C*-nucleosides is feasible. Further, *C*-nucleosides are suitable candidates for use as building blocks of oligonucleotides in gene therapy.[3,6e] We herein describe efficient and β-stereoselective synthesis of 3(5)-(β-D-ribofuranosyl)pyrazole **1**, which was obtained from 2,3,5-

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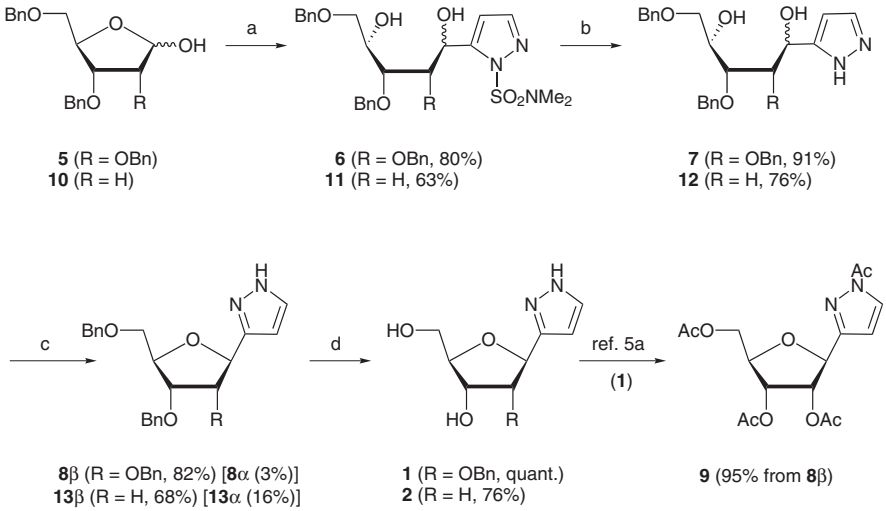


Scheme 2 Synthesis of pyrazole *C*-nucleosides. *Reagents and conditions*: a) **15**, Table 1, entry 3; b) aq 1.5 N HCl, THF, reflux, 15 h; c) i. Table 2, entry 2, ii. silica gel chromatography; d) $Pd(OH)_2/C$, cyclohexene

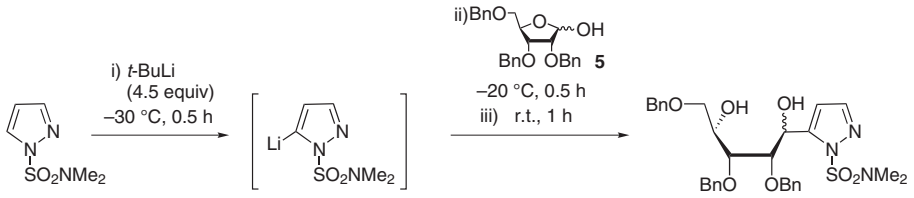
tri-*O*-benzyl-D-ribose (**5**)[9] in four steps and 60% overall yield with high stereoselectivity (β/α ratio = 27.3:1). In addition, under similar conditions, a novel 3(5)-(2-deoxy-β-D-ribofuranosyl)pyrazole (**2**) was synthesized from 3,5-di-*O*-benzyl-2-deoxy-D-ribose (**10**) via the β-anomer as the main product (β/α ratio = 4.1:1) (Scheme 2).

We first examined a coupling reaction of lithium salt **15** of *N*,*N*-dimethylpyrazole-1-sulfonamide (**14**)[10] with tribenzylated ribose **5** (Table 1). The reaction obviously depends on the kind of lithiating agents and solvents.

Use of BuLi for proton abstraction from C-5 of the pyrazole **14** did not give any products. However, the following procedure using *t*-BuLi and THF afforded the adduct **6**, albeit in only 18% yield (Table 1, entry 1): i) addition of *t*-BuLi to a THF solution of **14** at –30 °C, ii) treatment of tribenzylated ribose **5** to the resulting suspension at –20 °C, and iii) stirring the reaction mixture at room temperature for one hour. Further, use of toluene as the solvent markedly increased the yield of **6** (a 3:1 diastereomeric mixture) to 80% (entry 3).[6b] On the other hand, when THF was used for step i) followed by toluene for step ii) (entry 4) or the order of the two solvents was reversed (entry 5), the yields of **6** were suppressed to 46 and 51%, respectively. Accordingly, the entire reaction may be stabilized by the aggregation states in toluene in contrast to the use of polar solvents (entries 1 and 2).

