STEREOCONTROLLED ENTRY TO PYRIMIDINE HAMAMELO-C-NUCLEOSIDES[1]

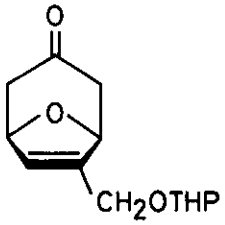
T. Sato, H. Kobayashi, and R. Noyori*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

Abstract — The reductive [3 + 4] cyclocoupling reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and a furan has been applied to the first synthesis of hamamelo-C-nucleosides.

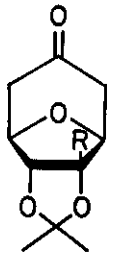
The reductive [3 + 4] cyclocoupling reaction of polybromo ketones and furans[2] has proved to be a powerful tool for the construction of ribofuranosyl frameworks.[3] When a 3-hydroxymethylfuran derivative is utilized as the C_4 component, a hamamelofuranosyl structure[4] can be elaborated. Disclosed herein is the first, general synthesis of pyrimidine C-nucleosides containing hamamelose (a rare branched-chain sugar) as the carbohydrate moiety.

Reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and 3-tetrahydropyranyloxymethylfuran with Zn-Ag couple in THF,[5] followed by treatment of the cycloadduct with saturated NH_4Cl/CH_3OH afforded the oxabicyclic ketone I.[6] Exposure of the unsaturated ketone I to N-methylmorpholine-N-oxide (1.6 equiv) and a catalytic amount of OsO_4 (1 mol %) in aqueous acetone[7] and subsequently a mixture of acetone, p-$CH_3C_6H_4SO_3H$, and anhydrous $CuSO_4$ gave the acetonide II (16%) and the alcohol III[8] (40%). The THP ether II was converted to III by the treatment with oxalic acid in aqueous THF. The specifically created α stereochemistry of III was deduced from the NMR spectrum.[9] Reaction of III with t-$C_4H_9(CH_3)_2SiCl$ and imidazole in DMF[10] afforded the silyl ether IV (90%). Baeyer-Villiger oxidation of IV with CF_3CO_3H (3 equiv, CH_2Cl_2, 20 °C, 36 h) produced a 74:26 mixture of the regioisomers V[11] and VI[12] (36%, or 94% based on consumed IV).[13] The major isomer V serves as a versatile key intermediate for the preparation of various hamamelo-C-nucleosides. When V was heated with t-$C_4H_9OCH[N(CH_3)_2]_2$ (excess) at 70 °C for 1 h, the corresponding dimethylaminomethylene lactone VII was obtained in 52% yield. Condensation of VII with urea in 1 M ethanolic C_2H_5ONa (reflux, 3 h) led to the uracil derivative VIII[14] (20%), deprotection of which by 10% HCl in CH_3OH gave (±)-5-(β-hamamelofuranosyl)uracil (IX)[15] (95%). In a similar manner, heterocycle formation with VII and thiourea gave the thiouracil derivative X (62%). Finally, the acid deblocking completed the synthesis of (±)-5-(β-hamamelofuranosyl)-2-thiouracil (XI).[16] Condensation of VII with guanidine, producing the isocytosine XII, and removal of the protective groups formed (±)-5-(β-hamamelofuranosyl)-isocytosine (XIII)[17] in 64% yield.

Thus this method allows ready construction of the otherwise difficult-to-make hamamelose skeleton[4] and introduction of pyrimidine rings at the C-1 position. The sequence via the bicyclic ketone leads in a predictable manner to the products possessing four chiral centers.



