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The Synthesis of cis- and trans-Fused Bicyclic Sugar Amino Acids


Keywords: Sugar amino acids / Ring-closing metathesis / Petasis olefination / Pyranopyran

Four isomeric bicyclic sugar amino acids (SAAs) were prepared from α-acetylenic-C-glucoside 6 by employing a Petasis olefination and a ring-closing metathesis (RCM) as key steps. The applicability of the resulting SAAs in solid-phase peptide synthesis was demonstrated by the synthesis of tetrapeptide 36. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

Introduction

In recent years sugar amino acids (SAAs) have come to the fore as versatile building blocks in organic and bio-organic chemistry. SAAs combine the wealth of functional and stereochemical information inherent to carbohydrates with the ease with which oligomers can be prepared by peptide bond formation. They are now explored in various directions: in peptide chemistry,[1] with the aim of developing peptidomimetics with an advantageous conformational bias[2] and in carbohydrate chemistry, to arrive at linear and cyclic oligosaccharide analogues (for instance as potential receptor molecules and as templates in combinatorial library synthesis).[3] SAAs have added value for several reasons, including the limited conformational freedom caused by the parent carbohydrate ring and the available functional groups (apart from the amine and carboxylate) that are appended to the carbohydrate core. A large variety of SAA building blocks differing in structural backbone (ring size), stereochemistry, and functional group pattern have been described in the literature, and the list is continuously expanding.

A recently added feature in SAA design is to introduce additional conformational strain by the attachment of a second ring onto the carbohydrate core.[4] In this context, we previously reported the synthesis of two cis-fused, glucopyranose-based pyranopyran SAAs 1 and 2, which have the amine functionality masked as an azide group.[4b] We here disclose full experimental detail for the synthesis of 1 and 2 (Figure 1). Further, the synthesis of the corresponding trans-fused pyranopyran SAAs 3 and 4 and the application of the latter in the synthesis of a hybrid peptide-SAA tetramer is presented.

Results and Discussion

The synthesis of pyranopyrans 1 and 2 commenced (Scheme 1) with 3,4,6-tri-O-benzyl-D-glucal 5, which was converted into α-C-glycoside 6 following a literature procedure (dimethyldioxirane-mediated epoxidation of the glucal[5] followed by treatment with lithium phenylacetylide and zinc chloride).[6] Partial reduction of the triple bond using Lindlar’s catalyst yielded the known glucoside 7 in quantitative yield. Alkylation of the hydroxy moiety with methyl bromoacetate gave compound 8 (95%),[7] which was treated with Petasis reagent[8] to provide enol ether 9. Ensuring ring-closing metathesis (RCM) under the agency of the second generation Grubbs ruthenium catalyst[9] gave pyranopyran derivative 10 (88%). Hydrolysis of the enol ether moiety afforded ketone 11, which was treated with L-selectride to give alcohol 12 as an inseparable mixture (endo/exo, 2:1).[10]
The mixture of alcohols was converted into the corresponding mesylates 13 (40%) and 14 (25%), which at this stage could be separated. Mesylates 13 and 14 were converted into triols 15 and 16, respectively. Introduction of the azide functionality was effected by treatment of the mesylates with sodium azide and 15-crown-5 in DMF at elevated temperature with concomitant reversal of configuration. SAAs 1 and 2 were generated from compounds 17 and 18, respectively, through a selective TEMPO-mediated oxidation of the primary hydroxy groups to their corresponding carboxylates (1: 53%, 2: 52%). The configuration of the azide functionality at position 4 of compounds 1 and 2 was unambiguously assigned on the basis of NOESY NMR experiments.

In order to access trans-fused pyranopyran SAAs 3 and 4 (Scheme 2) acetylenic α-glycoside 6 was epimerized into its corresponding β-glycoside 19 by using a three-step methodology originally developed by Isobe and coworkers.

Conversion of 19 into the target SAAs went uneventfully, following the same sequence of reactions as outlined for the synthesis of 1 and 2. Thus, partial reduction of 19 followed by alkylation, Petasis olefination, and RCM gave cyclic enol ether 23. Hydrolysis, reduction, and activation of the secondary hydroxy groups gave the corresponding mesylates 26 and 27, which were separated on silica gel. From these, pyranopyran SAAs 3 and 4 were readily prepared by the three step procedure described above. The stereochemistry at position 4 of compounds 3 and 4 could be unmistakably assigned using the respective coupling constants of H-4 with that of its neighboring protons.

