Synthesis of 3-Carbamoyl-4-[(β-D-ribofuranosyl)methyl]pyrazole, a Pyrazole Homo-*C*-nucleoside[1)]

Tsuneo SATO and Ryoji NOYORI*

Department of Chemistry, Nagoya University, Chikusa, Nagoya 464

(Received September 17, 1979)

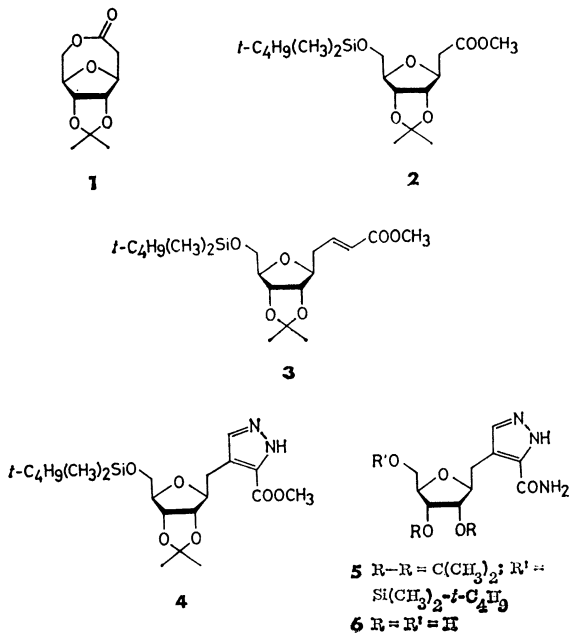
Synopsis. A facile, stereocontrolled synthesis of the title pyrazole homo-*C*-nucleoside is described.

Recently we have developed efficient routes to a variety of natural[2)] and unnatural *C*-nucleosides.[3)] Significant biological activities displayed by pyrazole nucleosides[4)] have prompted us to make the related *C*-nucleoside analogues. Outlined herein is the stereospecific synthesis of a pyrazole homo-*C*-nucleoside.[5)]

The readily accessible chiral lactone **1** was converted to **2**. The ester **2** was then reduced with diisobutylaluminum hydride[6)] to give the corresponding aldehyde in a high yield, which in turn was condensed with methoxycarbonylmethylenetriphenylphosphorane[7)] to produce **3**. 1,3-Dipolar cycloaddition across the electron-deficient double bond was effected by diazomethane and the resulting cycloadduct was aromatized by treating with bromine, giving rise to **4**. Ammonolysis of the ester function, giving **5**, and removal of the protective groups led to the desired homo-*C*-nucleoside **6**.

Experimental

General. All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrometer. ^1H and ^{13}C NMR spectra were obtained using a Varian HA-100D spectrometer and a Varian CFT-20 spectrometer, respectively. The chemical shifts are recorded in parts per million relative to tetramethylsilane as an internal standard. UV spectra were recorded on a Hitachi 323 recording spectrophotometer. Optical rotations were measured with a JASCO DIP-SL automatic polarimeter. Analytical thin-layer chromatography (TLC) was done using 0.25-mm layers of silica gel 60 PF_{254} (E. Merck) and preparative TLC was performed using 20×20 cm glass plates coated with a 1.0 mm layer of silica gel 60 PF_{254}. The position of spots is shown by R_f values. For column chromatography E. Merck Kiesergel 60 (70—230 mesh) was used.



Methyl 2-(2,3-O-Isopropylidene-5-O-t-butyldimethylsilyl-β-D-ribofuranosyl)acetate (2). A mixture of methyl 2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)acetate[8,11a)] (5.72 g, 23.3 mmol), *t*-butyldimethylsilyl chloride (5.41 g, 34.9 mmol), and imidazole (4.76 g, 69.8 mmol)[9)] in 40 ml of dry DMF was stirred at 25 °C for 12 h, and then evaporated *in vacuo*. The residue was partitioned between ethyl acetate (100 ml) and brine (20 ml), and organic phase was filtered, dried (Na_2SO_4), and evaporated, leaving a syrup. Chromatography on a silica gel column using hexane–ethyl acetate (5:1) as an eluent gave 8.51 g (100%) of **2** as a colorless syrup. R_f=0.46 (hexane–ethyl acetate (2:1)); $[\alpha]_D^{21}$ −13.6° (*c* 1.62, $CHCl_3$); IR (neat) 1738 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.02 (s, CH_3), 0.85 (s, t-C_4H_9), 1.29 and 1.46 (s, isopropylidene CH_3), 2.58 (d-like, J=6.1 Hz, CH_2CO-OCH_3), 3.84 (s, OCH_3), 3.66 (d-like, J=3 Hz, $H_{5'}$), 4.02 (m, $H_{4'}$), 4.28 (m, $H_{1'}$), 4.38 (dd, J=4.1, 6.1 Hz, $H_{2'}$), 4.63 (dd, J=3.0, 6.1 Hz, $H_{3'}$); ^{13}C NMR ($CDCl_3$) δ 17.89, 25.52, 25.82, 27.36, 38.62, 51.34, 63.79, 81.18, 82.06, 84.66, 84.97, 113.74, 170.74.

