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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 a α-acetylenic-C-glucoside 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.

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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. Ensuing 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[12] 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[4b].

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[13]

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

Scheme 1. Reagents and conditions: i) (a) dimethyldioxirane, acetone. (b) phenylacetylene, nBuLi, ZnCl2, THF, −70 °C to room temp[6] ii) H2, Lindlar’s catalyst, EtOAc.[9] iii) methyl bromoacetate, TBAI, NaH, DMF, 95%. iv) Cp2TiMe2, THF, 60 °C, 82%. v) dichlorido(1,3-dimesityl-2-imidazolidinylidene)(phenylmethylene)(tricyclohexylphosphane)ruthenium, CH2Cl2, reflux, 88%. vi) TFA, water, CH2Cl2, 92%. vii) L-selectride, THF, −78 °C to room temp., (endo/exo = 2:1). viii) MsCl, Et3N, CH2Cl2, 0 °C, 13 40%, 14 25%, two steps. ix) H2, Pd/C, EtOH, 15 quant., 16 quant. x) NaN3, DMF, 70 °C, 17 90%, 18 94%. xi) TEMPO, NaOCl, NaHCO3, MeCN, 0 °C, 1 53%, 2 52%.
The Synthesis of cis- and trans-Fused Bicyclic Sugar Amino Acids

Scheme 2. Reagents and conditions: i) (a) Co(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 %. vii) TF₂A, water, CH₂Cl₂, 90 %. viii) -selectride, THF, –78 °C to room temp. ix) MsCl, Et₃N, CH₂Cl₂, 0 °C, 26 36 %, 27 43 %, two steps, x) H₂, Pd/C, EtOH, 28 quant, 29 95 %. xi) NaN₃, DMF, 70 °C, 30 70 %, 31 74 %. x) 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, HOBT, and DIPEA as the condensation agents gave immobilized dipeptide 33. 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)₄·2H₂O (10 g/L) in H₂SO₄ (10 %) followed by charring at 150 °C. Column chromatography was performed on Merck silica gel (0.040–0.063 mm), and size exclusion chromatography was performed on Sephadex LH-20. Mass spectra were recorded with a PE/Sciex 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 24% (based on 32).

or CDCl$_3$ (13C NMR). Coupling constants are given in Hz. All presented 13C-APT spectra are proton decoupled. The atomic numbering of bicyclic compounds was performed as described in Figure 1. Optical rotations were measured with a Propol automatic polarimeter (Sodium D line, $\lambda$ = 589 nm) and attenuated total reflectance IR (ATR-IR) spectra were recorded with a Shimadzu FTIR-8300 spectrometer fitted with a single bounce DuraspampIR diamond crystal ATR-element. RP-HPLC was performed with a Gilson preparative HPLC system and a Phenomenex Gemini C18 column (150 × 21.2 mm).

**General Procedure I: Alkylation of Carbohydrate Alcohols with Methyl Bromoacetate**: To an anhydrous solution of the alcohol in DMF (0.1 M) were added methyl bromoacetate (3.0 equiv.) and tetrabutylammonium iodide (0.1 equiv.). After stirring for 5 min, sodium hydride (5.0 equiv.) was added in portions over a period of 4 h. Stirring was continued until TLC analysis showed no further progress of the reaction (16 h), and the mixture was partitioned between sat. aq. NH$_4$Cl and diethyl ether. The organic phase was washed with saturated aq. NaHCO$_3$ and brine, dried with MgSO$_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate in light petroleum.

**General Procedure II: Conversion of Esters into Enol Ethers Using Petasis Reagent**: Cp$_2$TiMe$_2$ (1.5 equiv.) was added to a solution of the methyl ester in THF (0.15 M). The mixture was heated at reflux for 48 h with the exclusion of light. The reaction mixture was cooled to –78 °C before adding a solution of l-selectride in THF (1.0 M, 2.0 equiv.) over the period of 1 h. The solution was warmed...
to ambient temperature, and stirring was continued for 16 h. The mixture was then quenched with saturated aq. NH₄Cl 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 CH₂Cl₂ (0.15 mL) was made after thorough coevaporation with 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) there was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred under a constant stream of H₂ (10 psi) for 2 h, filtered, and concentrated to give the protected product.