In the next stage, the compatibility of the trans-fused pyranopyran 4 with standard solid phase peptide synthesis techniques was ascertained by the synthesis of tetrapeptide 36, as follows. The synthesis of the oligomer commenced...
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Scheme 2. Reagents and conditions: i) (a) Co₂(CO)₈, CH₂Cl₂. (b) TfOH, CH₂Cl₂. (c) I₂, THF. ii) H₂, Lindlar’s catalyst, EtOAc. iii) methyl bromoacetate, TBAI, NaH, DMF, 87%. iv) Cp₂TiMe₂, THF, 60 °C, 72%. v) dichlorido(1,3-dimesityl-2-imidazolidinylidene) (phenylmethylene)tricyclophosphane)ruthenium, CH₂Cl₂, reflux, 86%. vi) TFA, water, CH₂Cl₂, 90%. vii) β-selectride, THF, –78 °C to room temp. viii) MsCl, Et₃N, CH₂Cl₂, 0 °C, 26% 36%, 27% 43%, two steps, ix) H₂, Pd/C, EtOH, quant, 29% 95%, x) NaN₃, DMF, 70 °C, 30% 70%, 31 74%, xi) TEMPO, NaOCl, NaHCO₃, MeCN, 0 °C, 4 49%, 3 72%.

with Fmoc-leucine immobilized on HMPB-functionalized MBHA resin (Scheme 3). Removal of the Fmoc group under standard conditions and ensuing condensation with pyranopyran SAA 4 using PyBOP[14] HOBT, and DIPEA as the condensation agents gave immobilized dipeptide 33[15]. Staudinger reduction of the azide followed by condensation with Fmoc-Leu gave compound 34. A second elongation cycle using SAA 4 led to immobilized tetrapeptide 35. Reduction of the azide followed by acid-mediated cleavage gave the target tetrapeptide 36, which was purified to homogeneity by reversed-phase HPLC (RP-HPLC) with an overall yield of 24% based on 32.

In conclusion, we have demonstrated a flexible and productive synthesis of four pyranopyran SAA building blocks 1, 2, 3, and 4 starting from a common intermediate, α-C-glucoside 6. The conformational behavior of these SAAs when incorporated in oligomeric structures such as 36 is currently being investigated.

Experimental Section

All reactions were performed under an inert atmosphere and at ambient temperature unless stated otherwise. Reactions were monitored by TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with H₂SO₄ in ethanol (20%) followed by charring at ~150 °C or by spraying with a solution of (NH₄)₆Mo₇O₂₄·4H₂O (25 g/L) and (NH₄)₄Ce(SO₄)₂·2H₂O (10 g/L) in H₂SO₄ (10%) followed by charring at ~150 °C. Column chromatography was performed on Merck silica gel (0.040–0.063 nm), and size exclusion chromatography was performed on Sephadex™ LH-20. Mass spectra were recorded with a PESciex API 165 instrument with a custom-built electrospray ionization (ESI) interface and HRMS (SIM mode) were recorded with a TSQ Quantum (Thermo Finnigan) spectrometer fitted with an accurate mass option, interpolating between PEG calibration peaks. 1H- and 13C-APT-NMR spectra were recorded with a Bruker AV-400 (400/100 MHz) spectrometer equipped with a pulsed-field gradient accessory. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as an internal standard (1H NMR).
Scheme 3. Reagents and conditions: i) piperidine/NMP, 1:4 v/v. ii) 4, PyBOP, HOBt, DIPEA, NMP. iii) (a) Me$_3$P, dioxane, (b) water, dioxane iv) FmocLeuOH, PyBOP, HOBt, DIPEA, NMP. v) TFA: CH$_2$Cl$_2$ 1:99 v/v, 36% (based on 32).
to ambient temperature, and stirring was continued for 16 h. The mixture was then quenched with saturated aq. NaHCO₃ and extracted with EtOAc. The combined organic phase was dried with anhydrous MgSO₄, filtered, and concentrated to afford the intermediate product as an inseparable mixture of isomers, which was directly used without further purification. A solution of the isomeric mixture in CDCl₃ (0.15 mL) was made after thorough coevaporation of toluene. To this solution were added triethylamine (3.0 equiv.) and methanesulfonyl chloride (3.0 equiv.), and the reaction mixture was stirred for 4 h, until all starting material was converted into two higher-running spots as determined by TLC analysis. The solution was diluted with CH₂Cl₂, extracted with saturated aq. NaHCO₃ and brine. The organic layer was dried with MgSO₄ and concentrated in vacuo. Purification and separation of the epimeric methanesulfonyl esters could be effected by silica gel chromatography using a gradient of light petroleum and ethyl acetate.