Methyl 4-(2,3-O-Isopropylidene-5-O-t-butyldimethylsilyl-β-D-ribofuranosyl)crotonate (3). A freshly prepared solution of diisobutylaluminum hydride[6)] in toluene (1.6 M, 17.0 ml, 27.1 mmol) was added dropwise over a period of 10 min to a slution of **2** (7.51 g, 20.9 mmol) in toluene (30 ml) at −78 °C under argon. The reaction mixture was then stirred at this temperature for additional 1 h. The mixture was diluted with ether (30 ml) and then saturated NH_4Cl solution (5 ml) was carefully added. The mixture was warmed to room temperature and filtered with a Celite 545 pad. The filtrate was evaporated under reduced pressure to give 2-(2,3-*O*-isopropylidene-5-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)acetaldehyde (6.32 g, 92%) as a colorless syrup. This material was subjected to the next reaction without purification. A mixture of this aldehyde (6.32 g, 19.2 mmol) and methoxycarbonylmethylenetriphenylphosphorane[7)] (20.9 g, 65.6 mmol) in dry dichloromethane (60 ml) was stirred for 12 h at 25 °C. The reaction mixture was evaporated and the residue was chromatographed on a silica gel column using hexane–ethyl acetate (10:1) as an eluent. The resulting product was evaporated, leaving 3.98 g (54%) of **3** as a colorless syrup. In addition, the starting aldehyde was recovered (2.28 g, 36%). R_f=0.53 (hexane–ethyl acetate (2:1)); $[\alpha]_D^{21}$ −28° (*c* 0.62, $CHCl_3$); IR (neat) 1724 (C=O), 1660 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.03 and 0.83 (s, t-C_4H_9, $(CH_3)_2$), 1.26 and 1.45 (s, isopropylidene CH_3), 2.44 (m, CH_2CH=CH), 3.66 (d-like, J=3 Hz, $H_{5'}$), 3.66 (s, OCH_3), 3.94 (m, $H_{1'}$ and $H_{4'}$), 4.24 (dd, J=5.0, 6.3 Hz, $H_{2'}$), 4.58 (dd, J=4.0, 6.3 Hz, $H_{3'}$), 5.86 (dt, J=1.4, 16.0 Hz, CH=C<u>H</u>COOCH$_3$), 6.90 (dt, J=7.0, 16.0 Hz, C<u>H</u>=CHCOOCH$_3$); ^{13}C NMR ($CDCl_3$) δ 18.32, 25.57, 25.88, 27.47, 36.32, 51.16, 63.67, 81.99, 83.19, 84.53, 84.77, 114.08, 123.41, 144.30, 166.46. Found: *m/e* 371.1873. Calcd for $C_{18}H_{31}O_6Si$: (M−CH_3), 371.1890.

3-Methoxycarbonyl-4-[(2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-β-D-ribofuranosyl)methyl]pyrazole (4). A solution of **3** (3.83 g, 9.92 mmol) in 10 ml of ether was cooled at 0 °C and to this was added a solution of diazomethane (49.6 mmol) in ether (50 ml). The resulting yellow solution was stirred at 25 °C for 12 h and then evaporated to dryness leaving 4.25 g (100%) of 3-methoxycarbonyl-4-[(2,3-*O*-isopropylidene-5-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)methyl]-2-pyrazoline as a yellow syrup. This material was not further purified. To the mixture of the pyrazoline (4.25 g, 9.92 mmol) and dry $NaHCO_3$ (4.17 g, 49.6 mmol) in dry chloroform (50 ml) was added drowpise a solution of bromine in chloroform (1.0 M solution, 16.9 mmol). The reaction mixture was stirred at 0 °C for 1 h. A solution of 10% sodium thiosulfate (30 ml) was added and the solution was stirred for additional 20 min. The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3×20 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column using hexane–ethyl acetate (1:1) as an eluent. The pyrazole **4** was obtained as a colorless syrup (1.27 g, 30%). R_f=0.29 (hexane–ethyl acetate (1:1)); $[\alpha]_D^{21}$ −25° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3460 (NH), 1728 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.03 and 0.90 (s, *t*-C_4H_9, $(CH_3)_2$), 1.32 and 1.52 (s, isopropylidene CH_3), 3.10 (m, CH_2-pyrazole), 3.74 (d-like, *J*=4.0 Hz, $H_{5'}$), 3.94 (s, OCH_3), 4.0—4.3 (m, $H_{1'}$ and $H_{4'}$), 4.40 (dd, *J*=4.1, 6.1 Hz, $H_{2'}$), 4.66 (dd, *J*=3.8, 6.1 Hz, $H_{3'}$), 7.70 (br s, H_5); ^{13}C NMR ($CDCl_3$) δ 18.20, 25.53, 25.78, 27.37, 28.72, 51.30, 63.78, 82.05, 84.26, 84.67, 113.67, 120.02, 132.51, 138.26, 162.67; UV λ_{max} (CH_3OH) 221 nm (ε 7350). Found: *m/e* 426.2181. Calcd for $C_{20}H_{34}O_6N_2Si$: M, 426.2186. The NMR data of **4** are consistent with the assigned β structure. The signals due to the isopropylidene methyls occur at δ 1.32 and 1.52 in the ^1H spectrum (Δδ 0.20 ppm)[10] and δ 25.53 and 27.37 in the ^{13}C spectrum (Δδ 1.84 ppm),[11] and the observed chemical shift differences are apparently in the β range.