**General Procedure VII: Substitution of Methanesulfonyl Esters Using Sodium Azide:** The mesylate was coevaporated twice with dry CH₂Cl₂, and extracted with saturated aq. NaHCO₃, aq. NaOCl (15% w/w), and saturated aq. NaCl (5:8:9 v/v/v). Solution A: KBr in saturated aq. NaHCO₃ (5.0 mg/mL). Solution B: 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) in CH₂Bn, and NaHCO₃, aq. NaOCl (15% w/w), and saturated aq. NaCl (5:8:9 v/v/v). Solution C was a mixture of saturated aq. NaHCO₃, aq. NaOCl (15% w/v), and saturated aq. NaCl (5:8:9 v/v/v).

To a solution of the alcohol in saturated aq. NaHCO₃ (0.07 mL) there were added solution A and B (2.6 mL/mL each). The solution 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. Removal of residual salts by HW-40 column chromatography yielded the acid.

**α-δ-Glucopyranosyl Derivative 9:** Methyl ester 8 (2.31 g, 3.8 mmol) was treated according to General Procedure II to yield the title compound (1.89 g, 3.12 mmol, 82%) as a colorless oil. Silica gel chromatography: petroleum → EtOAc/w/v, 19:1. 1H NMR (400 MHz, CDCl₃): δ: 7.53–7.14 (m, 20 H, CH arom. Bn, Ph), 8.66 (d, J = 11.8 Hz, 1 H, Ph-CH), 6.06 (dd, J = 11.8, 11.8 Hz, 1 H, =CH-CH₃), 5.00 (d, J = 10.8 Hz, 1 H, CH₂Bn), 4.86 (m, 1 H, H₃), 4.83 (d, J = 10.8 Hz, 1 H, CH₂Bn), 4.63 (d, J = 12.1 Hz, 1 H, CH₂Bn), 4.50 (d, J = 10.8 Hz, 1 H, CH₂Bn), 4.44 (d, J = 12.1 Hz, 1 H, CH₂Bn), 4.07 (m, 1 H, =CH-), 4.01 (d, J = 12.5 Hz, 1 H, OCH₂C=), 3.96–3.76 (m, 3 H, H₂OCH₂C=, =CH₂), 3.79 (m, 1 H, H₃), 3.75 (m, 1 H, H̄), 3.69 (m, 2 H, H⁺OCH₂), 3.50 (dd, J = 3.5 Hz, J = 12.3 Hz, 1 H, H₂OCH₂C=, =CH₂), 3.30 (s, 3 H, OMe), 3.20 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 3.14 (s, 3 H, OMe), ppm. 13C NMR (100 MHz, CDCl₃): δ: 127.6 (CH arom. Bn, Ph), 124.4 (=CH-CH₃), 135.9 (C q Ph), 129.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.5 (CH₃CHₐrom, Ph), 128.5 (=CH-CH₃), 84.0 (=CH₂), 82.7 (C₃), 80.4 (C₄), 78.1 (C₅), 75.0, 73.3 (3 × CH₂Bn), 72.2 (C₂), 71.5 (OCH₂OCH₂), 69.7 (C⁺), 68.8 (C⁺), 54.6 (OCH₃) ppm. ATR-IR (thin film): ν = 3001, 2929, 1507, 1456, 1447, 1425, 1397, 1379, 1357, 1299, 1257, 1153, 1074, 1043, 1028, 810.0, 732.9, 694.3 cm⁻¹. [α]D²⁰ = +188.4 (c = 1.00, CHCl₃). MS (ESI): m/z = 629.6 [M + Na⁺]. HRMS: calcd. for C₃₉H₄₂O₆Na 629.2879, found 629.2872.

