An Expeditious Route Towards Pyranopyran Sugar Amino Acids

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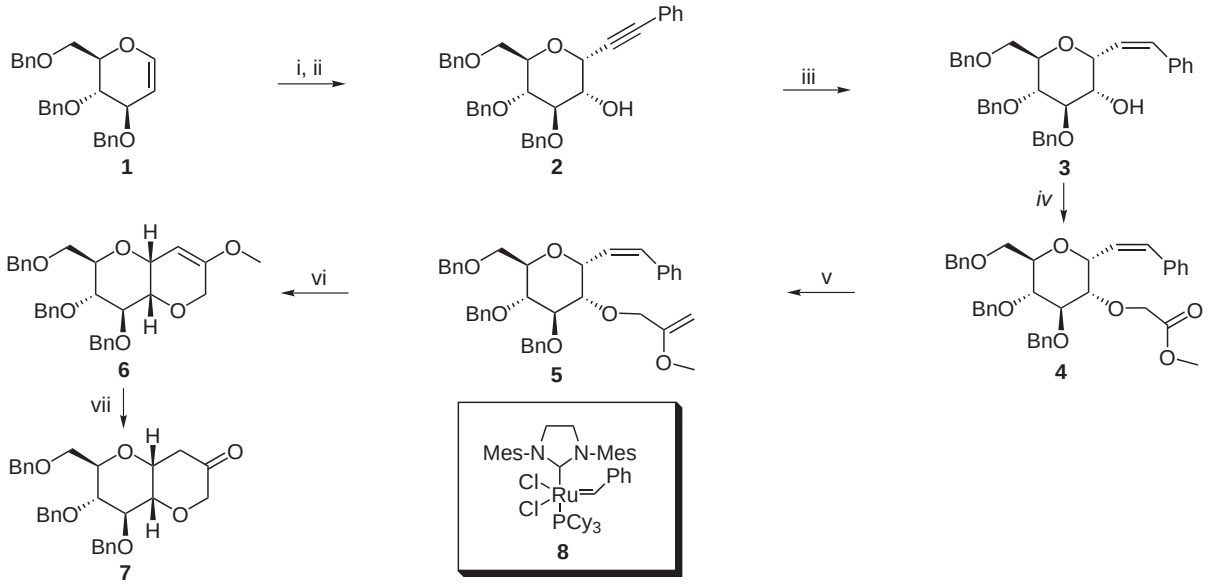
Abstract: The synthesis of two diastereoisomeric pyranopyran sugar amino acids, starting from (+)-D-3,4,6-tri-*O*-benzylglucal, is described. The key reaction sequence towards the bicyclic structure entails Petasis olefination followed by ring closing metathesis.

Key words: amino acids, bicyclic compounds, carbohydrates, pyranopyran, ring-closing metathesis

Sugar amino acids (SAAs), carbohydrate structures functionalized with an amine and a carboxylic acid, have found wide application as building blocks for the construction of both glyco- and peptidomimetic compounds.[1] Oligomeric structures of these molecular frameworks can be obtained through facile peptide bond formation. Apart from this, SAAs were found to be useful for the development of enantiopure, diversely functionalized scaffolds for application in dedicated library synthesis. The structural and functional diversity inherent to the parent sugars provides entry to a myriad of different structures with numerous variations in the number, nature and position of the functional groups attached to the parent carbohydrates.[2]

Several research groups, including ours, have reported on the use of SAAs for the introduction of conformational constraints in both linear and cyclic oligopeptides.[3] From these studies it became apparent that, although the conformational freedom of the target peptides is partially reduced, an equilibrium of a number of conformers is normally present.[4] This may be attributed to the inherent flexibility of the parent sugar ring from which the SAAs are derived. With the aim to increase conformational constraints, we, and others, have reported on the development of 'locked' SAAs, carbohydrate derived peptide building blocks with an additional ring fused to a furanoid SAA core.[5] In line with these studies, we here present the synthesis of two new conformationally constrained SAA building blocks having a glucose-based pyranopyran template.