**General Procedure VI: Cleavage of Benzyl Ether Protecting Groups by Catalytic Reduction:** To a solution of the benzylated methanesulfonyl ester in ethanol (0.1 mL) was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred under a constant stream of H₂(g) for 4 h, filtered through a pad of diatomaceous earth, and concentrated to give the deprotected product.

**General Procedure VII: Substitution of Methanesulfonyl Esters Using Sodium Azide:** The mesylate was coevaporated twice with dry toluene before being dissolved in DMF (0.1 mL). The solution was placed under an inert atmosphere, and sodium azide (5.0 equiv.) and 15-crown-5 (catalytic) were added. The mixture was stirred for 7 days at 0°C. The mixture was concentrated under reduced pressure, redissolved in MeOH/CH₂Cl₂ (1:1 v/v), filtered, and concentrated before being applied to a Dowex-Na⁺ column in order to remove 15-crown-5. Further purification was performed by silica gel column chromatography using a gradient of methanol in EtOAc.

**General Procedure VIII: TEMPO Oxidation of the Primary Hydroxy Groups to Carboxylates:** First, three solutions were prepared. Solution A: KBr in saturated aq. NaHCO₃ (5.0 mg/mL×1). Solution B: 2,2,6,6-tetramethyl-1-piperidinylxox free radical (TEMPO) in acetonitrile (1.0 mg/mL×1). Solution C: a mixture of saturated aq. NaHCO₃, aq. NaOCl (15% v/w), and saturated aq. NaCl (5:8:9 v/v/v). To a solution of the alcohol in saturated aq. NaHCO₃ (0.07 mL) were added solution A and B (2.6 mL/mmol×1 each). Solution C was added dropwise, causing the color of the mixture to oscillate between yellowish and colorless. When TLC analysis revealed completion of the reaction, addition of solution C was terminated, and the reaction was quenched with MeOH, acidified to pH 7 with HCl (1.0 mL), and extracted with CH₂Cl₂. Concentration of the aqueous layer yielded a crude product contaminated with inorganic salts, which were removed to a large extent by precipitation from MeOH.

**α-d-Glucopyranosyl Derivative 8:** 2-(3′,4′,6′-Tri-O-benzyl-a-d-glucopyranosyl)-(2)-stereoselectivity 70% (12.9 g, 23 mmol) was treated according to General Procedure I to yield the title compound (13.2 g, 21.7 mmol, 95%) as a pale yellow oil. Silica gel chromatography: petroleum/ethyl acetate, 1:1 v/v. ¹H NMR (400 MHz, CDCl₃); δ = 7.55–7.13 (m, 20 H, CH₃O₢Bn, Ph), 6.86 (d, J = 11.9 Hz, 1 H, Ph-CH₂), 6.01 (dd, J = 7.9, 11.9 Hz, 1 H, =CH-CH₂), 5.04 (dd, J = 1.3, 7.9, 7.3 Hz, 1 H, H₂C), 4.99 (d, J = 10.9 Hz, 1 H, CH₂Bn), 4.87 (d, J = 10.9 Hz, 1 H, CH₂Bn), 4.85 (d, J = 10.7 Hz, 1 H, CH₂Bn), 4.62 (d, J = 12.2 Hz, 1 H, CH₂Bn), 4.51 (d, J = 10.7 Hz, 1 H, CH₂Bn), 4.45 (d, J = 12.2 Hz, 1 H, CH₂Bn), 4.19 (d, J = 16.3 Hz, 1 H, CH₂C-O), 4.12 (d, J = 16.3 Hz, 1 H, CH₂C-O), 3.97 (dd, Jₛₓ = Jₛₓ = 8.9 Hz, 1 H, H₁Bn), 3.72 (m, 2 H, H₈Bn, H₁Bn), 3.68 (m, 2 H, H₅Bn, H₆Bn), 3.58 (s, 3 H, OMe), 3.46 (dd, J₀₁₋₀₂ = 3.5 Hz, J₀₁₋₀₂ = 12.3 Hz, 1 H, H₁Bn) ppm. ¹³C NMR (100 MHz, CDCl₃); δ = 170.3 (C=O), 138.6, 132.8, 137.9 (C₆Bn), 137.4 (=CH-Ph), 135.9 (C₆Bn), 129.5, 128.4, 128.3, 128.1, 127.9, 127.7 (CH₂Bn, Ph), 124.4 (=CH₂), 83.8 (C₅), 81.3 (C₄), 78.2 (C₃), 75.0, 73.4 (3 × CH₂Bn), 72.3 (C₂), 69.8 (C₁), 68.7 (C₀), 68.5 (OCH₂C=O), 51.7 (OCH₃) ppm. ATR-IR (thin film) ν = 2862.2, 1755.1, 1496.7, 1452.3, 1436.9, 1361.7, 1211.2, 1137.9, 1095.5, 1028.0, 736.8, 698.2 cm⁻¹ [α]D² = +145.6 (c = 1.00, CHCl₃). MS (ESI): m/z = 6314. [M + Na]+. HRMS: calcld. for C₄₃H₉₀O₂Na 692.2879, found 692.2872.