**α,β-Disubstituted Bicyclic Sugar Amino Acids**


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**FULL PAPER**

The Synthesis of *cis* and *trans*-Fused Bicyclic Sugar Amino Acids
(1R,4R,S,8R,9S,10S)-9,10-Bis(benzyloxy)-8-benzylxymethyl-2,7-dioxabicyclo[4.4.0]decane-4-yl Methanesulfonate (13): Benzylated 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. 1H NMR (400 MHz, CD3OD/CDCl3): δ = 7.43 (1 H, H6), 4.15 (1 H, H6), 4.02 (dd, J9,10 = 8.1 Hz, 1 H, H9), 3.85 (dd, J8,9a = 4.3 Hz, J8,9b = 11.9 Hz, 1 H, H8eq), 3.79 (J9,10 = 3.9 Hz, 2 H, H10), 3.72 (J9a,9b = 8.3 Hz, J9b,9eq = 11.9 Hz, 1 H, H9), 3.65 (3 H, H1, H9, H10), 3.59 (1 H, H1), 3.43 (dd, J8b,8a = 8.1 Hz, 1 H, H8), 3.11 (3 H, SO2CH3), 2.25 (2 H, H2, H4), 2.03 (1 H, CH2), 1.70 (1 H, CH2), 1.19 (1 H, CH2), 1.09 (1 H, CH2), 0.98 (1 H, CH2), 0.95 (1 H, CH2), 0.84 (1 H, CH2), 0.73 (1 H, CH2), 0.69 (1 H, CH2), 0.62 (1 H, CH2), 0.57 (1 H, CH2), 0.55 (1 H, CH2). HRMS: calcd for C30H32O6SNa 489.2277, found 489.2276.

Compound (0.17 mmol) was treated according to General Procedure VIII to yield the title compound (23 mg, 0.09 mmol, 53%) as an oil. 1H NMR (400 MHz, D2O): δ = 4.49 (m, 1 H, H1), 4.09 (d, J9,9 = 5.3 Hz, 1 H, H10), 4.05 (dd, J9,9 = 5.3 Hz, J10,10 = 5.9 Hz, 1 H, H10), 4.02 (m, 2 H, H3ax, H3eq), 3.89 (dd, J9,9 = 5.3 Hz, J10,10 = 5.9 Hz, 1 H, H10), 3.65 (dd, J9,9 = 3.5 Hz, J10,10 = 5.9 Hz, 1 H, H10), 3.45 (dd, J9,9 = 17.3 Hz, J9,10 = 7.5 Hz, J9,10 = 12.4 Hz, 1 H, H6), 2.37 (m, 1 H, H5eq), 1.86 (m, 1 H, H5eq) ppm. 13C NMR (100 MHz, D2O): δ = 57.8 (C5), 76.8 (C52) (70.9 Hz, C52), 67.0 (C60), 66.7 (C60), 54.9 (C50), 30.7 (C50) ppm. ATR-IR (thin film): v = 3398.1, 2920.0, 2120.1, 1605.6, 1545.5, 1385.0, 1315.5, 1247.7, 1096.9, 1076.7, 1062.2, 1001.4, 947.8, 923.1, 789.1, 811.4 cm⁻¹. [α]D = +39.0 (c = 1.00, CHCl3) MS (ESI): m/z = 260.0 [M+H]+, 282.1 [M+Na]+, 541.1 [2M+Na]+. HRMS: calcd. for C35H24O6Na2 282.07020, found 282.06943.

