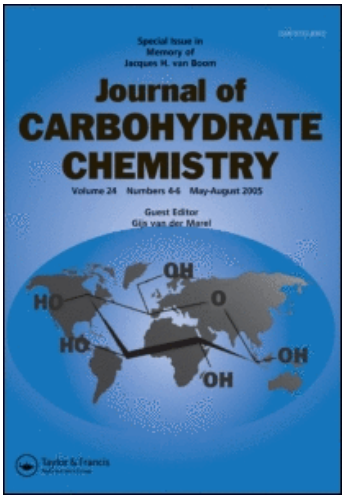

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Synthesis of Highly Functionalized Piperidines via a Tandem Retro-Michael-[2+3]-Cycloaddition

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ABSTRACT

The highly functionalized piperidine **5a** was synthesized in only 4 steps starting from ribose using a tandem retro-Michael-[2+3]-cycloaddition process as the key transformation. The versatility of the tandem retro-Michael-[2+3]-cycloaddition was demonstrated by the synthesis of novel piperidines **5b**, **5c**, **11** and **16**.

Tandem reactions have been frequently used in the construction of natural products and their derivatives.[1–5] Tandem processes involving cycloadditions as a key step have often been used *en route* to cyclic compounds. In this respect, the tandem Wittig-[2+3]-cycloaddition reaction of 5-deoxy-5-azidosugars forms an attractive route towards highly functionalized piperidines.[6–9] For instance, Herdeis and co-workers showed that piperidine **5a** (Scheme 1, R = CO_2Et), a useful intermediate for the construction of glycosidase inhibitors,[10–14] is readily available from the carbohydrate derived azide **1**.[6] This tandem process is thought to proceed through the initially

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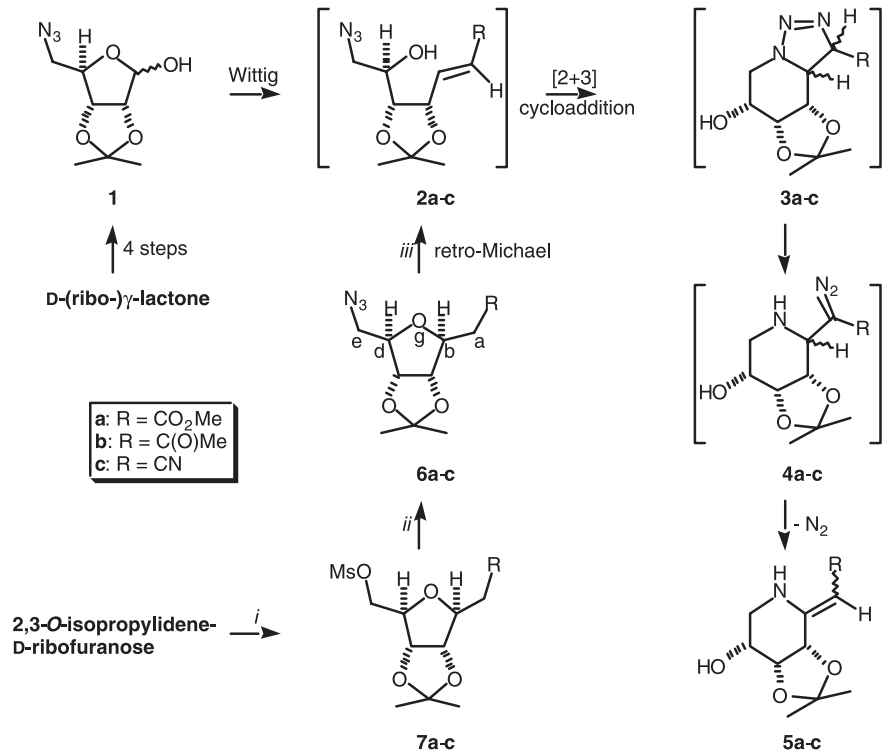

Scheme 1. Reagents and conditions: *i*. a. $Ph_3P=CHR$, CH_3CN. b. MsCl, pyridine. *ii*. NaN_3, DMF. *iii*. NaOMe (0.3 equiv), DMF, Δ.

formed Wittig intermediate **2a** followed by a [2 + 3] cycloaddition reaction of the azide and the double bond[15–19] functionalities to produce the triazole intermediate **3a**. Opening of the triazole ring through a 1,3-H shift gives rise to the observed diazo derivative **4a**, which, upon heating, further rearranges via the extrusion of nitrogen and concomitant 1,2-H shift to the enamine **5a** (R = CO_2Et).