3-Carbamoyl-4-[(β-D-ribofuranosyl)methyl]pyrazole (6). A solution of the pyrazole **4** (1.00 g, 2.35 mmol) in methanol (50 ml) was saturated with ammonia at 0 °C and stirred at 25 °C for 4 d. Evaporation of the solvent gave yellow powder. Purification on silica gel plates eluting with hexane–ethyl acetate (1:2) gave 3-carbamoyl-4-[(2,3-*O*-isopropylidene-5-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)methyl]-pyrazole (**5**) (313 mg, 32%) as a white powder. This compound was recrystallized from ethyl acetate, mp 202—204 °C. In addition, unreacted **4** was recovered (630 mg, 63%). R_f=0.15 (hexane–ethyl acetate (1:1)); $[\alpha]_D^{20}$ −15° (*c* 0.15, CH_3OH); IR ($CHCl_3$) 3200—3540 (NH and NH_2), 1678 cm^{-1} (C=O); ^1H NMR (acetone-d_6) δ 0.05 and 0.91 (s, *t*-C_4H_9, $(CH_3)_2$), 1.15 and 1.33 (s, isopropylidene CH_3), 3.00 (m, CH_2-pyrazole), 3.64 (m, $H_{5'}$), 3.82 (m, $H_{1'}$), 4.08 (m, $H_{4'}$), 4.40 (dd, *J*=3.5, 6.5 Hz, $H_{2'}$), 4.55 (dd, *J*=3.2, 6.5 Hz, $H_{3'}$), 6.30 and 6.98 (br, NH_2), 7.60 (m, H_5), 11.10 (br, NH); ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 17.96, 25.41, 25.79, 27.25, 28.31, 63.74, 81.71, 84.02, 84.15, 84.36, 112.78, 117.27, 130.52, 130.63, 164.55; UV λ_{max} (CH_3OH) 221 nm (ε 7800). Found: C, 55.69; H, 8.22; N, 10.14%. Calcd for $C_{19}H_{33}O_5N_3Si$: C, 55.45; H, 8.08; N, 10.21%.

The amide **5** (300 mg, 0.730 mmol) was stirred in 3 ml of 90% aqueous trifluoroacetic acid at 25 °C for 10 min and the mixture was evaporated to dryness *in vacuo*. The crude product was triturated with ether (3×3 ml). Compound **6** was obtained as a hygroscopic white powder (159 mg, 85%). ^1H NMR (dimethyl-d_6 sulfoxide) δ 2.92 (m, CH_2-pyrazole), 3.21 (m, $H_{5'}$), 3.64 (m, $H_{1'}$, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 4.4—5.8 (br, OH), 7.10 (m, H_5), 7.10 and 7.64 (br, NH_2); ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 29.18 (CH_2-pyrazole), 62.76 ($C_{5'}$), 72.34, 75.09, 84.02, 85.14 ($C_{1'}$–$C_{4'}$ of ribose), 119.38, 132.02, 132.15, 165.84; UV λ_{max} (CH_3OH) 222 nm.

This work was supported in part by the Ministry of Education, Japanese Government (Grant-in-Aid, No. 401538). We express our thanks to Fujisawa Pharmaceutical Co. for performing the elemental analysis and Ono Pharmaceutical Co. for obtaining the exact mass spectra.

References

1) *C*-Nucleoside Synthesis. IX. Part VIII: T. Sato and R. Noyori, *Heterocycles*, **13**, 141 (1979).

2) R. Noyori, T. Sato, and Y. Hayakawa, *J. Am. Chem. Soc.*, **100**, 2561 (1978); T. Sato, R. Ito, Y. Hayakawa, and R. Noyori, *Tetrahedron Lett.*, **1978**, 1829.

3) For example, T. Sato, M. Watanabe, and R. Noyori, *Tetrahedron Lett.*, **1979**, 2897.

4) For example, R. W. Sidwell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski, and R. K. Robins, *Science*, **177**, 705 (1972).

5) Homo-*C*-nucleosides refer to a class of compounds that possess a methylene unit between the ribose moiety and an sp^2-carbon of the nitrogen heterocycles.

6) L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Lett.*, **1962**, 619.

7) O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

8) T. Sato, K. Marunouchi, and R. Noyori, *Tetrahedron Lett.*, **1979**, 3669.

9) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

10) J. -L. Imbach, *Ann. N. Y. Acad. Sci.*, **255**, 177 (1975).

11) a) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602 (1975); b) J. A. Secrist III, *J. Org. Chem.*, **43**, 2925 (1978).