β-d-Glucopyranosyl Derivative 21: 2'-3'4',6'-Tri-O-benzyl-β-d-glucopyranosyl)-Y-stereone (20b) (64.0 g, 11.9 mmol) was treated according to General Procedure I to yield the title compound (63.4 g, 10.4 mmol, 87%) as a colorless oil. Silica gel chromatography: petroleum/ether/EtOAc, 1:1 v/v H NMR (400 MHz, CDCl3): δ = 7.33–7.13 (m, 20 H, HPhom), 6.83–6.80 (d, J = 11.6 Hz, 1 H, PhCH3), 5.79–5.74 (d, J = 11.6 Hz, 1 H, 1H, PhCH3), 4.96–4.93(d, J = 11.1 Hz, 1 H, CH2N), 4.89–4.86 (d, J = 11.1 Hz, 1 H, CH2N), 4.82–4.79 (d, J = 11.0 Hz, 1 H, CH2N), 4.63–4.59 (d, J = 12.1 Hz, 1 H, CH2N), 4.55–4.52 (d, J = 11.0 Hz, 1 H, CH2N), 4.52–4.49 (d, J = 12.1 Hz, 1 H, CH2N), 4.43–4.38 (d, J = 15.6 Hz, 1 H, CH2C=O), 4.31–4.27 (d, J = 15.6 Hz, 1 H, CH2C=O), 4.22 (d, J9,10 = 9.3 Hz, J9,10 = 9.1 Hz, 1 H, H3eq), 3.73–3.65 (m, 2 H, OCH, 2 H, H1eq), 3.64 (s, 3 H, OMe), 3.45 (m, J9,10 = 9.3 Hz, 1 H, OCH3, t, J9,9 = 8.9 Hz, 1 H, H3eq) ppm. 13C NMR (100 MHz, CDCl3): δ = 177.4 (C=O), 152.2 (53.0 Hz, C32), 128.7 (C60), 126.2 (C60), 125.5 (C60), 125.7 (C60), 68.6 (C60), 66.7 (C60), 66.7 (C60), ppm. ATR-IR (thin film): v = 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 [α]D = +68.0 (c = 1.00, CHCl3). MS (ESI): m/z = 260.0 [M+H]+, 282.1 [M+Na]+.

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/ether/EtOAc v/v/v, 19:1. 1H NMR (400 MHz, CDC13): δ = 7.47–7.13 (m, 20 H, HPhom), 6.80–6.77 (d, J = 11.6 Hz, 1 H, =CH–C₅), 5.75–5.70 (dd, J = 11.6 Hz, J = 9.2 Hz, 1 H, =CH–C₅), 5.02–5.00 (d, J = 10.8 Hz, 1 H, CH3Bn), 4.84–4.83 (d, J = 3.9 Hz, 1 H, CH3Bn), 4.81–4.80 (d, J = 3.9 Hz, 1 H, CH3Bn), 4.60–4.57 (d, J = 12.5 Hz, 1 H, CH3Bn), 4.54–4.51 (d, J = 10.8 Hz, 1 H, CH3Bn), 4.50–4.47 (d, J = 12.5 Hz, 1 H, CH3Bn), 4.23–4.18 (dd, J9,10 = 9.2 Hz, J9,10 = 9.2 Hz, 1 H, CH3Bn), 4.15–4.14 (dd, J = 2.2 Hz, 1 H, =CH–C₅), 4.01–4.00 (dd, J = 2.2 Hz, 1 H, =CH–C₅), 3.71–3.64 (m, 4 H, H3, H5, H8), 3.45 (s, 3 H, OMe), 3.50–3.39 (m, 2 H, H2), ppm. 13C NMR (100 MHz, CDCl3): δ = 160.1 (=C(OMe)), 138.8, 133.2, 131.8 (C3Bn), 132.6 (C3Bn), 134. (=C(–CH3)), 129.0–127.3 (C=CH =CH–Ph), 86.4 (C4), 83.8 (=CH3), 82.8 (C2), 78.3, 78.0 (C4, C5), 75.4, 74.8 (2×CH3Bn), 74.8 (C4), 73.4 (CH3Bn), 73.1 (C4), 69.1 (C9) 54.6 (C6) ppm. ATR-IR (thin film): v = 1496.7, 1452.3, 1373.1, 1389.9, 1237.3, 1104.1, 1098.2, 1001.0, 930.6, 901.3, 810.0, 753.5, 735.2, 692.3, 650.0, 619.1 cm⁻¹. [α]D = +73.6 (c = 1.00, CHCl3). HRMS: calcd. For C34H36O4N6a 624.33251, found 624.33369.

