Stereoselective synthesis of 3-β-D-ribofuranosylpyrazole from 2,3-*O*-Isopropylidene-D-ribose; a new route to pyrazole *C*-nucleosides

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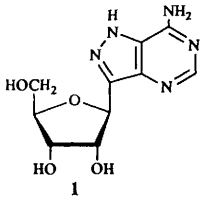
2,3-*O*-Isopropylidene-D-ribose has been converted stereoselectively into 3(5)-(β-D-ribofuranosyl)pyrazole **11**, a precursor for the *C*-nucleoside antibiotics pyrazofurin and formycin.

Since the isolation of the *C*-nucleoside antibiotics, there has been considerable interest in synthetic approaches to these compounds, including in particular the pyrazole *C*-nucleosides formycin **1** and pyrazofurin **2**.[1] Previous work in one of our



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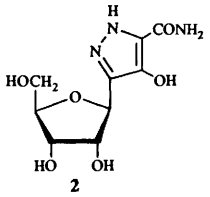

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laboratories has led to the development of routes to pentofuranosylpyrazoles using acetylenic intermediates, and we have shown that the ribofuranosylpyrazole **3** can be efficiently converted in one step into the 1,4-dinitropyrazole **4** (Scheme 1) by treatment with NH_4NO_3,trifluoroacetic acid and trifluoroacetic anhydride,[2] and that **4** can be transformed, also in one high-yielding step, to the doubly functionalized pyrazole **5** using NaCN in aqueous ethanol.[3] Formycin **1**[3] and pyrazofurin **2**[4] can then be obtained from **4**. The synthesis of **3**, however, was not totally satisfactory, depending on the addition of an acetylenic Grignard reagent to 2,3,5-tri-*O*-benzyl-D-ribofuranose which proceeds with somewhat low stereoselectivity.[5] We here describe a new and more direct synthesis of intermediate **3** from 2,3-*O*-isopropylidene-D-ribofuranose, a derivative of ribose which is much more easily prepared than is the tribenzyl ether, and which relies upon the stereoselective reduction of an acetylenic hemiketal.

The lactone **6** (Scheme 2) is easily prepared from 2,3-*O*-isopropylidene-D-ribofuranose[6] by silylation followed by oxidation using $KMnO_4$. Treatment of **6** with the lithium derivative of 1,1-diethoxyprop-2-yne gave the hemiketal **7** (85%), which on reduction with $NaBH_4$ gave the *syn*- (*threo*-) diol **8**, as an inseparable 6:1 mixture with its diastereoisomer (90% combined yield). The diastereoselectivity in this reduction is in the sense predicted from a Felkin–Anh model[7] for the transition state; we have recently described a similar stereoselectivity in the reduction of the adduct from **6** and allylmagnesium chloride,[8] and other related hemiacetals behave similarly.[9] Treatment of this mixture of diols with TsCl in pyridine led, by selective sulfonation at the prop-2-ynlic alcohol,[5] to the formation of the β-alkyne **9** (52%), together with the α-anomer (10%); a third product of β-L-*lyxo*-configuration was also formed (7%) as a result of sulfonation at the alternative alcohol.† The structure of the major product **9** was supported by the observation of small values (2.85 and 1.85 Hz respectively) for the coupling constants $J_{4,5}$ and $J_{6,7}$, and the observation of strong NOE effects between 4-H and 7-H. When **9** was treated with acetic acid and aqueous HCl, followed by hydrazine hydrate, the pyrazolyl diol **10** was obtained. This on desilylation gave 3(5)-(β-D-ribosuranosyl)pyrazole **11**, which could be acetylated to produce the tetra-acetyl compound **3**, with spectroscopic and optical properties {$[\alpha]_D$ −10.9 (*c* 1.28 $CHCl_3$)},‡ in excellent agreement with those reported {$[\alpha]_D$ −9.9 (*c* 3.4, $CHCl_3$)}.[2]

Our findings described here, together with earlier reports of the efficient conversion of **3** into formycin and pyrazofurin,[2–4] offer an effective route to these antibiotics. The strategy used is likely to be of value in gaining stereocontrolled access to other *C*-glycosides and *C*-nucleosides.