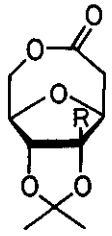
I



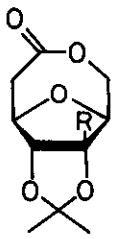
II, R = CH_2OTHP

III, R = CH_2OH

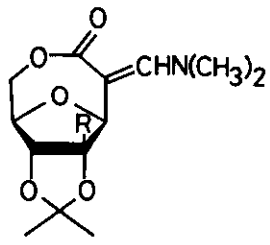
IV, R = $CH_2OTBDMS$



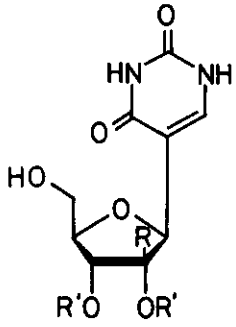
V, R = $CH_2OTBDMS$



VI, R = $CH_2OTBDMS$

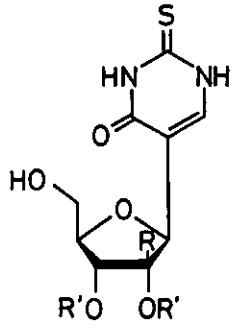


VII, R = $CH_2OTBDMS$



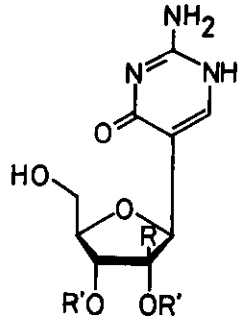
VIII, R = $CH_2OTBDMS$; R'–R' = $C(CH_3)_2$

IX, R = CH_2OH; R' = H



X, R = $CH_2OTBDMS$; R'–R' = $C(CH_3)_2$

XI, R = CH_2OH; R' = H



XII, R = $CH_2OTBDMS$; R'–R' = $C(CH_3)_2$

XIII, R = CH_2OH; R' = H (HCl salt)

TBDMS = $Si(CH_3)_2$-t-C_4H_9

Acknowledgment. This work was partially supported by the Ministry of Education, Japanese Government (Grant-in-aid, 484026).

REFERENCES AND NOTES

1. C-Nucleoside Synthesis. 16. Part 15: R. Noyori, H. Kobayashi, and T. Sato, Tetrahedron Lett., 1980, 21, 2573.
2. R. Noyori, Acc. Chem. Res., 1979, 12, 61.
3. R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 1978, 100, 2561.
4. F. Shafizadeh, Adv. Carbohydr. Chem., 1956, 11, 263; W. G. Overend and N. R. Williams, J. Chem. Soc., 1965, 3446; P.-T. Ho, Tetrahedron Lett., 1978, 1623.
5. T. Sato and R. Noyori, Bull. Chem. Soc. Jpn., 1978, 51, 2745.
6. IR (neat) 1715 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.4–1.9 (m, 6H, CH_2), 2.19–2.92 (m, 4H, $CH_2C{=}O$), 3.32–3.95 (m, 2H, CH_2O), 4.14 (d, J = 13.6 Hz, CH_aH_bOTHP), 4.36 (d, J = 13.6 Hz, CH_aH_bOTHP), 4.60 (br, 1H, $OCHOCH_2$), 4.98 (m, 2H, $OCHCH_2C{=}O$), 6.08 (m, 1H, HC=).
7. V. VanRheenen, R. C. Kelly, and D. Y. Cha, Tetrahedron Lett., 1976, 1973; V. VanRheenen, D. Y. Cha, and W. M. Hartley, Org. Synth., 1978, 58, 43.
8. Mp 138–140 °C. IR ($CHCl_3$) 3590 (OH), 1721 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.40 and 1.52 (s, isopropylidene CH_3), 2.2–2.9 (m, H_5 and $H_{5'}$), 3.65 (d, J = 12.0 Hz, CH_aH_bOH), 3.85 (d, J = 12.0 Hz, CH_aH_bOH), 4.24 (s, $H_{3'}$), 4.58 (m, $H_{1'}$ and $H_{4'}$).
9. The occurrence of the C-3' proton (nucleoside numbering) as a singlet at δ 4.24 confirmed the assigned α stereochemistry.[3]
10. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 1972, 94, 6190.
11. Mp 79.0–80.0 °C. IR ($CHCl_3$) 1735 cm^{-1} (C=O). ^1H NMR (C_6D_6) δ 0.08 and 0.95 (s, t-$C_4H_9(CH_3)_2Si$), 1.39 and 1.56 (s, isopropylidene CH_3), 2.44 (dd, J = 3.0, 16.8 Hz, H_{5a}), 3.02 (dd, J = 4.2, 16.8 Hz, H_{5b}), 3.42 (dd, J = 3.4, 13.6 Hz, $H_{5'a}$), 3.62 (dd, J = 1.0, 13.6 Hz, $H_{5'b}$), 3.84 (d-like, J = 3.0 Hz, CH_2OSi), 3.84 (m, $H_{1'}$), 4.15 (m, $H_{4'}$), 4.44 (s, $H_{3'}$).
12. Mp 99.0–100 °C. IR ($CHCl_3$) 1732 cm^{-1} (C=O). ^1H NMR (C_6D_6) δ 0.08 and 0.96 (s, t-$C_4H_9(CH_3)_2Si$), 1.38 and 1.54 (s, isopropylidene CH_3), 2.29 (dd, J = 2.8, 16.2 Hz, H_{5a}), 2.54 (dd, J = 5.0, 16.2 Hz, H_{5b}), 3.6–4.2 (m, $H_{1'}$, $H_{4'}$, and $H_{5'}$), 4.00 (s, $H_{3'}$), 4.20 (s, CH_2OSi).
13. For the origin of the unique regioselectivity, see ref 1.
14. Mp 238–242 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 0.06 and 0.84 (s, t-$C_4H_9(CH_3)_2Si$), 1.33 and 1.51 (s, isopropylidene CH_3), 3.49 (s, CH_2OSi), 3.57 (m, $H_{5'}$), 3.96 (m, $H_{4'}$), 4.52 (d, J = 2.8 Hz, $H_{3'}$), 4.82 (s, $H_{1'}$), 7.34 (br, H_6), 10.86 (br, H_1), 11.02 (s, H_3). UV λ_{max} (CH_3OH) 266 nm (ε 7150), λ_{max} (0.1 N NaOH) 289 nm (ε 6150).
15. Mp 125–130 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 3.28 (s, CH_2OH), 3.4–3.9 (m, $H_{3'}$, $H_{4'}$, and $H_{5'}$), 4.68 (s, $H_{1'}$), 7.50 (d, J = 4.8 Hz, H_6), 12.28 (d, J = 4.8 Hz, H_1), 12.40 (br, H_3). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 60.56 and 63.21 ($C_{5'}$ and CH_2OH), 70.58, 79.62, 80.42,