(IR,6R,8S,9S,10S)-9,10-Bis(benzoxyl)-8-benzoxymethyl-4-methoxy-2,7-dioxabicyclo[4.4.4]decan-4-ene (10): Enol ether 9 (0.66 g, 1.1 mmol) was treated according to General Procedure III to yield the title compound (0.49 g, 0.97 mmol, 88%) as a clear oil. Silica gel chromatography: petroleum/toluene, 1:1 → petroleum/EtOAc, 1:1. ¹H NMR (400 MHz, CDCl₃); δ = 7.37–7.18 (m, 15 H, CH₃O₢Bn), 4.86 (d, J = 11.3 Hz, 1 H, CH₂Bn), 4.80 (d, J = 10.6 Hz, 1 H, CH₂Bn), 4.77 (d, J = 11.3 Hz, 1 H, CH₂Bn), 4.69 (d, J = 11.1 Hz, 1 H, CH₂Bn), 4.66 (m, 1 H, H₆), 4.59 (d, J = 12.1 Hz, 1 H, CH₂Bn), 4.50 (d, J = 12.1 Hz, 1 H, CH₂Bn), 3.99–3.88 (m, 3 H, H₃, H₄, H₅), 3.77–3.64 (m, 4 H, H₄, H₅, H₆), 3.55 (s, 3 H, OMe) ppm. ¹³C NMR (100 MHz, CDCl₃); δ = 156.4 (C₁), 138.5, 138.1 (C₆Bn), 128.3, 128.0, 127.8, 127.7, 126.7 (CH₂Bn, Ph), 129.2 (C₁), 78.8, 76.6, 75.9, 72.6 (C₂, C₃, C₀), 74.6, 73.6, 73.4 (3 × CH₂Bn), 69.5 (C₄), 67.5 (C₅), 61.4 (C₆), 54.4 (OCH₃) ppm. ATR-IR (thin film) ν = 2910.6, 1672.2, 1496.7, 1452.3, 1355.9, 1274.7, 1174.6, 1093.6, 1072.3, 1026.1, 1004.8, 939.0, 846.7, 734.8, 696.3 cm⁻¹ [α]D² = +188.4 (c = 1.00, CHCl₃). MS (ESI): m/z = 629.6 [M + Na]+. HRMS: calcld. for C₄₃H₈₀O₂Na 629.2879, found 629.2872.

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Compound 13:

Chromatography: petroleum/EtOAc, 2:1 v/v.

**HRMS:** calcd. for C$_{30}$H$_{32}$O$_6$H $\tilde{m}$/z 489.2277, found 489.2276.

CDCl$_3$: 3.80 (m, 2 H, H$_8$,H$_{10}$), 3.73 (m, 1 H, CH$_{arom.}$ Bn), 4.82 (d, $J_{16,10} = 6.8$ Hz, H$_{10}$), 4.81 (d, $J_{16,10} = 10.5$ Hz, H$_{11}$)$_{H_2}$, 3.57 (dd, $J_{16,11b} = 2.6$ Hz, $J_{16,11a} = 10.5$ Hz, H$_{11}$)$_{H_1}$, 2.70 (d, $J = 5.3$ Hz, 2 H, H$_2$)$_{H_2}$ ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 207.7 (C$_{1}$), 138.0 (C$_{Bn}$), 128.4, 128.1, 127.9, 127.8, 127.6 (CH$_{arom.}$ Bn), 79.1, 77.7 (C$_1$, C$_4$), 75.4, 74.1 (C$_3$, C$_6$), 74.1, 73.5, 73.2 (3 x CH$_2$ Bn), 71.1 (C$_{10}$), 69.5 (C$_{9}$), 68.2 (C$_2$), 41.6 (C$_{16}$) ppm. ATR-IR (thin film) $\tilde{\nu}$ = 2864.1, 1573.0, 1454.2, 1363.6, 1207.4, 1089.7, 1028.0, 912.3, 736.8, 696.3 cm$^{-1}$. [a]$_{D}^{28}$ = +32.2 (c = 1.00, CHCl$_3$), MS (ESI): $m$/z = 511.4 [M + Na]$^+$. HRMS: calcd. for C$_{31}$H$_{35}$O$_7$Si $\tilde{m}$/z 498.2277, found 498.2276.