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Compound 27 (1.82 g, 2.1 mmol) was treated according to General Procedure VI to yield the title compound (0.68 g, 2.31 mmol, 95%) as a transparent oil. 1H NMR [400 MHz, CDCl3/D2O (9:1 v/v)] δ 7.35–7.11 (m, 15 H, H arom), 4.93–4.91 (d, J = 11.3 Hz, 1 H, CH3Bn), 4.86–4.83 (d, J = 10.6 Hz, 1 H, CH3Bn), 4.72–4.65 (m, 1 H, H6), 4.61–4.58 (d, J = 12.2 Hz, 1 H, CH3Bn), 4.53–4.50 (d, J = 12.2 Hz, 1 H, CH3Bn), 4.49–4.47 (d, J = 10.6 Hz, 1 H, CH3Bn), 4.24–4.20 (dd, Jax,ax = 10.8 Hz, Jax,ax = 5.3 Hz, Jax,ax = 1.7 Hz, 1 H, H10eq), 3.77–3.57 (m, 4 H, H3, H4, H9, H10), 3.49–3.44 (m, 1 H, H8), 3.35–3.29 (t, Jax,ax = 10.8 Hz, 1 H, H10eq), 3.21–3.09 (dd, 1 H, H7, 1 H, H8), 3.03 (s, 3 H, OMs), 2.66–2.63 (m, Jax,ax = 11.2 Hz, Jax,ax = 4.3 Hz, Jax,ax = 1.7 Hz, 1 H, H8eq), 1.80–1.77 (dd, Jax,ax = 11.2 Hz, Jax,ax = 5.3 Hz, Jax,ax = 11.2 Hz, 1 H, H8eq) ppm. 13C NMR (100 MHz, CDCl3): δ = 138.6, 138.0, 137.9 (C19, 129–127.6 (C8, Bn), 83.7 (C9(C10)), 82.1 (C8), 79.4 (C7), 77.4 (C7(C8)), 75.2, 75.0, 73.6 (3 × CH3 Bn), 73.1 (C6) 72.6(C6), 69.0 (C7), 68.8 (C6), 38.6 (OMs), 36.0 (C6) ppm. ATR-IR (thin film): ν = 3357.8, 3267.2, 2924.8, 2857.5, 2008.1, 1736.0, 1549.1, 1379.3, 1311.0, 1242.6, 1125.7, 1036.1, 965.2, 904.0, 873.8 cm⁻¹, [α]D29 +8.2 (c = 1.00, CHCl3). C: calcd. for C31H32O8SNa: 591.2023, found 591.1977.