Hydrolysis of **6** in refluxing 1.5 N HCl afforded a diol **7** having unsubstituted pyrazole in 91% yield (Scheme 2

Table 1 Coupling Reaction of **15** with **5**

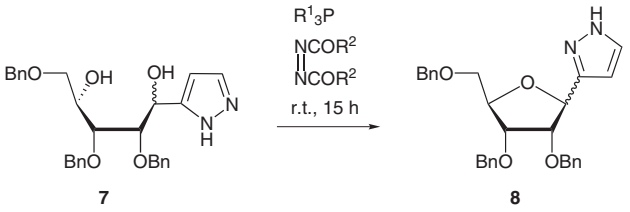


Entry	Solvent		Yield (%)
1	i) THF	ii) THF	18 (9)[a]
2	i) Et_2O	ii) Et_2O	18
3	i) toluene	ii) toluene	80[b]
4[c]	i) THF	ii) toluene	46
5[d]	i) toluene	ii) THF	51

[a] The diol **6** was obtained in only 9% at –50 °C.
[b] A 3:1 diastereomeric mixture.
[c] THF–toluene (5:1).
[d] Toluene–THF (5:1).

and Table 2). The cyclization of **7** with *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[11] and Bu_3P at room temperature in benzene, as expected, produced a 5:1 mixture of β- and α-anomers of **8αβ** in 61% yield (Table 2, entry 1).

Table 2 Synthesis of **8** by Cyclization of **7**



Entry	R^1	R^2	Solvent	β/α	Products (%)
1	Bu	NMe_2	benzene	5:1[a]	**8αβ** (61)[b]
2	Bu	NMe_2	THF	27.3:1	**8β** (82), **8α** (3)[c]
3	Et	NMe_2	THF	7:1[a]	**8αβ** (80)
4	Ph	OEt	THF	–	complex mixture

[a] The ratio was determined by ^{1}H NMR spectroscopy.
[b] Isolated yield of **8αβ**.
[c] Isolated yields of **8α** and **8β**.

The ratio was assigned from the intensities of the signals for methine protons (δ = 5.22 for **8β** vs 5.27 for **8α**) at C-1′ or those for C-4 protons (δ = 6.10 for **8β** vs 6.32 for **8α**) of the pyrazole ring in the ^{1}H NMR spectra.[4b] The correctness of their stereochemical assignment was indicated by the observation of NOESY between the C-1′ and C-4′ protons of **8β** (Figure 3). It is also known that the chemical shift of the anomeric proton in the α-isomer appears downfield from that of the β-isomer, since the β-face location of the anomeric proton of the α-isomer placed it out of the shielding influence of the 2′-oxygen.[12] Further, we found that THF remarkably increased the yield and α/β ratio of the *C*-nucleoside **8** (entry 2). The cyclization of **7** in THF exclusively produced the desired β-anomer **8β** in 82% yield, together with a small amount of the α-anomer (**8α**, 3%). The ratio of β/α-isomers was 27.3:1. On the other hand, the Et_3P/TMAD system led to **8αβ** (80%), but in a low α/β ratio (entry 3). Standard Mitsunobu conditions [diethyl azodicarboxylate (DEAD)/Ph_3P] gave only a complex mixture containing **8αβ** (entry 4).