(1R,4R,6R,8R,9S,10S)-9,10-Bis(benzyloxy)-8-benzyloxymethyl-2,7-dioxabicyclo[4.4.4]decane-4-yl Methanesulfonate (13): Benzylation of mesylate 13 (301 mg, 0.53 mmol) was treated according to General Procedure VI to yield the title compound (158 mg, 0.53 mmol, quantitative) as a colorless oil that solidified upon standing. $^1$H NMR (400 MHz, CD$_2$OD/CDCl$_3$): $\delta =$ 4.73 (1 H, H$_1$), 4.15 (1 H, H$_9$), 4.02 (dd, $J_{10,11} = 8.1$ Hz, 1 H, H$_{10}$)$_{H_2}$, 3.85 (dd, $J_{8,9a} = 4.3$ Hz, $J_{9a,9b} = 11.9$ Hz, 1 H, H$_{9b}$)$_{H_2}$, 3.79 (d, $J = 3.9$ Hz, 2 H, H$_{11}$)$_{H_2}$, 3.72 (dd, $J_{ax,ax} = 8.3$ Hz, $J_{ax,ax} = 11.9$ Hz, 1 H, H$_{11}$)$_{H_2}$, 3.65 (m, 1 H, H$_{11}$)$_{H_1}$, 3.59 (1 H, H$_9$)$_{H_2}$, 3.43 (dd, $J_{8,9a} = 8.1$ Hz, 1 H, H$_9$)$_{H_2}$, 3.11 (3 H, SO$_2$CH$_3$), 2.24 (2 H, H$_2$)$_{H_2}$ ppm. $^{13}$C NMR (100 MHz, CD$_2$OD/CDCl$_3$): $\delta =$ 74.5 (C$_5$), 73.2 (C$_4$), 70.0 (C$_6$), 67.3 (C$_8$), 67.0 (C$_9$), 63.2 (C$_1$), 38.0 (SO$_2$CH$_3$), 30.5 (C$_{10}$) ppm. ATR-IR (thin film) $\tilde{\nu}$ = 3332.8, 2937.4, 1346.2, 1279.2, 1176.2, 1083.9, 1003.7, 960.6, 896.8, 831.3 cm$^{-1}$. [a]$_{D}^{28}$ = +44.6 (c = 1.00, 1/1 v/v MeOH/CHCl$_3$). MS (ESI): $m$/z = 298.9 [M + H]$^+$, 320.9 [M + Na]$^+$. HRMS: calcd. for C$_{19}$H$_{22}$O$_{5}$Si $\tilde{m}$/z 316.1066, found 316.1044.

(1R,4R,6R,8R,9S,10S)-9,10-Dihydroxy-8-hydroxymethyl-2,7-dioxabicyclo[4.4.4]decane-4-yl Methanesulfonate (16): Benzylation of mesylate 14 (191 mg, 0.34 mmol) was treated according to General Procedure VI to yield the title compound (101 mg, 0.34 mmol, quantitative) as a colorless oil that solidified upon standing. $^1$H NMR (400 MHz, CD$_2$OD/CDCl$_3$): $\delta =$ 4.90 (1 m, H$_9$)$_{H_2}$, 3.19 (3 H, SO$_2$CH$_3$), 2.27 (1 H, H$_5$), 1.91 (1 H, H$_{10}$)$_{H_2}$ ppm. $^{13}$C NMR (100 MHz, CD$_2$OD/CDCl$_3$): $\delta =$ 77.2 (C$_7$), 77.0 (C$_6$), 71.3 (C$_3$), 69.3 (C$_5$), 66.8 (C$_2$), 65.5 (C$_8$), 38.4 (SO$_2$CH$_3$), 31.4 (C$_{10}$) ppm. ATR-IR (thin film) $\tilde{\nu}$ = 3271.0, 2933.5, 1326.9, 1234.4, 1170.7, 1083.9, 1029.9, 933.5, 894.2, 875.6, 813.9, 771.5 cm$^{-1}$. [a]$_{D}^{28}$ = +22.0 (c = 1.00, 1/1 v/v MeOH/CHCl$_3$). MS (ESI): $m$/z = 298.9 [M + H]$^+$, 320.9 [M + Na]$^+$. HRMS: calcd. for C$_{19}$H$_{22}$O$_{5}$Si $\tilde{m}$/z 316.1066, found 316.1087.