Scheme 1 *i*) DMDO (1.2 equiv), CH_2Cl_2, 0 °C, 10 min, quant.; *ii*) lithium phenylacetylide (2 equiv), $ZnCl_2$ (2 equiv), THF, –70 °C to r.t., 1 h, 78%; *iii*) H_2, Lindlar (cat.), quinoline, EtOAc, quant.; *iv*) methylbromoacetate (3 equiv), TBAI (0.1 equiv), NaH (7 equiv), DMF, 16 h, **4**; 72% and recovered **3**; 23%; *v*) Cp_2TiMe_2 (2.5 equiv), THF, 60 °C, 48 h, 82%; *vi*) **8** (0.05 equiv), CH_2Cl_2, reflux, 48 h, 88%; *vii*) TFA/H_2O (3:7 v/v), CH_2Cl_2, 1 h, 92%.

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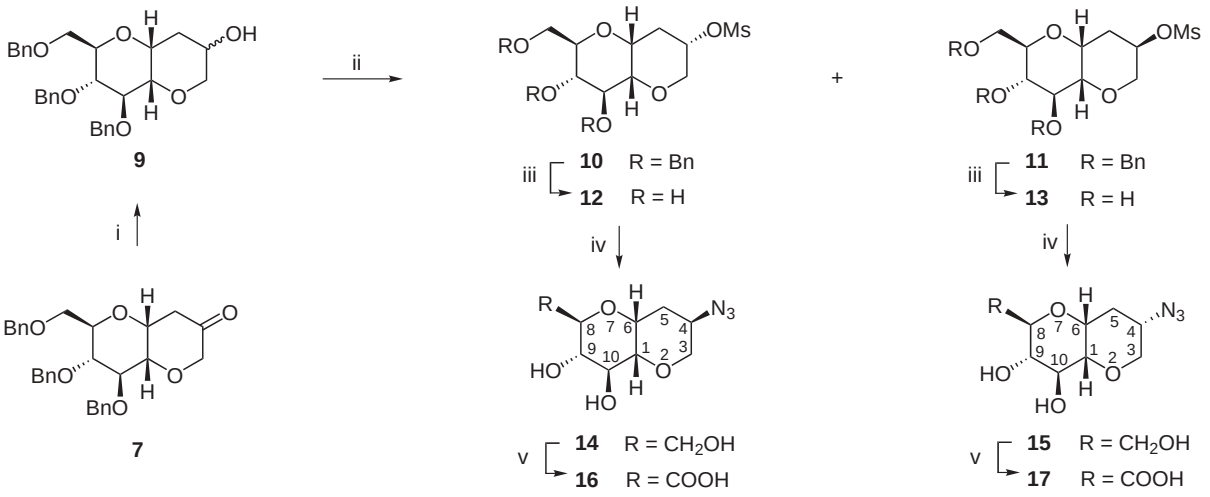

Scheme 2 *i*) L-selectride (1.5 equiv), THF, –78 °C to r.t., 16 h, 71% (*endo*:*exo* = 2:1); *ii*) MsCl (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C to r.t., **10**; 56% and **11**; 36%; *iii*) H_2, 10% Pd/C (cat.), EtOH, 3 h, **12**; quant. and **13**; quant.; *iv*) NaN_3 (5 equiv), DMF, 70 °C, 16 h, **14**; 90% and **15**; 94%; *v*) TEMPO (cat.), NaOCl, $NaHCO_3$ (aq), MeCN, 0 °C, **16**; 53% and **17**; 52%.