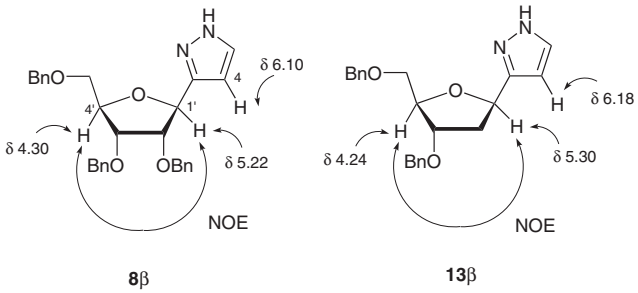
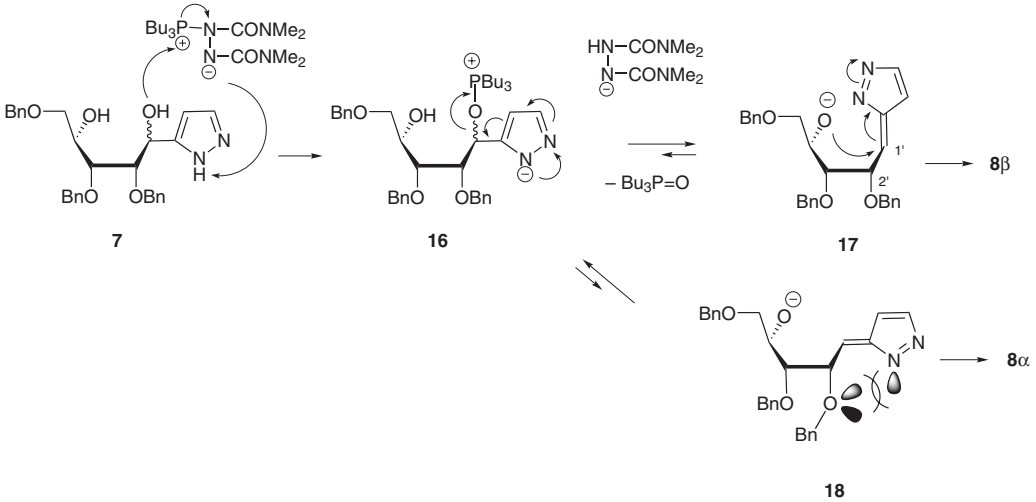


Figure 3 NOESY experiments and selected ^{1}H NMR of **8**β and **13**β

From these experiments, it became clear that not only the directing group at C-2′ but also the solvent effect significantly influences the β/α ratio of the *C*-nucleosides **8**. The β-selectivity in this reaction may be explained by a 5-*exo-trig* process of 1,2-diazafulvene intermediate **17**, as illustrated in Scheme 3.[6a,b,f] The β-stereoselectivity of the ribofuranosylpyrazole **8** may be facilitated by stereoelectronic repulsion in the alternative diazafulvene intermediate **18**.

Debenzylation of **8β** thus obtained with $Pd(OH)_2$/C in cyclohexene afforded 3(5)-(β-D-ribofuranosyl)pyrazole **1** (quant), as shown in Scheme 2. The structure of **1** was identified by conversion into *N*,*O*,*O*,*O*-tetraacetyl derivative **9**,[5a] which was a common key intermediate in the route of formycin and pyrazofurin synthesis by Buchanan and Wightman et al.[5] The spectroscopic and optical properties of **9** were consistent with those reported.

We next applied this synthetic methodology to the synthesis of novel 3(5)-(2-deoxy-β-D-ribofuranosyl)pyrazole (**2**)



Scheme 3 Mechanistic aspect for the formation of **8**

(Scheme 2), as C-2′-deoxy-D-ribonucleosides are of interest as potential antiviral and antitumor agents.[13] Reaction of 3,5-di-*O*-benzyl-2-deoxy-D-ribose (**10**) with 5-lithiopyrazole **15** followed by deprotection of the resulting diol **11** afforded an adduct **12**. TMAD/Bu_3P cyclization of **12** in THF produced β-anomer **13β** (68%) and α-anomer **13α** (16%) in a ratio of 4.1:1. The ratio was assigned from C-4 protons of the pyrazole ring in ^{1}H NMR (δ = 6.18 for **13β** vs 6.26 for **13α**), and a NOESY experiment on **13β** indicated an NOE between the C-1′ and C-4′ -protons (Figure 3). On the other hand, cyclization of **12** in benzene afforded a mixture of β- and α-anomers in 60% yield and only in a ratio of 2.8:1. The somewhat low selectivity (β/α = 4.1:1) in THF of the 2′-deoxy compounds **13** may be due to lack of the OBn group at C-2′. Debenzylation of **13β** completed the synthesis of 2′-deoxy compound **2**.

In summary, efficient and highly stereocontrolled synthesis of 4(5)-(β-D-ribofuranosyl)pyrazole **1** and its 2′-deoxy derivative **2** was achieved based on the second synthetic approach in *C*-nucleosides. This study would enable the supply of a variety of pyrazole *C*-nucleoside derivatives by which their biological activity can be assessed.

Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR were taken with tetramethylsilane as internal reference. Reactions with air- and moisture-sensitive compounds were carried out under argon. Unless otherwise noted, all extracts were dried over Na_2SO_4 or $MgSO_4$, and the solvents were removed in a rotary evaporator under reduced pressure. Chromatography was performed on silica gel. Anhyd THF was purchased from Wako Pure Chemical Industries.

_N_,_N_-Dimethylpyrazole-1-sulfonamide (14)

Under stirring, 60% NaH (441 mg, 11.0 mmol) in mineral oil was added to THF (0.6 mL) to give a suspension. A solution of pyrazole (500 mg, 7.4 mmol) in THF (2 mL) was added to the suspension, and the resulting mixture was stirred at r.t. for 1 h. Then, a solution of *N*,*N*-dimethylsulfamoyl chloride (1.2 mL, 11.0 mmol) was added. After 1.5 h, H_2O was added and the whole was evaporated to give a residue which was subsequently dissolved with EtOAc. The organic layer was washed with brine, dried, concentrated to one-third of its original volume, and a small amount of silica gel was added to the solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column. Chromatography with EtOAc–hexane (3:17) gave **14**[10] (1.28 g, 99%) as a colorless oil.

5-(2,3,5-Tri-*O*-benzyl-D-ribosyl)-*N*,*N*-dimethylpyrazole-1-sulfonamide (6)

A 1.6 M solution of *t*-BuLi in pentane (1.4 mL, 2.25 mmol) was added over 25 min to a solution of **14** (263 mg, 1.50 mmol) in toluene (10 mL) at –30 °C, and the resulting mixture was stirred for 30 min at the same temperature to give a yellow suspension. After adding a solution of **5** (210 mg, 0.5 mmol) in toluene (2 mL) slowly at –30 °C, the resulting mixture was stirred at –20 °C for 30 min. The dry ice bath was removed, and the reaction mixture was stirred at r.t. for 1 h to give a yellow-brown solution. The reaction was quenched with H_2O, and toluene was evaporated. The residue was dissolved in EtOAc, and the solution was washed with H_2O, brine, dried, and evaporated to give a crude oil. Chromatography on silica gel using EtOAc–hexane (3:2) as eluent gave **6** (240 mg, 80%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.95, 2.97 (each s, 3 H), 3.60–3.78 (m, 1 H), 3.80–3.82 (m, 1 H), 4.10–4.25 (m, 3 H), 4.40–4.60 (m, 6 H), 5.46 (s, H, 1′-H), 5.64 (s, H, 1′-H), 6.40 (s, H, 4-H), 6.58 (s, H, 4-H), 7.10–7.38 (m, 15 H), 7.60 (s, 1 H).

MS (SIMS): *m*/*z* = 596 (M^+ + 1).

HRMS: *m*/*z* (M^+ + 1) calcd for $C_{31}H_{38}N_3O_7S$: 596.2428; found: 596.2429.

3(5)-(2,3,5-Tri-*O*-benzyl-D-ribosyl)pyrazole (7)

A solution of **6** (231 mg, 0.39 mmol) in THF (5 mL) was refluxed with 1.5 N HCl (3.0 mL) for 15 h and cooled. After neutralization by addition of 30% NH_4OH, the mixture was extracted with EtOAc (3 ×) by salting-out techniques. The extract was dried and evaporated to give an oil, which was subjected to column chromatography. Elution with EtOAc–hexane (7:3) afforded **7** (172 mg, 91%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 3.52–3.68 (m, 2 H), 3.72–3.82 (m, 1 H), 3.96–4.06, 4.14–4.22 (m, 2 H), 4.30–4.62 (m, 6 H), 5.14–5.18 (m, 1 H), 6.20 (br s, 1 H), 7.15–7.40 (m, 16 H).

MS (SIMS): *m*/*z* = 489 (M^+ + 1).

HRMS: *m*/*z* (M^+ + 1) calcd for $C_{29}H_{33}N_2O_5$: 489.2388; found: 489.2383.

3(5)-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole (8β)

To a solution of diol **7** (138 mg, 0.28 mmol) and Bu_3P (0.10 mL, 0.42 mmol) in THF (4.0 mL) at 0 °C was added TMAD (72 mg, 0.42 mmol). The resulting mixture was stirred at r.t. for 15 h. The solvent was evaporated to give a residual oil, which was dissolved with EtOAc and H_2O. The EtOAc layer was washed with brine, dried, and evaporated to give a crude oil. It was carefully isolated by column chromatography using EtOAc–hexane (1:1) for elution to give **8β** as a white wax (102 mg, 77%)[4b] and a 3:2 mixture of the desirable **8β** and **8α** as pale yellow oils (10 mg, 7%), in that order.