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The title compound (4.57 g, 7.5 mmol, 72%). Silica gel chromatography: petroleum to petrolatum/ElOAc v/v, 19:1. 1H NMR (400 MHz, CDCl3): δ = 7.47–7.13 (m, 20 H, H arom). 6.80–6.77 (d, J = 11.6 Hz, 1 H, =CH–C)), 5.75–5.70 (dd, J = 11.6 Hz, J = 9.2 Hz, 1 H, =CH–Ph), 5.02–5.00 (d, J = 10.8 Hz, 1 H, CH3–Bn), 4.84–4.83 (d, J = 3.9 Hz, 1 H, CH3–Bn), 4.81–4.80 (d, J = 3.9 Hz, 1 H, CH3–Bn), 4.60–4.57 (d, J = 12.5 Hz, 1 H, CH3–Bn), 4.54–4.51 (d, J = 10.8 Hz, 1 H, CH3–Bn), 4.50–4.47 (d, J = 12.5 Hz, 1 H, CH3–Bn), 4.23–4.18 (dd, Jd, =CH–C═ = 9.2 Hz, 1 H, =CH), 4.18 (2 s, 2 CH3–C═), 4.15–4.14 (dd, J = 2.2 Hz, 1 H, =CH3), 4.01–4.00 (dd, J = 2.2 Hz, 1 H, =CH3), 3.71–3.64 (m, 4 H, H3, H4, H5, H6), 3.45 (3 H, OMe), 3.50–3.39 (m, 2 H, H3, H2) ppm. 13C NMR (100 MHz, CDCl3): δ = 160.1 (=COO Me), 138.8, 132.8, 131.4 (C3 Bn), 136.2 (C2 Ph), 134.6 (C–C═), 129.0–127.6 (CH3–CH–Ph), 126.4 (C3 Bn), 123.5 (C2 Ph), 121.5 (1 H, =CH–Ph), 119.8 (2 H, OCH), 116.3, 107.5 (2 H, C–CH2), 83.3, 82.8, 82.5, 78.3, 78.0 (C4), 75.4, 74.8 (2 × CH3–Bn), 74.8 (C11) ppm. HRMS (APR– thin film): ν = 1496.7, 1452.3, 1361.7, 1257.5, 1074.6, 1056.9, 1028.0, 1001.0, 950.8, 910.3, 810.0, 775.3, 732.9, 694.3, 650.0, 619.1 ppm. δ3 = +73.6 (c = 1.00, CHCl3). HRMS: calcd. For C38H40O7Na, 624.33251, found 624.33369.

β-d-Glucopyranosyl Derivative 22: Compound 21 (6.34 g, 10.4 mmol) was treated according to General Procedure II to yield the title compound (4.57 g, 7.5 mmol, 72%). Silica gel chromatography: petroleum to petrolatum/ElOAc v/v, 19:1. 1H NMR (400 MHz, CDCl3): δ = 7.47–7.13 (m, 20 H, H arom). 6.80–6.77 (d, J = 11.6 Hz, 1 H, =CH–C)), 5.75–5.70 (dd, J = 11.6 Hz, J = 9.2 Hz, 1 H, =CH–Ph), 5.02–5.00 (d, J = 10.8 Hz, 1 H, CH3–Bn), 4.84–4.83 (d, J = 3.9 Hz, 1 H, CH3–Bn), 4.81–4.80 (d, J = 3.9 Hz, 1 H, CH3–Bn), 4.60–4.57 (d, J = 12.5 Hz, 1 H, CH3–Bn), 4.54–4.51 (d, J = 10.8 Hz, 1 H, CH3–Bn), 4.50–4.47 (d, J = 12.5 Hz, 1 H, CH3–Bn), 4.23–4.18 (dd, Jd, =CH–C═ = 9.2 Hz, 1 H, =CH), 4.18 (2 s, 2 CH3–C═), 4.15–4.14 (dd, J = 2.2 Hz, 1 H, =CH3), 4.01–4.00 (dd, J = 2.2 Hz, 1 H, =CH3), 3.71–3.64 (m, 4 H, H3, H4, H5, H6), 3.45 (3 H, OMe), 3.50–3.39 (m, 2 H, H3, H2) ppm. 13C NMR (100 MHz, CDCl3): δ = 160.1 (=COO Me), 138.8, 132.8, 131.4 (C3 Bn), 136.2 (C2 Ph), 134.6 (C–C═), 129.0–127.6 (CH3–CH–Ph), 126.4 (C3 Bn), 123.5 (C2 Ph), 121.5 (1 H, =CH–Ph), 119.8 (2 H, OCH), 116.3, 107.5 (2 H, C–CH2), 83.3, 82.8, 82.5, 78.3, 78.0 (C4), 75.4, 74.8 (2 × CH3–Bn), 74.8 (C11) ppm. HRMS (APR– thin film): ν = 1496.7, 1452.3, 1361.7, 1257.5, 1074.6, 1056.9, 1028.0, 1001.0, 950.8, 910.3, 810.0, 775.3, 732.9, 694.3, 650.0, 619.1 ppm. δ3 = +73.6 (c = 1.00, CHCl3). HRMS: calcd. For C38H40O7Na, 624.33251, found 624.33369.
dioxa-bicyclo[4.4.0]decan-4-yl Methanesulfonate (27):