We have previously reported the facile construction of C-glycosidic alkene **3** and its use in the assembly of a variety of fused oxacycles.[6] Starting from commercially available (+)-D-3,4,6-tri-*O*-benzylglucal **1** (Scheme 1), epoxidation of the enol ether by reaction with dimethyldioxirane (DMDO), followed by $ZnCl_2$-mediated propargylation furnished the α-substituted **2** as the major product. Selective hydrogenolysis of the acetylene moiety employing Lindlar's catalyst gave alkene **3** in good yield.[6] Adaptation of these synthetic studies enables the construction of pyranopyran-based SAAs, as follows.

Alkylation of the free hydroxyl functionality in compound **3**, using an excess of sodium hydride and methylbromoacetate in the presence of a catalytic amount of tetrabutylammonium iodide, afforded methyl ester **4** in 72% with recovery of 23% of alcohol **3** (a repeated alkylation step resulted in an overall yield of 95% of **4**).[7] Olefination of the methyl ester in **4**, employing freshly prepared Cp_2TiMe_2 (Petasis reagent)[8] yielded enol ether **5** in 82%. Ring-closing metathesis of **5** in refluxing dichloromethane under the agency of ruthenium-alkylidene **8**[9] afforded the fused oxacycle **6** in 88% yield. Hydrolysis of the enol ether by treatment with aqueous TFA in CH_2Cl_2 gave bicyclic ketone **7** in 92%. Reduction of ketone **7** (Scheme 2) by the sterically congested lithium tri-*sec*-butyl borohydride (L-selectride®) in THF afforded an inseparable mixture of alcohols **9** in 71% yield (*endo*:*exo* 2:1, as judged by ^1H NMR analysis).[10] Installation of the mesylate functionality using methylsulfonylchloride and triethylamine in CH_2Cl_2 gave, after silicagel column chromatography, *endo*-substituted **10** and *exo*-substituted **11** in a 56% and 36% yield, respectively. Hydrogenation of the benzyl protective groups in mesylates **10** and **11** furnished triols **12** and **13**, respectively, in near quantitative yield. Nucleophilic substitution on the endo-mesylate **12** by prolonged heating in DMF in the presence of an excess of NaN_3 afforded *exo*-azide **14** in 90%. Similarly, *exo*-mesylate **13** was readily converted into *endo*-azide **15** in 94%. Finally, the carboxylic acid was installed by selective oxidation of the primary alcohol of **14** and **15** using a catalytic amount of TEMPO (2,2,6,6-tetramethyl-piperidinyl-1-oxy) and NaOCl as co-oxidant, delivering SAAs **16**[11] and **17**[12] in 53% and 52% yield, respectively. The structures of *cis*-fused oxacycles **16** and **17** were analyzed by ^1H NMR and ^{13}C NMR spectroscopy using a combination of COSY, NOESY and HMQC data sets. Characteristic NOEs and long range couplings (Figure 1) confirmed the rigid structure adopted by the pyranopyran sugar amino acids.

In conclusion, we have developed an efficient route to *cis*-fused pyranopyranoid ε-SAAs. Starting from differently functionalized monosaccharides, our strategy may give access to a range of carbohydrate-derived bicyclic amino acids. Research effort is currently focussed on further implementing the presented strategy towards *trans*-fused pyranopyran SAAs. The required β-substituted *C*-glycoside precursors are accessible through $Co_2(CO)_8$ complexation to acetylene **2**, followed by acid-catalyzed epimerisation and oxidative release of the cobalt complex.[6] Finally, the application of the *cis*- and *trans*-fused pyranopyran SAA building blocks in oligomeric structures as well as their in depth conformational analysis is currently pursued and will be reported in due course.

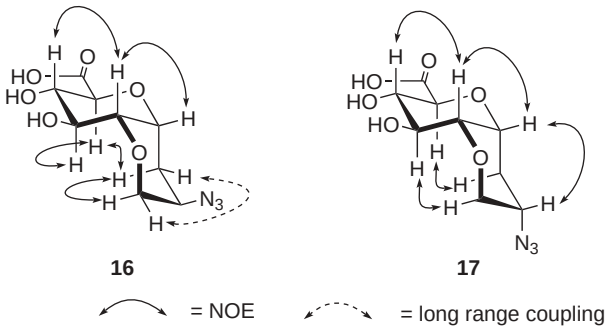

Figure 1 ^1H NMR evaluation of the SAAs **16** and **17**.

