

STEREOCONTROLLED ENTRY TO PYRIMIDINE HAMAMELO-C-NUCLEOSIDES¹

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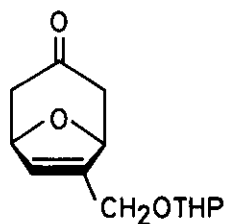
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Abstract — The reductive [3 + 4] cyclocoupling reaction of $\alpha, \alpha, \alpha', \alpha'$ -tetrabromoacetone and a furan has been applied to the first synthesis of hamamelo-C-nucleosides.

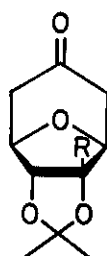
The reductive [3 + 4] cyclocoupling reaction of polybromo ketones and furans² has proved to be a powerful tool for the construction of ribofuranosyl frameworks.³ When a 3-hydroxymethylfuran derivative is utilized as the C₄ component, a hamamelofuranosyl structure⁴ can be elaborated. Disclosed herein 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 NH₄Cl/CH₃OH 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 OsO₄ (1 mol %) in aqueous acetone⁷ and subsequently a mixture of acetone, *p*-CH₃C₆H₄SO₃H, and anhydrous CuSO₄ gave the acetone II (16%) and the alcohol III⁸ (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*-C₄H₉(CH₃)₂SiCl and imidazole in DMF¹⁰ afforded the silyl ether IV (90%). Baeyer-Villiger oxidation of IV with CF₃CO₃H (3 equiv, CH₂Cl₂, 20 °C, 36 h) produced a 74:26 mixture of the regioisomers V¹¹ and VI¹² (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*-C₄H₉OCH[N(CH₃)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 C₂H₅ONa (reflux, 3 h) led to the uracil derivative VIII¹⁴ (20%), deprotection of which by 10% HCl in CH₃OH gave (+)-5-(β -hamamelofuranosyl)uracil (IX)¹⁵ (95%). In a similar manner, heterocycle formation with VII and thiourea gave the thioracil derivative X (62%). Finally, the acid deblocking completed the synthesis of (+)-5-(β -hamamelofuranosyl)-2-thioracil (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 skeleton⁴ 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.



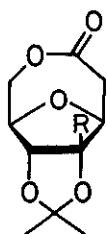
I



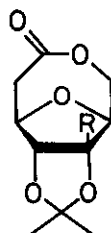
II, R = CH₂OTHP

III, R = CH₂OH

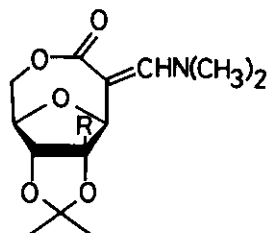
IV, R = CH₂OTBDMS



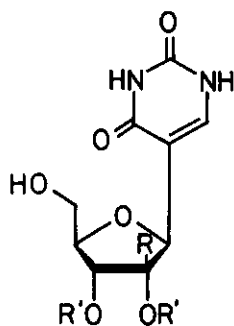
V, R = CH₂OTBDMS



VI, R = CH₂OTBDMS



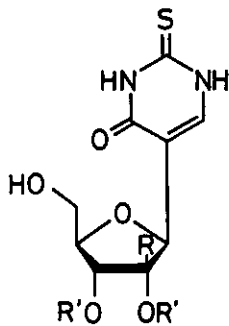
VII, R = CH₂OTBDMS



VIII, R = CH₂OTBDMS;

R'-R' = C(CH₃)₂

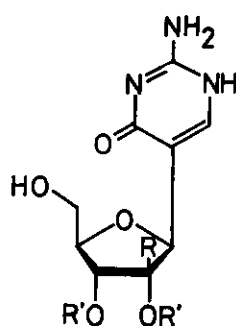
IX, R = CH₂OH; R' = H



X, R = CH₂OTBDMS;

R'-R' = C(CH₃)₂

XI, R = CH₂OH; R' = H



XII, R = CH₂OTBDMS;

R'-R' = C(CH₃)₂

XIII, R = CH₂OH; R' = H (HCl salt)

TBDMS = Si(CH₃)₂-t-C₄H₉

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REFERENCES AND NOTES

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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.
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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, $\text{CH}_2\text{C=O}$), 3.32–3.95 (m, 2H, CH_2O), 4.14 (d, $J = 13.6$ Hz, $\text{CH}_a\text{H}_b\text{OTHP}$), 4.36 (d, $J = 13.6$ Hz, $\text{CH}_a\text{H}_b\text{OTHP}$), 4.60 (br, 1H, OCH_2CH_2), 4.98 (m, 2H, $\text{OCHCH}_2\text{C=O}$), 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, $\text{CH}_a\text{H}_b\text{OH}$), 3.85 (d, $J = 12.0$ Hz, $\text{CH}_a\text{H}_b\text{OH}$), 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, $t\text{-C}_4\text{H}_9(\text{CH}_3)_2\text{Si}$), 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, $\text{H}_{5'a}$), 3.62 (dd, $J = 1.0$, 13.6 Hz, $\text{H}_{5'b}$), 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, $t\text{-C}_4\text{H}_9(\text{CH}_3)_2\text{Si}$), 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, $t\text{-C}_4\text{H}_9(\text{CH}_3)_2\text{Si}$), 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 $\lambda_{\max}$ (CH_3OH) 267 nm (ϵ 5710), $\lambda_{\max}$ (0.1 N NaOH) 285 nm (ϵ 3780), $\lambda_{\max}$ (0.1 N HCl) 266 nm (ϵ 5140).
16. Mp 140–145 °C. 1H NMR (dimethyl- d_6 sulfoxide) δ 3.27 (s, $\underline{CH_2OH}$), 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- d_6 sulfoxide) δ 60.54 and 62.70 ($C_{5'}$ and $\underline{CH_2OH}$), 70.17, 79.88, 80.16, 82.05 ($C_{1'}$ – $C_{4'}$ of ribose), 116.58, 138.54, 160.90, 174.63. UV $\lambda_{\max}$ (CH_3OH) 215 nm (ϵ 9080), 277 (11700), $\lambda_{\max}$ (0.1 N NaOH) 220 nm (ϵ 11700), 264 (9060), $\lambda_{\max}$ (0.1 N HCl) 215 nm (ϵ 9400), 276 (11000).
17. Mp 215–217 °C. 1H NMR (dimethyl- d_6 sulfoxide) δ 3.30 (s, $\underline{CH_2OH}$), 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- d_6 sulfoxide) δ 60.70 and 62.50 ($C_{5'}$ and $\underline{CH_2OH}$), 70.01, 80.20, 82.00 ($C_{1'}$ – $C_{4'}$ of ribose), 116.48, 137.80, 152.49, 159.18. UV $\lambda_{\max}$ (CH_3OH) 224 nm (ϵ 12500), 265 (7770), $\lambda_{\max}$ (0.1 N NaOH) 232 nm (ϵ 8800), 280 (6420).

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