Experimental

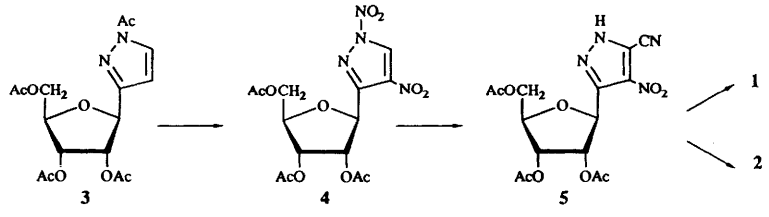
8-*O*-*tert*-Butyldiphenylsilyl-2,2,3,3-tetradehydro-2,3-dideoxy-5,6-*O*-isopropylidene-D-*altro*-octose diethyl acetal 8

Sodium boranuide (1.07 g) was added in portions over 10 min to a stirred solution of the hemiacetal **7** (1.57 g) in methanol (75 cm^3) at 0 °C. After 1 h, the mixture was evaporated and the residue was partitioned between water (120 cm^3) and ethyl acetate (4 × 100 cm^3). The organic layers were dried (Na_2SO_4) and evaporated to give an oil which was chromatographed on silica, with light petroleum–diethyl ether (7:3) as eluent to give the *diol* **8** (1.42 g, 90%) as a 6:1 mixture with the D-*allo*-epimer, $[\alpha]_D$ −10.9 (*c* 2.94, $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 1.07 (9 H, s), 1.20 (6 H, t), 1.38 (6 H, s), 3.05 (1 H, d, *J* 5.3),§ 3.4–3.95 (7 H,

† The structures of the minor products were supported by NMR data, in particular the progressive upfield shifts of C-4, -5, -6 and -7 in the series **9**, α-anomer, β-L-*lyxo*-isomer, as would be expected on the basis of steric factors.

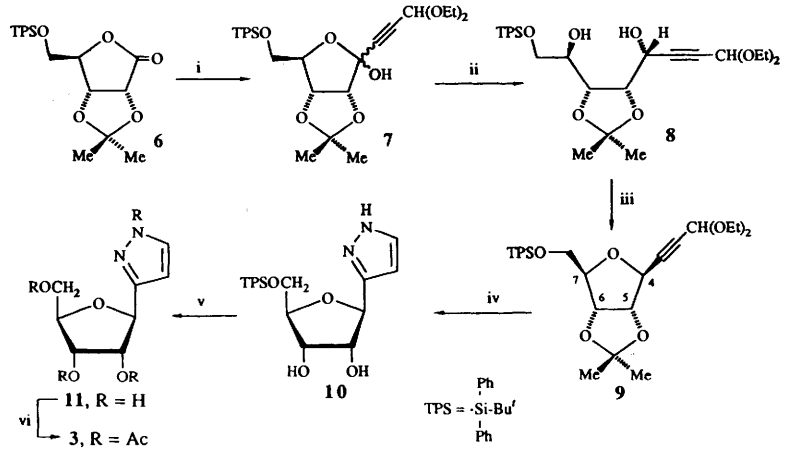
‡ $[\alpha]_D$ values in 10^{-1} deg cm^2 g^{-1}.

§ *J* Values in Hz.



3 **4** **5**

Scheme 1



Scheme 2 i, $LiC{\equiv}C{-}CH(OEt)_2$, −78 °C, 3 h; ii, $NaBH_4$, MeOH, 0 °C, 1 h; iii, TsCl, C_5H_5N, 90 °C, 25 h; iv, HOAc, HCl aq., room temp., then $N_2H_4{\cdot}H_2O$, heat (55%); v, Bu_4NF, THF, room temp. (95%); vi, Ac_2O, C_5H_5N, DMAP, room temp., 5 h (95%)

m), 4.15–4.4 (3 H, m), 4.82 (1 H, ddd, *J* 1.0, 1.9, 3.8), 5.30 (1 H, br s), 7.4 (6 H, m) and 7.7 (4 H, m) [Found: MNH_4^+ (CI, NH_3) 574.3200. Calc. for $C_{31}H_{48}NO_7Si$, 574.3200].