8β

^{1}H NMR ($CDCl_3$): δ = 3.60 (dd, 1 H, *J* = 10.0, 2.9 Hz), 3.80 (dd, 1 H, *J* = 10.0, 2.9 Hz), 3.97 (t, 1 H, *J* = 4.3 Hz), 4.10 (dd, 1 H, *J* = 5.7, 4.3 Hz), 4.30 (m, 1 H), 4.40–4.64 (m, 6 H), 5.22 (d, 1 H, *J* = 3.8 Hz), 6.10 (s, 1 H), 7.28–7.36 (m, 15 H), 7.50 (s, 1 H).

MS (EIMS): *m*/*z* = 470 (M^+).

HRMS: *m*/*z* (M^+) calcd for $C_{29}H_{30}N_2O_4$: 470.2204; found: 470.2198.

8α

^{1}H NMR ($CDCl_3$): δ (selected values) = 3.50–3.64 (m, 2 H), 5.27 (d, 1 H, *J* = 4.5 Hz), 6.32 (s, 1 H, 4-H).

1-Acetyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole (9)

The tri-*O*-benzyl derivative **8β** (73 mg, 0.16 mmol) in EtOH (3.0 mL) and cyclohexene (0.5 mL, 4.8 mmol) was refluxed with 20% $Pd(OH)_2$/C (66 mg) for 18 h. The cooled mixture was filtered through Celite, which was washed well with EtOAc. The organic layers were evaporated to give 3(5)-(β-D-ribofuranosyl)pyrazole **1** (quant) as a colorless oil, the purification of which was not required as revealed from its ^{1}H NMR spectrum.[4a,c] The oil was subsequently dissolved in Ac_2O (0.4 mL) and pyridine (0.8 mL). The mixture was stirred for 16 h at r.t. and then evaporated to give a residue which was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O (2 ×), brine, dried, and evaporated. The residual oil was chromatographed on silica using EtOAc–hexane (1:1) as eluent to give the tetraacetyl compound **9** (95%, 56 mg) as a colorless oil;[5a] $[\alpha]_D^{26}$ –9.2 (*c* = 4.5, $CHCl_3$) {Lit.[5a] $[\alpha]_D$ –9.9 (*c* = 3.4, $CHCl_3$)}.

^{1}H NMR ($CDCl_3$): δ = 2.08, 2.12, 2.14 (s each, 3 H), 2.68 (s, 3 H), 4.18–4.42 (m, 3 H), 5.10 (d, 1 H, *J* = 5.1 Hz), 5.35 (t like, 1 H, *J* = 5.1 Hz), 5.50 (t like, 1 H, *J* = 5.1 Hz), 6.50 (d, 1 H, *J* = 2.8 Hz), 8.21 (d, 1 H, *J* = 2.8 Hz).

MS (SIMS): *m*/*z* = 369 (M^+ + 1).

5-(3,5-Di-*O*-benzyl-D-2-deoxyribosyl)-*N*,*N*-dimethylpyrazole-1-sulfonamide (11)

Following the same procedure as for the preparation of **6**, a 1.46 M solution of *t*-BuLi in pentane (1.54 mL, 2.25 mmol) was added to a toluene solution of **14** (263 mg, 1.50 mmol) to generate the lithium salt **15** in situ. A solution of **10** (157 mg, 0.5 mmol) in toluene (1.6 mL) was added to the mixture to give **11** (154 mg, 63%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.04–2.28 (m, 2 H), 3.00 (s, 6 H), 3.54–3.68 (m, 2 H), 3.76–3.86 (m, 1 H), 3.98–4.06 (m, 1 H), 4.50–4.64 (m, 4 H), 5.34 (dd, H, *J* = 10.0, 2.9 Hz), 5.42 (dd, H, *J* = 8.6, 2.9 Hz), 6.32 (s, H), 6.36 (s, H), 7.28–7.36 (m, 10 H), 7.56 (s, 1 H).

MS (SIMS): *m*/*z* = 490 (M^+ + 1).