1H NMR (400 MHz, CDCl3): (1.18 g, 2.1 mmol) was treated according to General Procedure VI

\[ \delta = 7.35-7.13 (m, 15 H, CH), 4.99-4.75 (q, d, 1 J = 11.2 Hz, 1 H), CH(Bn), 4.86-4.84 (d, J = 10.7 Hz, 1 H, CH(Bn)), 4.78-4.75 (d, J = 10.7 Hz, 1 H, CH(Bn)), 4.61-4.58 (d, J = 12.2 Hz, 1 H, CH(Bn)), 4.50-4.47 (d, J = 11.2 Hz, 1 H, CH(Bn)), 4.53-4.50 (d, J = 12.2 Hz, 1 H, CH(Bn)), 4.20-4.16 (dd, J = 13.3 Hz, H 1, CH 2Bn), 4.53-4.50 (d, J = 12.2 Hz, 1 H, CH(Bn)), 4.20-4.16 (dd, J = 13.3 Hz, H 1, CH 2Bn), 4.18-4.15 (dd, J = 13.3 Hz, H 2, CH 2Bn), 4.18-4.15 (dd, J = 13.3 Hz, H 2, CH 2Bn), 1.00 (s, 9 H, Me(4)), 0.91 (s, 6 H, Me(3)), 0.80 (d, J = 6.6 Hz, 1 H, H 4, CH 2Bn), 0.80 (d, J = 6.6 Hz, 1 H, H 4, CH 2Bn), 0.74 (s, 3 H, Me(2)), 0.72-0.66 (m, 2 H, Me(1a), Me(1b)), 0.66-0.63 (m, 2 H, Me(1a), Me(1b)), 0.51-0.46 (m, 1 H, H 2, CH 2Bn), 0.43-0.39 (m, 1 H, H 2, CH 2Bn), 0.34-0.29 (m, 1 H, H 2, CH 2Bn), 0.28-0.23 (m, 1 H, H 2, CH 2Bn), 0.18-0.12 (m, 2 H, Me(1a), Me(1b)), 0.12-0.07 (m, 2 H, Me(1a), Me(1b)), 0.05-0.01 (s, 3 H, Me(2)), 0.01 (s, 3 H, Me(2)), 0.01 (s, 3 H, Me(2)).

13C NMR (100 MHz, CDCl3): [D6]DMSO (10 %): \[ \delta = 82.4 (C 1), 82.1 (C 2), 79.4 (C 3), 77.4 (C 4), 75.2, 75.0, 73.6 (3 C, CH 3), 73.6 (3 C, CH 3), 73.0 (C 7), 66.0 (C 8), 66.8 (C 9), 38.6 (OMs), 36.0 (Cp) ppm.

ATR-IR (thin film): \[ \nu = 3886, 3884, 2942, 2857, 2785, 2081, 1736, 1459, 1278, 1226, 1103.6, 1036.1, 970.5, 903.4, 938.4, 920.4, 897.3, 842.6, 804.9, 794.0, 702.2 cm\(^{-1}\).

HRMS: c13H23O2NaS m/z = 270.1442 [M + Na\(^+\)]\textsuperscript{*}. Calculated for C13H23O2NaS: 270.1443 [M + Na\(^+\)]\textsuperscript{*}.