4,7-Anhydro-8-*O*-*tert*-butyldiphenylsilyl-2,2,3,3-tetradehydro-2,3-dideoxy-5,6-*O*-isopropylidene-D-*allo*-octose diethyl acetal 9

A solution of the diol **8** (1.03 g) and toluene-*p*-sulfonyl chloride (1.27 g) in dry pyridine (40 cm^3) was heated at 85–90 °C for 25 h. After cooling of the reaction mixture it was diluted with water (0.5 cm^3) and evaporated. Trituration of the residue with hot ether (3 × 30 cm^3) and evaporation gave an oil which was chromatographed on silica, with light petroleum–diethyl ether (1 : 1) as eluent to give firstly the β-D-*ribofuranosylalkyne* **9** (0.52 g, 52%) as an oil, $[\alpha]_D$ −5.5 (*c* 2.52, $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 1.07 (9 H, s, CMe_3), 1.16 (6 H, dt, CH_2Me), 1.35 and 1.53 (each 3 H, s, CMe_2), 3.45–3.55 and 3.59–3.68 (each 2 H, m, CH_2Me), 3.78 (1 H, dd, *J* 10.8, 5.1, 8_a-H), 3.81 (1 H, dd, *J* 10.8, 6.6, 8_b-H), 4.19 (1 H, ddd, *J* 6.7, 5.1, 1.85, 7-H), 4.68 (1 H, dd, $J_{4,5}$ 2.9, $^5J_{4,1}$ 1.4, 4-H), 4.75 (1 H, dd, $J_{5,6}$ 6.2, $J_{5,4}$ 2.85, 5-H), 4.78 (1 H, dd, $J_{6,5}$ 6.2, $J_{6,7}$ 1.85, 6-H), 5.15 (1 H, d, $J_{1,4}$ 1.4, 1-H), 7.4 (6 H, m, Ph) and 7.7 (4 H, m, Ph); δ_C(22.4 MHz, $CDCl_3$) 19.2 (CMe_3), 14.9, 25.3 and 26.8 (each Me), 60.8 and 63.5 (CH_2), 74.5, 82.7, 85.8 and 86.1 (C-4–C-7), 82.0 and 82.9 (alkyne), 91.4 [$CH(OEt)_2$], 113.5 (CMe_2), 127.6, 129.7, 133.2 and 135.6 [Found: MNH_4^+ (CI, NH_3) 556.3090. Calc. for $C_{31}H_{46}NO_6Si$, 556.3086].

Further elution of the column gave the α-D-ribofuranosylalkyne (0.106 g, 10%), as an oil, $[\alpha]_D$ −35.0 (*c* 0.8, $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 1.03 (9 H, s, CMe_3), 1.23 (6 H, dt, CH_2Me), 1.38 and 1.57 (each 3 H, s, CMe_2), 3.52–3.88 (6 H, m), 4.18 (1 H, t, *J* 2.8, 7-H), 4.85 (2 H, m), 5.05 (1 H, dd, *J* 3.5, 1.25, 4-H), 5.38 (1 H, d, *J* 1.25, 1-H), 7.4 (6 H, m, Ph) and 7.6 (4 H, m, Ph); δ_C(22.4 MHz, $CDCl_3$) 73.8, 82.4, 83.1 and 84.3 (C-4–C-7).

Further elution gave the β-L-*lyxo*-isomer (0.074 g, 7%) as an oil, $[\alpha]_D$ −34.5 (*c* 0.52, $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 1.06 (9 H, s, CMe_3), 1.22 (6 H, dt, CH_2Me), 1.33 and 1.40 (each 3 H, s, CMe_2), 3.50–3.82 (5 H, m), 3.90 (1 H, dd, *J* 10.3, 5.8, 8_a-H), 3.99 (1 H, dd, *J* 10.3, 6.7, 8_b-H), 4.24 (1 H, dd, *J* 3.5, 1.2, 4-H), 4.72 (2 H, m, 2-H, 3-H), 5.33 (1 H, d, *J* 1.2, 1-H), 7.4 (6 H, m, Ph) and 7.7 (4 H, m, Ph); δ_C(22.4 MHz, $CDCl_3$) 72.5, 80.7, 81.7 and 82.1 (C-4–C-7).

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