STEREOCONTROLLED ENTRY TO PYRIMIDINE HAMAMELO-\(\text{C}\)-NUCLEOSIDES\(^1\)

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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 hamamel-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 \(\text{C}_4\) component, a hamamelofuranosyl structure\(^4\) can be elaborated. Disclosed herein is the first, general synthesis of pyrimidine \(\text{C}\)-nucleosides containing hamamelose (a rare branched-chain sugar) as the carbohydrate moiety.

Reaction of \(\alpha,\alpha,\alpha',\alpha'\)-tetrabromoacetone and 3-tetrahydropyranyloxymethylfuran with \(\text{Zn-Ag}\) couple in THF,\(^5\) followed by treatment of the cycloaduct with saturated \(\text{NH}_4\text{Cl}/\text{CH}_3\text{OH}\) afforded the oxabicyclic ketone \(I\).\(^6\) Exposure of the unsaturated ketone \(I\) to \(\text{N-methylmorpholine-N-oxide}\)\(^7\) and subsequently a mixture of acetone, \(\text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}\), and anhydrous \(\text{CuSO}_4\) gave the acetonide \(II\) (16%) and the alcohol \(III\) (40%). The THF ether \(II\) was converted to \(III\) by the treatment with oxalic acid in aqueous THF. The specifically created \(\alpha\) stereochemistry of \(III\) was deduced from the NMR spectrum.\(^9\) Reaction of \(III\) with t-C\(_4\)H\(_9\)(CH\(_3\))\(_2\)SiCl and imidazole in DMF\(^10\) afforded the silyl ether \(IV\) (90%). Baeyer-Villiger oxidation of \(IV\) with \(\text{CF}_3\text{CO}_2\text{H}\) (3 equiv, \(\text{CH}_2\text{Cl}_2\), 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 hamamel-C-nucleosides. When \(V\) was heated with t-C\(_4\)H\(_9\)OCH[\(\text{N(CH}_3\text{)}_2\)]\(_2\) (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 \(\text{C}_2\text{H}_5\text{ONa}\) (reflux, 3 h) led to the uracil derivative \(VIII\)\(^14\) (20%), deprotection of which by 10% HCl in \(\text{CH}_3\text{OH}\) gave \((\pm)-5-(\delta\)-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 \((\pm)-5-(\delta\)-hamamelofuranosyl)-2-thiouracil (XI).\(^16\) Condensation of \(VII\) with guanidine, producing the isocytosine XII, and removal of the protective groups formed \((\pm)-3-(\delta\)-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 \(\text{C}-1\) position. The sequence via the bicyclic ketone leads in a predictable manner to the products possessing four chiral centers.
V. \( R = \text{CH}_2\text{OTBDMS} \)

VI. \( R = \text{CH}_2\text{OTBDMS} \)

VII. \( R = \text{CH}_2\text{OTBDMS} \)

VIII. \( R = \text{CH}_2\text{OTBDMS}; \quad R'-R'' = \text{C(CH}_3\text{)}_2 \)
IX. \( R = \text{CH}_2\text{OH}; \quad R' = \text{H} \)

X. \( R = \text{CH}_2\text{OTBDMS}; \quad R'-R'' = \text{C(CH}_3\text{)}_2 \)
XI. \( R = \text{CH}_2\text{OH}; \quad R' = \text{H} \)

XII. \( R = \text{CH}_2\text{OTBDMS}; \quad R'-R'' = \text{C(CH}_3\text{)}_2 \)
XIII. \( R = \text{CH}_2\text{OH}; \quad R' = \text{H} \) (HCl salt)

TBDMS = \( \text{Si(CH}_3\text{)}_2\text{-t-C}_4\text{H}_9 \)

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-322-
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REFERENCES AND NOTES


6. IR (neat) 1715 cm⁻¹ (C=O). ¹H NMR (CDCl₃) δ 1.4—1.9 (m, 6H, CH₂), 2.19—2.92 (m, 4H, CH₂C=O), 3.32—3.95 (m, 2H, CH₂O), 4.13 (dd, J = 13.6 Hz, CH₃H₂OTHP), 4.36 (d, J = 13.6 Hz, CH₃H₂OTHP), 4.60 (br, 1H, OCHOCH₂), 4.98 (m, 2H, OCHCH₂C=O), 6.08 (m, 1H, HC=O).


8. Mp 138—140°C. IR (CHCl₃) 3590 (OH), 1721 cm⁻¹ (C=O). ¹H NMR (CDCl₃) δ 1.40 and 1.52 (s, isopropylidene CH₃), 2.2—2.9 (m, H₅ and H₇), 3.65 (d, J = 12.0 Hz, CH₃H₂OH), 3.85 (d, J = 12.0 Hz, CH₃H₂OH), 4.24 (2H, CH₃). The occurrence of the C-3' proton (nucleoside numbering) as a singlet at δ 4.24 confirmed the assigned α stereochemistry.


