Highly Stereocontrolled Total Synthesis of 6-Deoxy-6-aminoheptopyranuronic Acid Derivatives

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An extremely selective synthesis of two novel α-aminouronic acids, the enantio-pair D-**10** and L-**10**, through the butenolide intermediates D-**2** and L-**2** is described.

α-Aminodeoxyuronic acids constitute the core part of important bioactive peptidyl nucleosides,[1] *e.g.* polyoxins,[2] neopolyoxins[3] and amipurimycin.[4] Their unique molecular structure combines the characteristics of both the amino acid and the sugar, which are linked by a chemo- and bio-resistant carbon–carbon bond. While the synthesis of glycofuranosyl derivatives has been well studied,[5] little attention has been paid to date to the development of stereoselective routes to the quite unusual glycopyranosyl analogues.[6]

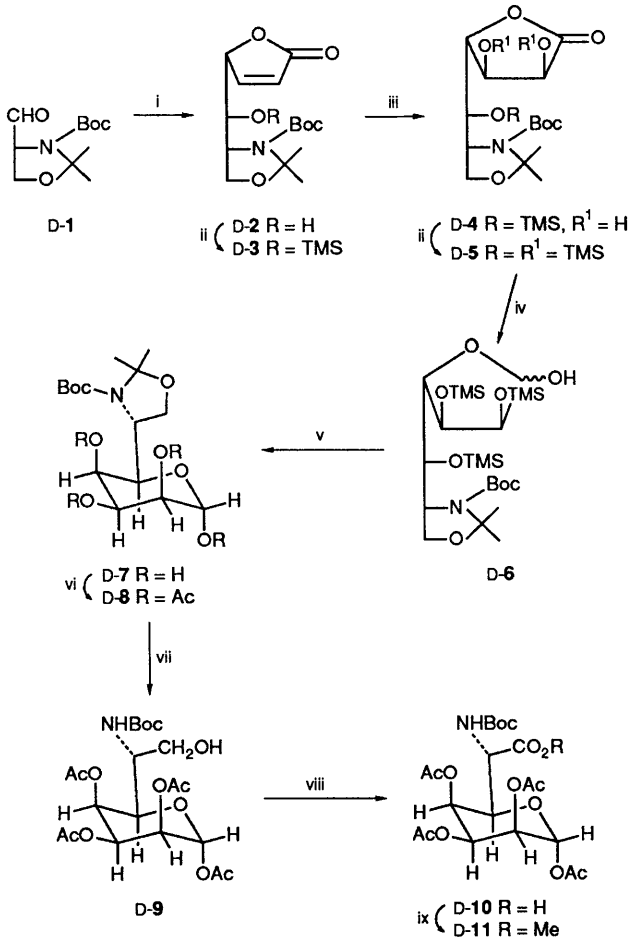
Recent studies, primarily in this laboratory,[7] have begun to realize the merits of higher butenolide units in the stereocontrolled assembly of complex carbohydrates and, in this paper, we record the exploitation of these materials *en route* to α-aminodeoxyhepturonic acid derivatives, exemplified by the total synthesis of the enantio-couple D-**10** and L-**10**.

As summarized in Scheme 1 (only D-stereochemical series depicted), the synthesis commences with the enantiomerically pure template D-**2**, generated by diastereoselective four-carbon homologation of the D-serinal derivative D-**1**, using 2-(trimethylsiloxy)furan.[7a] Crystalline D-**2** {86%; m.p. 129–131 °C; $[\alpha]_D$ +68.91° (*c* 1.48, $CHCl_3$); enantiomeric excess (e.e.) >98%} upon silylation [trimethylsilyl chloride(TMSCl), pyridine, cat. 4-dimethylaminopyridine (DMAP), room temp. give D-**3** {quantitative; m.p. 108–110 °C; $[\alpha]_D$ +150.00° (*c* 2.2, $CHCl_3$)}.† Subsequent *anti*-stereospecific *cis*-dihydroxylation using a solid $KMnO_4$–dicyclohexano-18-crown-6 system[5i] in CH_2Cl_2 at 0 to 15 °C affords the heptonolactone D-**4** {68%; m.p. 184–186 °C; $[\alpha]_D$ +19.46° (*c* 2.98, MeOH)} as the sole stereoisomer, which is converted into its TMS ether D-**5** in the usual manner {quantitative; m.p. 77–79 °C; $[\alpha]_D$ +15.38° (*c* 1.3, $CHCl_3$)}.

Lactone to lactol reduction is performed cleanly and quantitatively using diisobutylaluminium hydride (DIBAL-H) in CH_2Cl_2 at −80 °C, giving D-**6** as a mixture of α- and β-anomers {7:1 ratio; 68%; a glass; $[\alpha]_D$ +12.66° (*c* 2.37, $CHCl_3$)}. Hydrolytic workup with 5% methanolic citric acid and purification by flash chromatography (ethyl acetate–methanol 10:0.5) affords a single diastereoisomeric ribopyranosyl derivative D-**7** {75%; m.p. 191–193 °C; $[\alpha]_D$ +54.38° (*c* 1.14, MeOH)}, which is peracetylated (Ac_2O, pyridine, cat. DMAP, room temp.) to α-pyranose tetraacetate D-**8** {98%; a glass; $[\alpha]_D$ +81.25° (*c* 0.32, $CHCl_3$)}.