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(7) A competing reaction occurred, resulting in the formation of significant quantities of *trans*-cyclopropane-1,2,3-tricarboxylic acid trimethyl ester. This side product was separated from the target compound **4** by size exclusion chromatography (Sephadex LH-20).

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(10) Reduction with sodium borohydride gave a diastereoisomeric mixture of alcohols **9**; *endo*:*exo* = 9:1, as judged by ^{1}H NMR analysis.

(11) **Physical Data for SAA 16:** ^{1}H NMR (400 MHz, D_2O): δ = 4.49 (m, 1 H, H_6), 4.09 (d, 1 H, H_8, $J_{8,9}$ = 5.3 Hz), 4.05 (dd, 1 H, H_{10}, $J_{10,9}$ = 5.5 Hz, $J_{10,1}$ = 5.9 Hz), 4.02 (m, 2 H, H_{3ax}, H_4), 3.89 (dd, 1 H, H_9, $J_{9,8}$ = 5.3 Hz, $J_{9,10}$ = 5.5 Hz), 3.65 (dd, 1 H, H_1, $J_{1,6}$ = 3.5 Hz, $J_{1,10}$ = 5.9 Hz), 3.45 (ddd, 1 H, H_{3eq}, $J_{3eq,5eq}$ = 1.7 Hz, $J_{3eq,4}$ = 7.8 Hz, $J_{3eq,3ax}$ = 12.4 Hz), 2.37 (m, 1 H, H_{5ax}), 1.86 (m, 1 H, H_{5eq}). ^{13}C NMR (100 MHz, D_2O): δ = 177.3 (C=O), 76.8 (C_8) 75.2 (C_1), 70.9 (C_9), 67.6 (C_{10}), 66.7 (C_3), 66.0 (C_6), 54.9 (C_4), 30.7 (C_5). ATR-IR (thin film): ν = 3398.1, 2920.0, 2120.1, 1605.6, 1454.5, 1385.0, 1315.5, 1247.7, 1096.9, 1076.7, 1062.2, 1001.4, 947.7, 923.1, 879.9, 811.4 cm^{-1}. MS (ESI): *m/z* = 260.0 $[M + H]^+$, 282.1 $[M + Na]^+$, 541.1 $[2 M + Na]^+$.

(12) **Physical Data for SAA 17**: ^{1}H NMR (400 MHz, D_2O): δ = 4.31 (m, 1 H, H_6), 4.10 (d, 1 H, H_8, $J_{8,9}$ = 5.8 Hz), 4.07 (dd, 1 H, H_{10}, $J_{10,9}$ = 6.1 Hz, $J_{10,1}$ = 6.3 Hz), 3.83 (dd, 1 H, H_9, $J_{9,8}$ = 5.8 Hz, $J_{9,10}$ = 6.1 Hz), 3.78 (m, 3 H, H_3, H_4), 3.70 (dd, 1 H, H_1, $J_{1,6}$ = 3.8 Hz, $J_{1,10}$ = 6.3 Hz), 2.15 (m, 2 H, H_5). ^{13}C NMR (100 MHz, D_2O): δ = 177.4 (C=O), 76.7 (C_8) 75.6 (C_1), 71.5 (C_9), 68.2 (C_{10}), 66.8 (C_3, C_6), 55.2 (C_4), 30.3 (C_5). ATR-IR (thin film): ν = 3353.3, 2955.6, 2955.6, 2924.6, 2853.7, 2102.1, 1606.7, 1370.7, 1271.5, 1246.9, 1116.3, 1077.8, 1008.8. 967.4, 941.3 cm^{-1} MS (ESI): *m/z* = 260.0 $[M + H]^+$, 282.1 $[M + Na]^+$.