HRMS: *m*/*z* (M^+ + 1) calcd for $C_{24}H_{32}N_3O_6S$: 490.2010; found: 490.2008.

3(5)-(3,5-Di-*O*-benzyl-D-2-deoxyribosyl)pyrazole (12)

A mixture of **11** (114 mg, 0.23 mmol) in THF (3 mL) and 1.5 N HCl (2.0 mL) was refluxed for 15 h, as described for the preparation of **7**, to give **12** (67 mg, 76%) as an oil.

^{1}H NMR ($CDCl_3$): δ = 2.04–2.28 (m, 2 H), 3.54–3.72 (m, 2 H), 3.80–3.86 (m, 1 H), 3.90–4.04 (m, 1 H), 4.46–4.58 (m, 4 H), 5.00–5.10 (m, 1 H), 5.74 (br s, 2 H), 6.08 (s, 1 H), 6.15 (s, 1 H), 7.18–7.40 (m, 11 H).

SIMS: *m*/*z* = 383 (M^+ + 1).

HRMS: *m*/*z* (M^+ +1) calcd for $C_{22}H_{27}N_2O_4$: 383.1969; found: 383.1969.

3(5)-(3,5-Di-*O*-benzyl-β-D-2-deoxyribofuranosyl)pyrazole (13β)

Following the same procedure as for the preparation of **8β**, a mixture of **12** (172 mg, 0.19 mmol), Bu_3P (0.07 mL, 0.29 mmol), and TMAD (50 mg, 0.29 mmol) in THF (2.0 mL) was stirred for 17 h at r.t. to give **13β** (22 mg, 32%) as a pale yellow oil and a 2.2:1 mixture of **13β** and **13α** as an oil (36 mg, 52%).

13β

^{1}H NMR ($CDCl_3$): δ = 2.16 (ddd, 1 H, *J* = 7.4, 5.2, 3.3 Hz), 2.40 (ddd, 1 H, *J* = 7.4, 3.3, 1.4 Hz), 3.60 (d, 2 H, *J* = 1.6 Hz), 4.06–4.21 (m, 1 H), 4.24 (dd, 1 H, *J* = 2.6, 1.4 Hz), 4.45–4.60 (m, 4 H), 5.30 (dd, 1 H, *J* = 8.6, 5.7 Hz), 6.18 (s, 1 H,), 7.20–7.40 (m, 10 H), 7.52 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 39.4, 70.8, 71.2, 73.5, 73.9, 80.7, 83.6, 102.5, 127.3, 127.3, 127.4, 127.4, 128.0, 128.1, 134.3, 137.3, 137.4, 147.6.

MS (EIMS): *m*/*z* = 365 (M^+ + 1).

HRMS: *m*/*z* (M^+ + 1) calcd for $C_{22}H_{25}N_2O_3$: 365.1864; found: 365.1867.

13α

^{1}H NMR ($CDCl_3$): δ (selected values) = 2.22–2.28 (m, 1 H), 2.54–2.64 (m, 1 H), 3.52–3.54 (m, 2 H), 6.26 (s, 1 H).

3(5)-(β-D-2-Deoxyribofuranosyl)pyrazole (2)

Following the same procedure as for the debenzylation of **8β**, the tri-*O*-benzyl derivative **13β** (21.1 mg, 0.06 mmol) in EtOH (1.0 mL) and cyclohexene (0.18 mL, 1.74 mmol) was refluxed with 20% $Pd(OH)_2$/C (12.7 mg) for 4 h to give **2** (8.1 mg, 76%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ = 2.16 (m, 2 H), 3.60 (dd, 1 H, *J* = 11.7, 5.0 Hz), 3.66 (dd, 1 H, *J* = 11.7, 4.6 Hz), 3.90 (td, 1 H, *J* = 4.8, 2.7 Hz), 4.33 (dt, 1 H, *J* = 5.0, 2.7 Hz), 5.20 (dd, 1 H, *J* = 9.4, 6.6 Hz), 6.30 (s, 1 H), 7.52 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 43.2 (C-2′), 63.7 (C-5′), 73.8 (C-3′), 88.8 (C-1′ and C-4′, overlapped) 103.3 (C-4).

MS (SIMS): *m*/*z* = 185 (M^+ + 1).

HRMS: *m*/*z* (M^+ + 1) calcd for $C_8H_{13}N_2O_3$: 185.0925; found: 185.0923.

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