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Tetrahedron Letters 45 (2004) 1477–1479
Tetrahedron Letters

Synthesis of pyranoid δ-sugar amino acids and their oligomers from per-benzylated β-*C*-vinyl glucoside

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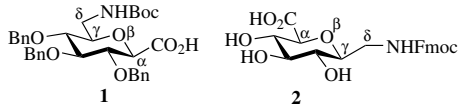
Received 30 October 2003; revised 2 December 2003; accepted 8 December 2003

Abstract—Two pyranoid δ-sugar amino acids were prepared from the common per-benzylated β-*C*-vinyl glucoside and easily oligomerised using solution-phase coupling methodology.

Recently, sugar amino acids (SAAs) have found wide applications in the creation of diverse novel structures with unique properties.[1] For example, the pyranoid δ-SAAs **1**[2] and **2**[3] (Fig. 1) have been used in the synthesis of sulfated β-1,6-linked oligosaccharide mimetics with potent inhibitory activity towards HIV replication[2] or in the preparation of cyclic homooligomers as potential host molecules.[3] Compound **1** was prepared in several steps from methyl 2,6-anhydro-D-glycero-D-gulo-hepturonate, by introducing the 6-amino group after selective protection.[2] On the other hand, the SAA **2** was synthesised from D-glucose using a nucleophilic aldol reaction to introduce a nitromethylene group at the anomeric position as an aminomethylene equivalent, followed by selective oxidation of the primary hydroxyl group to a carboxylic acid.[3,4] As part of our ongoing efforts in the synthesis of SAAs,[5] we report herein an alternative approach to pyranoid δ-SAAs from the per-benzylated β-*C*-vinyl glucoside **3**[6] and their use in the synthesis of several oligomers.



1 2

Figure 1. Structure of pyranoid δ-sugar amino acids.

Scheme 1 summarises the synthesis of SAA **4** and its octamer **5**. Starting with the β-*C*-vinyl glucoside **3**, selective acetolysis of the 6-benzyloxy group[7] afforded the alcohol **6**[8] after Zemplén deacetylation. Oxidation of the primary hydroxyl function with PCC in the presence of ^{t}BuOH and Ac_2O[9] gave the *tert*-butyl ester **7** in 58% yield. Oxidative cleavage followed by reduction transformed the vinyl function into alcohol **8**, which was converted into azide **9**[10] by displacement of the mesylate. The ester group of **9** was hydrolysed with TFA to give **10**, which was used for the next coupling reaction without purification. Finally the amino ester **4** was obtained after reduction of the azido function by a Staudinger reaction. The coupling of **4** with **10** was carried out with diethylphosphoryl cyanide (DEPC)/Et_3N[11] to give the dimer **11** in 77% yield. Repetition of the same synthetic manipulation: (i) removal of the ^{t}Bu group, (ii) reduction of the azido function and (iii) coupling furnished readily the tetramer **14**[12] and the octamer **5**.[12]

Alternatively, transformation of the primary hydroxyl function of **6** into the azide **17** gave access to an analogue of SAA **1** (Scheme 2). However, direct oxidation of the olefin **17** failed to furnish the anomerically pure β-acid **19**. Furthermore, ozonolysis of **17** followed by treatment with an excess of H_2O_2 did not furnish the desired acid **19** either: the intermediate ozonide remaining unchanged under the reaction conditions. We then decided to reduce the ozonide into alcohol **18**,