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The Synthesis of *cis*- and *trans*-Fused Bicyclic Sugar Amino Acids

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J_{6,5ax} = 11.6 Hz, J_{6,5a} = 9.2 Hz, J_{5,6eq} = 4.5 Hz, 1 H, H^{5a}) 3.22–3.21 (m, 2 H, H^5H^6), 2.83–2.78 (dd, J_{5,6} = 9.2 Hz, J_{1,9} = 9.1 Hz, 1 H, H^10), 2.15–2.11 (m, J_{5,8,9,10} = 13.4 Hz, J_{5,6eq} = 4.5 Hz, J_{5,6ax} = 2.4 Hz, J_{5,6ax} = 2.5 Hz, 1 H, H^{5eq}), 1.70–1.63 (dd, J_{6,5ax} = 13.4 Hz, J_{6,5eq} = 11.6 Hz, 1 H, H^{5ax}) ppm. 13C NMR (100 MHz, CD2OD): δ = 82.9 (C1), 81.2 (CH3), 76.7 (C8), 72.2 (OCH2), 72.1 (C9), 67.9 (C7), 62.9 (C5), 58.5 (C4), 34.0 (C5) ppm. ATR-IR (thin film): ν = 3369.0, 2926.0, 2870.0, 2095.7, 1746.6, 1446.5, 1312.5, 1283.7, 1329.7, 1174.9, 1128.9, 1036.5, 995.7, 961.9, 948.6, 888.3, 843.9 cm⁻¹; [α]D = +1.6 (c = 1.00, MeOH). MS (ESI): m/z = 268.0 [M + Na]+, 284.0 [M + K]+, 513.2 [M – M + Na]+, 529.1 [M – M + K]+. HRMS: calcld. for C_{9}H_{13}N_{3}O_{5}Na, 263.13854, found 263.13895.

(1R,4R,6S,8S,9S,10S)-4-Azido-9,10-dihydroxy-2,7-diazabicyclo[4.4.0]decane-8-carboxylic Acid (3): Compound 30 (85 mg, 0.35 mmol) was treated according to General Procedure VIII to yield the title compound (65 mg, 0.25 mmol, 72%) as an oil. 1H NMR (CDCl₃): δ = 4.13–4.01 (dd, J_{5,6ax} = 11.9 Hz, J_{5,6eq} = 5.1 Hz, J_{5,6eq} = 1.7 Hz, 1 H, H^{5eq}), 3.80–3.71 (m, 1 H, H^2), 3.78–3.76 (d, J_{1,6} = 9.6 Hz, 1 H, H^1), 3.63–3.58 (dd, J_{5,10} = 9.2 Hz, 1 H, H^10), 3.55–3.50 (dd, J_{9,10} = 9.6 Hz, J_{9,10} = 9.2 Hz, 1 H, H^10), 3.45–3.40 (dd, J_{9,10} = 11.6 Hz, J_{9,10} = 9.3 Hz, J_{9,10} = 4.3 Hz, 1 H, H^10), 3.35–3.29 (dd, J_{9,10} = 11.1 Hz, 1 H, H^10), 3.11–3.07 (dd, J_{1,6} = 9.3 Hz, J_{1,9} = 9.2 Hz, 1 H, H^1), 3.10–3.03 (dd, J_{1,6} = 9.1 Hz, J_{1,9} = 9.2 Hz, 1 H, H^1), 2.80–2.75 (m, J_{1,6} = 9.4 Hz, J_{1,6} = 9.4 Hz, J_{1,6} = 9.1 Hz, H^6), 1.65–1.57 (dd, J_{5,6eq} = 11.6 Hz, J_{5,6eq} = 4.3 Hz, 1 H, H^5eq) ppm. 13C NMR (D2O): δ = 171.1 (C1'), 81.1 (C5), 80.7 (C7), 75.3 (C9), 73.5 (C6), 67.9 (C4), 55.5 (C3), 34.7 (C2) ppm. ATR-IR (thin film): ν = 3402.9, 2914.1, 2868.8, 2105.4, 1734.1, 1604.5, 1425.4, 1346.0, 1309.4, 1246.9, 1129.0, 1088.1, 1042.9, 992.8, 967.4, 887.5. [α]D = +36 (c = 1.00, MeOH). MS (ESI): m/z = 282.1 [M + Na]+, 541.1 [M – M + Na]+. HRMS: calcld. for C_{9}H_{13}N_{3}O_{5}Na, 282.07020, found 282.06943.

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During the reaction a considerable amount of trans-cyclopropane-1,2,3-tricarboxylic acid trimethylester was formed. This side product could be removed by means of size exclusion chromatography (Sephadex LH-20).