The pyranose nature of D-**8** follows directly from the ^1H NMR coupling constants and difference NOE experiments. The distinct NOE observed between the C-3 and C-5 protons and *vice versa* provides clear-cut evidence supporting this structure, the protons being in close proximity (diaxial orientation) only in the $^4C_1$ (D) conformation. In addition, a ^4J of 1.5 Hz between H-2 and H-4 is observed, due to their diequatorial disposition.

Careful acetonide deblocking, preserving the integrity of the *N*-Boc protection, is performed by 70% AcOH at 50 °C. 6-Deoxy-6-*tert*-butoxycarbonylamino-α-D-*glycero*-D-*talo*-heptopyranose tetraacetate D-**9**, a potential precursor of destomic acid analogues,[8] is obtained in 70% yield {a glass; $[\alpha]_D$ +81.82° (*c* 0.66, $CHCl_3$)}. Oxidation of D-**9** by the $NaIO_4$–RuO_2 protocol[5j] then generates 1,2,3,4-tetra-*O*-acetyl-6-



Scheme 1 *Reagents and conditions*: i, 2-(trimethylsiloxy)furan, $BF_3{\cdot}Et_2O$, −80 °C (see Ref. 7*a*), 85%; ii, TMSCl, pyridine, cat. DMAP, room temp., 2 h, quantitative; iii, $KMnO_4$, dicyclohexano-18-crown-6, CH_2Cl_2, 0 to 15 °C, 6 h, 68%; iv, DIBAL-H, CH_2Cl_2, −80 °C, 5 h, 68%; v, 5% citric acid, MeOH, room temp., 2 h, 75%; vi, Ac_2O, pyridine, cat. DMAP, room temp., 2 h, 98% vii, 70% AcOH, 50 °C, 4 h, 70%; viii, $NaIO_4$, cat. $RuO_2{\cdot}H_2O$, acetone–H_2O 2:1, room temp., 7 h, 88%; ix, CH_2N_2, Et_2O, room temp., 5 h, quantitative

† All new substances exhibited spectroscopic data in accord with the assigned structures and provided acceptable microanalytical data. *Selected ^1H NMR data* for D-**8**: (300 MHz, C_6D_6, 65 °C) δ 6.33 (d, *J* 0.8 Hz, 1H, 1-H), 5.52 (m, 1H, 4-H), 5.46 (t, *J* 3.9 Hz, 1H, 3-H), 5.28 (ddd, *J* 3.9, 1.5 and 0.9 Hz, 1H, 2-H), 4.47(dm, *J* 4.6 Hz, 1H, 5-H), 4.25 (m, 2H, 6-H-b and 7a-H), 3.63 (dd, *J* 9.0 and 6.1 Hz, 1H, 76-H), 1.96 (bs, 3H, OAc), 1.78 (s, 3H, OAc), 1.73 (s, 3H, OAc), 1.62 (s, 3H, OAc) and 1.40 (m, 15H, Me_2 and Bu^t).

For D-**11**: (300 MHz, $CDCl_3$, 25 °C) δ 6.08 (d, *J* 1.2 Hz, 1H, 1-H), 5.39 (m, 1H, 4-H), 5.29 (t, *J* 3.6 Hz, 1H, 3-H), 5.07 (ddd, *J* 3.9, 1.5 and 0.9 Hz, 1H, 2-H), 4.81 (d, *J* 10.2 Hz, 1H, NH), 4.67 (t, J 9.6 Hz, 1H, 6-H), 4.11 (m, 1H, 5-H), 3.74 (s, 3H, CO_2Me), 2.16 (s, 3H, OAc), 2.15 (s 3H, OAc), 2.12 (s, 3H, OAc), 2.00 (s, 3H, OAc) and 1.39 (s, 9H, Bu^t).

deoxy-6-*tert*-butoxycarbonylamino-α-D-*glycero*-D-*talo*-heptopyranuronic acid D-**10** {88%; white foam; $[\alpha]_D$ +51.52° (*c* 0.33, $CHCl_3$)}, which is fully characterized as its methyl ester D-**11** {CH_2N_2–Et_2O at room temp.; quantitative; a glass; $[\alpha]_D$ +59.06° (*c* 1.27, $CHCl_3$)}.

The synthesis of the L-**10** enantiomer, starting with the serinal derivative L-**1** *via* the butenolide intermediate L-**2**, exactly parallels that of D-**10**. Except for the optical rotation, which is nearly equal but reversed, D- and L-derivatives are spectroscopically identical. The entire sequence to **10** requires nine steps from **1** and provides the *N*-Boc–amino acid couple in 18–20% overall yield. The route is highly stereoselective and truly viable. In each stage of the sequence, the appropriate product emerges either exclusively or very predominantly, often avoiding time and material consuming chromatographic separations. Also, by working on a multigram scale, gram quantity of amino acids **10** are synthesized. This plan can be adapted through the use of varied protocols during the butenolide manipulation to provide differently configurated α-aminodeoxyheptopyranuronic acids.

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