Keywords: δ-Sugar amino acid; C-Glucoside; Oligomer.
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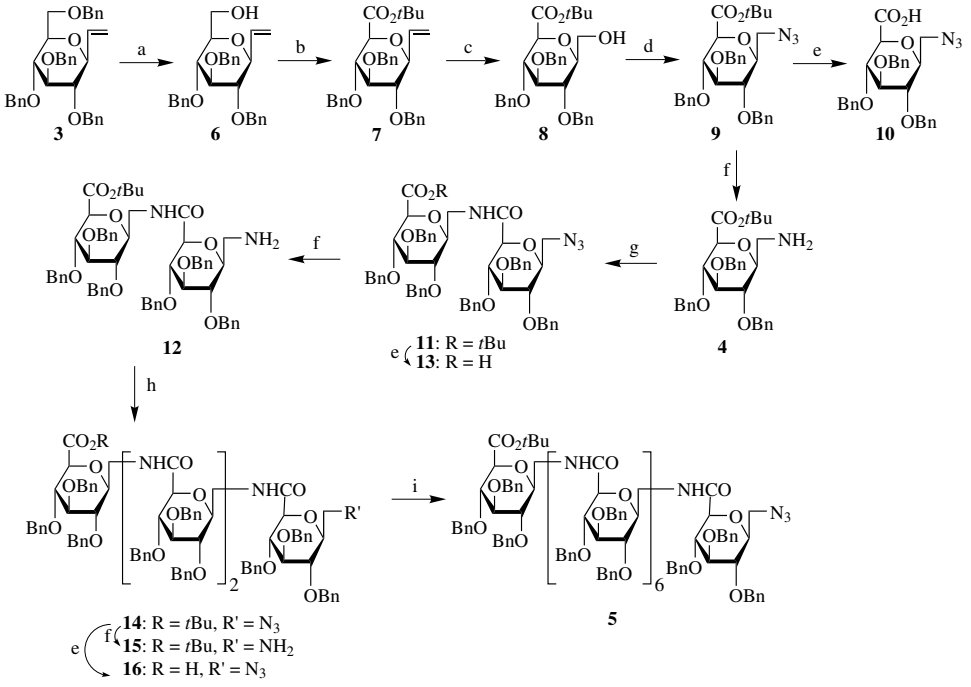
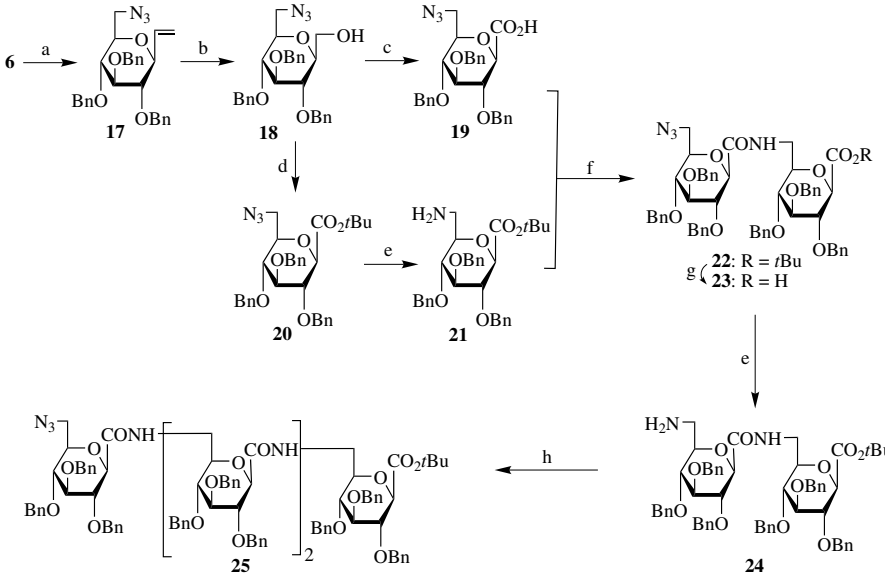
doi:10.1016/j.tetlet.2003.12.032



Scheme 1. Reagents and conditions: (a) (i) 1 equiv TMSOTf, 53 equiv Ac_2O, CH_2Cl_2, −40 °C, 1 h, 80%; (ii) 1 equiv NaOMe (1 M), MeOH, rt, 20 h, 66%; (b) 2 equiv PCC, 10 equiv Ac_2O, 20 equiv ^{t}BuOH, CH_2Cl_2, rt, 48 h, 58%; (c) (i) O_3, CH_2Cl_2, −78 °C, 30 min; (ii) 1.5 equiv $NaBH_4$, MeOH, rt, 20 h, 71% overall; (d) (i) 1.5 equiv MsCl, 2 equiv Et_3N, CH_2Cl_2, rt, 20 h; (ii) 5 equiv NaN_3, DMF, 90 °C, 20 h, 74% overall; (e) 20 equiv TFA, CH_2Cl_2, rt, 20 h, 100%; (f) 1.1 equiv PPh_3, 12 equiv H_2O, THF, rt, 20 h, 89% for **4**, 79% for **12** and 46% for **15**; (g) 1.1 equiv **10**, 1.5 equiv DEPC, 3 equiv Et_3N, DMF, rt, 72 h, 77%; (h) 1.2 equiv **13**, 1.5 equiv DEPC, 3 equiv Et_3N, DMF, rt, 72 h, 99%; (i) 1.12 equiv **16**, 1.5 equiv DEPC, 3 equiv Et_3N, DMF, rt, 72 h, 65%.