10. Mp 79.0—80.0°C. IR (CHCl₃) 1735 cm⁻¹ (C=O). ¹H NMR (CDCl₃) δ 0.08 and 0.04 (s, t-C₄H₉(CH₃)₂Si), 1.39 and 1.55 (s, isopropylidene CH₃), 2.44 (dd, J = 3.0, 16.8 Hz, H₅α), 3.62 (dd, J = 1.0, 13.6 Hz, H₅b), 3.84 (d-like, J = 3.0 Hz, CH₂OSi), 3.84 (m, H₁), 4.15 (m, H₄), 4.44 (s, H₃).

11. Mp 99.0—100°C. IR (CHCl₃) 1732 cm⁻¹ (C=O). ¹H NMR (CDCl₃) δ 0.08 and 0.06 (s, t-C₄H₉(CH₃)₂Si), 1.38 and 1.54 (s, isopropylidene CH₃), 2.29 (dd, J = 2.8, 16.2 Hz, H₅α), 2.54 (dd, J = 5.0, 16.2 Hz, H₅b), 3.6—4.2 (m, H₁, H₄, and H₅), 4.00 (s, H₃), 4.20 (s, CH₂OSi).

12. For the origin of the unique regioselectivity, see ref 1.

13. ¹H NMR (dimethyl-d₆ sulfoxide) δ 3.06 (s, CH₃OH) 286 nm (ε 7150), λmax (0.1 N NaOH) 289 nm (ε 6150).

14. Mp 238—242°C. ¹H NMR (dimethyl-d₆ sulfoxide) δ 0.06 and 0.04 (s, t-C₄H₉(CH₃)₂Si), 1.33 and 1.51 (s, isopropylidene CH₃), 3.40 (s, CH₂OSi), 3.57 (m, H₅), 3.96 (m, H₄), 4.52 (d, J = 2.8 Hz, H₃α), 4.82 (s, H₁), 7.34 (br, H₆), 10.86 (br, H₄), 11.02 (s, H₃). UV λmax (CH₃OH) 286 nm (ε 7150), λmax (0.1 N NaOH) 289 nm (ε 6150).

15. Mp 125—130°C. ¹H NMR (dimethyl-d₆ sulfoxide) δ 3.28 (s, CH₃OH), 3.4—3.9 (m, H₃, H₄, and H₅), 4.68 (s, H₁), 7.50 (d, J = 4.8 Hz, H₆), 12.28 (d, J = 4.8 Hz, H₄), 12.40 (br, H₃). ¹³C NMR (dimethyl-d₆ sulfoxide) δ 60.56 and 63.21 (C₅, and CH₂OH), 70.58, 79.62, 80.42,
16. **Mp 140–145 °C.** $^1$H NMR (dimethyl-$d_6$ sulfoxide) $\delta$ 3.27 (s, CH$_3$OH), 3.4–3.7 (m, H$_3$, and H$_4'$), 3.64 (d, $J$ = 8.0 Hz, H$_5'a$), 3.85 (d, $J$ = 8.0 Hz, H$_5'b$), 4.25 (br, OH), 4.68 (s, H$_1'$), 7.50 (d, $J$ = 5.5 Hz, H$_6$), 12.26 (d, $J$ = 5.5 Hz, H$_1$), 12.38 (br, H$_3$). $^{13}$C NMR (dimethyl-$d_6$ sulfoxide) $\delta$ 60.54 and 62.70 (C$_5$, and CH$_2$OH), 70.17, 79.98, 80.16, 82.05 (C$_1'$–C$_4'$ of ribose), 116.58, 138.54, 160.90, 174.63. UV $\lambda_{\text{max}}$ (CH$_3$OH) 215 nm ($\varepsilon$ 9080), 227 (11700), $\lambda_{\text{max}}$ (0.1 N NaOH) 220 nm ($\varepsilon$ 11700), 264 (9060), $\lambda_{\text{max}}$ (0.1 N HCl) 215 nm ($\varepsilon$ 9400), 276 (11000).

17. **Mp 215–217 °C.** $^1$H NMR (dimethyl-$d_6$ sulfoxide) $\delta$ 3.30 (s, CH$_2$OH), 3.4–3.9 (m, H$_3$, and H$_4'$), 3.67 (d, $J$ = 8.8 Hz, H$_5'a$), 3.92 (d, $J$ = 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) $\delta$ 60.70 and 62.50 (C$_5$, and CH$_2$OH), 70.01, 80.20, 82.00 (C$_1'$–C$_4'$ of ribose), 116.48, 137.80, 152.49, 159.18. UV $\lambda_{\text{max}}$ (CH$_3$OH) 224 nm ($\varepsilon$ 12500), 265 (7770), $\lambda_{\text{max}}$ (0.1 N NaOH) 232 nm ($\varepsilon$ 8800), 280 (6420).

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