(1R,4S,6S,8R,9S,10S)-9,10-Dihydroxy-8-hydroxymethyl-2,7-dioxabicyclo[4.4.0]decano-4-yl Methanesulfonate (28): Compound 27 (1.18 g, 2.1 mmol) was treated according to General Procedure VI to yield the title compound (0.63 g, 2.1 mmol, quantitative) as a colorless oil. 1H NMR (400 MHz, CDCl3): δ = 4.91 (m, 1 H, H5), 4.06–4.03 (dd, Jax,ax = 13.3 Hz, Jax,ax = 2.3 Hz, 1 H, H10), 3.79–3.76 (dd, 1 H, H8eq), 3.60–3.57 (m, 2 H, H11b, H11c), 3.48–3.39 (t, Jax,ax = 9.1 Hz, 1 H, H4), dd, Jax,ax = 11.9 Hz, Jax,ax = 9.1 Hz, Jax,ax = 9.1 Hz, Jax,ax = 1.8 Hz, Jax,ax = 2.5 Hz, 1 H, H10eq), 3.82 (m, 1 H, H4), 3.76–3.73 (dd, 1 H, H11b), 3.56–3.52 (m, 1 H, H11b), 3.52–3.40 (dd, Jax,ax = 12.6 Hz, Jax,ax = 1.8 Hz, Jax,ax = 1.8 Hz, H10eq), 3.38–3.36 (dd, Jax,ax = 9.1 Hz, Jax,ax = 9.1 Hz, H10eq). HRMS: calcd. for C31H28O10SNa: 529.2 [M + Na+] ppm. C: calcd. for C31H28O10SNa: 529.2 529.2 [M + Na+] ppm. C: calcd. for C31H28O10SNa: 529.2 [M + Na+] ppm. C: calcd. for C31H28O10SNa: 529.2 [M + Na+] ppm.
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\[ J_{\text{H},\text{Sax}} = 11.6 \text{ Hz}, J_{\text{H},\text{Sax}} = 9.2 \text{ Hz}, J_{\text{H},\text{Sax}} = 4.5 \text{ Hz}, 1 \text{ H, H}^\text{\text{19}} \text{H}], 3.22–3.21 (m, 2 \text{ H, H}^\text{\text{19}} \text{H}], 2.83–2.78 (dd, J_{\text{H},\text{Sax}} = 9.2 \text{ Hz}, J_{\text{H},\text{Sax}} = 9.1 \text{ Hz, 1 H, H}^\text{\text{19}} \text{H}], 2.15–2.11 (m, J_{\text{Sax},\text{Sax}} = 13.4 \text{ Hz}, J_{\text{Sax},\text{Sax}} = 4.5 \text{ Hz}, J_{\text{Sax},\text{Sax}} = 2.4 \text{ Hz}, J_{\text{Sax},\text{Sax}} = 2.5 \text{ Hz, 1 H, H}^\text{\text{19}} \text{H}], 1.70–1.63 (dd, J_{\text{Sax},\text{Sax}} = 13.4 \text{ Hz}, J_{\text{Sax},\text{Sax}} = 11.6 \text{ Hz, 1 H, H}^\text{\text{19}} \text{H}], ppm).

\[ ^{13}C \text{NMR (100 MHz, CD}_{2}\text{OD): } \delta = 82.9 (C^1 \text{S}, 81.5, 80.7 (C^\text{\text{19}} \text{H}], 75.3 (C^\text{\text{20}} \text{H}], 73.5(C^\text{\text{21}} \text{H}], 69.9(C^\text{\text{22}} \text{H}], 55.5(C^\text{\text{23}} \text{H}], 34.7(C^\text{\text{24}} \text{H}], ppm.)

ATR-IR (thin film): \nu = 3490.2, 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, 986.7, 978.8 ppm. [\text{ESI: } m/z = 282 (M+Na)^\text{+}, 541 (M+M+Na)^\text{+}].

HRMS: calculated for C_{93}H_{19}N_{19}O_{19}Na_2 282.07020, found 282.06943.

\[ ^{13}C \text{NMR (CDCl3): } \delta = 177.1 (C^\text{\text{11}} \text{C}], 81.1 (C^\text{\text{16}} \text{C}], 80.7 (C^\text{\text{13}} \text{C}], 75.3 (C^\text{\text{17}} \text{C}], 73.5 (C^\text{\text{19}} \text{C}], 69.9 (C^\text{\text{22}} \text{C}], 55.5 (C^\text{\text{23}} \text{C}], 34.7 (C^\text{\text{24}} \text{C}], ppm.)

ATR-IR (thin film): \nu = 3490.2, 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, 986.7, 978.8 ppm. [\text{ESI: } m/z = 282 (M+Na)^\text{+}, 541 (M+M+Na)^\text{+}].

HRMS: calculated for C_{93}H_{19}N_{19}O_{19}Na_2 282.07020, found 282.06943.

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[7] 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).


[11] The rate of substitution of the mesylates was greatly enhanced upon addition of 15-Crown-5, which is also known as 1,4,7,10,13-pentaoxacyclopentadecane.


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