Scheme 2. Reagents and conditions: (a) (i) 1.5 equiv MsCl, 2 equiv Et_3N, CH_2Cl_2, rt, 20 h; (ii) 5 equiv NaN_3, DMF, 90 °C, 20 h, 82% overall; (b) (i) O_3, CH_2Cl_2, −78 °C, 30 min; (ii) 3 equiv $NaBH_4$, MeOH, rt, 20 h, 62% overall; (c) 1.1 equiv TEMPO, 12 equiv NaOCl, 0.1 equiv KBr, $NaHCO_3$, acetone, rt, 1 h, 100%; (d) 2 equiv PCC, 10 equiv Ac_2O, 20 equiv ^{t}BuOH, CH_2Cl_2, rt, 48 h, 62%; (e) 1.1 equiv PPh_3, 12 equiv H_2O, THF, rt, 20 h, 89% for **21**, 77% for **24**; (f) 1.5 equiv DEPC, 3 equiv Et_3N, DMF, rt, 72 h, 72%; (g) 20 equiv TFA, CH_2Cl_2, rt, 20 h, 100%; (h) 1.1 equiv **23**, 1.5 equiv DEPC, 3 equiv Et_3N, DMF, rt, 72 h, 79%.

which was oxidised quantitatively to acid **19** with TEMPO. Treatment of **18** with PCC/Ac_2O/^{t}BuOH afforded the ester **20**[10] in 62% yield, which was reduced to amino ester **21** with PPh_3. Finally, coupling of **21** with **19** catalysed by DEPC gave the dimer **22** in 72% yield. Repetitive coupling as described before produced the tetramer **25**.[12]

In summary, we have demonstrated alternative syntheses of two pyranoid δ-SAAs from per-benzylated β-*C*-

vinyl glucoside. These monomeric SAAs can be easily oligomerised using a solution-phase coupling procedure.

References and notes

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10. Selected physical data. *tert*-Butyl 2,6-anhydro-7-azido-3,4,5-tri-*O*-benzyl-7-deoxy-L-glycero-L-gluco-hepturonate **9**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29–7.16 (m, 15H, Ph), 4.87–4.78 (m, 3H, OCH_2Ph), 4.74 (d, 1H, $J = 10.8$ Hz, OCH_2Ph), 4.62 (d, 1H, $J = 10.8$ Hz, OCH_2Ph), 4.52 (d, 1H, $J = 11$ Hz, OCH_2Ph), 3.82–3.61 (m, 3H), 3.48–3.36 (m, 3H), 3.24–3.21 (m, 1H, H-7), 1.41 (s, 9H, ^{t}Bu); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.0 ($CO_2{}^t$Bu), 138.4, 137.6 (C_{ipso}), 128.6–127.8 (CH-Ph), 86.1 (CH), 82.4 (C_q ^{t}Bu), 79.9, 79.3, 79.0, 78.3 (4×CH), 75.7, 75.3, 75.1 (3×OCH_2Ph), 51.0 (C-7), 27.9 (CH_3 ^{t}Bu). *tert*-Butyl 2,6-anhydro-7-azido-3,4,5-tri-*O*-benzyl-7-deoxy-D-glycero-D-gulo-hepturonate **20**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27–7.12 (m, 15H, Ph), 4.85–4.76 (m, 3H, OCH_2Ph), 4.73 (d, 1H, $J = 10.5$ Hz, OCH_2Ph), 4.61 (d, 1H, $J = 10.5$ Hz, OCH_2Ph), 4.50 (d, 1H, $J = 11$ Hz, OCH_2Ph), 3.85–3.59 (m, 3H), 3.49–3.33 (m, 3H), 3.23–3.15 (m, 1H, H-7), 1.39 (s, 9H, ^{t}Bu); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.8 ($CO_2{}^t$Bu), 138.3, 137.9, 137.7 (C_{ipso}), 128.6–127.8 (CH-Ph), 86.1 (CH), 82.4 (C_q ^{t}Bu), 79.9, 79.3, 79.1, 78.3 (4×CH), 75.7, 75.3, 75.1 (3×OCH_2Ph), 51.0 (C-7), 27.9 (CH_3 ^{t}Bu).
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12. The structures of the oligomers have been confirmed by ^{1}H, ^{13}C NMR data and fast atom bombardment mass spectroscopy.