82.06 ($C_{1'}$–$C_{4'}$ of ribose), 110.75, 139. 17, 150.96, 164.18. UV λ_{max} (CH_3OH) 267 nm (ε 5710), λ_{max} (0.1 N NaOH) 285 nm (ε 3780), λ_{max} (0.1 N HCl) 266 nm (ε 5140).

16. Mp 140–145 °C. ^{1}H NMR (dimethyl-$\underline{d}_6$ sulfoxide) δ 3.27 (s, C$\underline{H}_2$OH), 3.4–3.7 (m, $H_{3'}$ and $H_{4'}$), 3.64 (d, $\underline{J}$ = 8.0 Hz, $H_{5'a}$), 3.85 (d, $\underline{J}$ = 8.0 Hz, $H_{5'b}$), 4.25 (br, OH), 4.68 (s, $H_{1'}$), 7.50 (d, $\underline{J}$ = 5.5 Hz, H_6), 12.26 (d, $\underline{J}$ = 5.5 Hz, H_1), 12.38 (br, H_3). ^{13}C NMR (dimethyl-$\underline{d}_6$ sulfoxide) δ 60.54 and 62.70 ($C_{5'}$ and CH_2OH), 70.17, 79.88, 80.16, 82.05 ($C_{1'}$–$C_{4'}$ of ribose), 116.58, 138.54, 160.90, 174.63. UV λ_{max} (CH_3OH) 215 nm (ε 9080), 277 (11700), λ_{max} (0.1 N NaOH) 220 nm (ε 11700), 264 (9060), λ_{max} (0.1 N HCl) 215 nm (ε 9400), 276 (11000).

17. Mp 215–217 °C. ^{1}H NMR (dimethyl-$\underline{d}_6$ sulfoxide) δ 3.30 (s, C$\underline{H}_2$OH), 3.4–3.9 (m, $H_{3'}$ and $H_{4'}$), 3.67 (d, $\underline{J}$ = 8.8 Hz, $H_{5'a}$), 3.92 (d, $\underline{J}$ = 8.8 Hz, $H_{5'b}$), 4.71 (s, $H_{1'}$), 7.76 (s, H_6), 8.48 (br, NH_2). ^{13}C NMR (dimethyl-$\underline{d}_6$ sulfoxide) δ 60.70 and 62.50 ($C_{5'}$ and CH_2OH), 70.01, 80.20, 82.00 ($C_{1'}$–$C_{4'}$ of ribose), 116.48, 137.80, 152.49, 159.18. UV λ_{max} (CH_3OH) 224 nm (ε 12500), 265 (7770), λ_{max} (0.1 N NaOH) 232 nm (ε 8800), 280 (6420).

Received, 28th July, 1980