As part of a program directed towards the construction of conformationally restricted peptide isosters[20–23] we previously synthesized fully protected ε-sugar amino acid[24] **6a** in four steps from D-ribose. Compound **6a** belongs to the class of *C*-glycosides which are known to epimerize[25] upon deprotonation at the α-position via a retro-Michael intermediate of type **2** (R = an electron withdrawing substituent, Scheme 1). As the latter intermediate can subsequently participate in a [2 + 3]-cycloaddition reaction with the azide functionality, we consequently reasoned that compound **6a** and structurally related azides may provide an alternative entrance to the construction of piperidine **5a** and derivatives. We here demonstrate the viability of this tandem retro-Michael-[2 + 3]-cycloaddition process in the transformation of both penta- and hexafuranose derivatives into highly functionalized piperidines.

To investigate the feasibility of our approach we set out to transform the readily available fully protected azido-*C*-glycoside **6a** into piperidine **5a**. Heating compound

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6a in the presence of a catalytic amount of sodium methoxide[a] followed by standard work-up of the reaction mixture and purification using silica gel column chromatography gave compound **5a** in a yield of 70% (Scheme 1). The analytical data were in full agreement with those of a conventionally prepared[6] sample of **5a**. Moreover, compound **5a** could also be obtained (60% yield) by heating mesylate **7a**, the precursor of **6a**, under reflux in DMF in the presence of NaN_3 and NaOMe, thus omitting a separate synthetic step.

Encouraged by these findings we set out to evaluate the scope of the tandem retro-Michael-[2 + 3]-cycloaddition process. Reaction of readily available 2,3-*O*-isopropylidene-D-ribofuranose with the Wittig reagents[25] $Ph_3P{=}CHCOMe$ and $Ph_3P{=}CHCN$, followed by treatment of the corresponding *C*-glycosides with methanesulfonyl chloride and pyridine, afforded compounds **7b** and **7c**, in 72% and 84% yield, respectively (Scheme 1). Subjection of **7b**,**c** to the above described reaction conditions led to the isolation of the novel piperidine derivatives **5b** and **5c** in 63% and 47% yield, respectively. Interestingly, both **5a** and **5b** were isolated as the single *Z*-isomer, whereas **5c** was formed as an inseparable mixture of *Z*- and *E* isomers (*Z*:*E* = 2:1). In the IR spectra of compounds **5a** and **b** the double bond stretch is found at 1615 and 1572 cm^{-1}, respectively, because of a hydrogen bonding interaction between N-H and the C=O. The IR-spectrum of the compound **5c** (*E* and *Z*) mixture showed two distinct C=C stretch bands, at 1623 cm^{-1} (*Z*) and 1675 cm^{-1} (*E*), presumably because of a weaker hydrogen bonding interaction between the hydrogen of the amine and the nitrogen of the nitrile[26] It is plausible that extrusion of nitrogen and concomitant 1,2-H-shift of the diazo intermediate (**4** to **5**) when R = CO_2Me or C(O)Me (**4a** resp. **4b**) may involve a six-atom transition state facilitated by intramolecular hydrogen bonding of the carbonyl moiety to the nearby amine-bearing proton, thereby affording only *Z*-isomeric products (**5a** resp. **5b**). For the analogous transformation of nitrile **4c**, a less optimal geometric transition state may occur, resulting in the inseparable *E*- and *Z*-isomeric mixture of **5c**.[b]

Next, application of the tandem retro-Michael-[2 + 3]-Wittig procedure to the transformation of suitably functionalized lyxofuranose and mannofuranose derivatives into the corresponding piperidines was investigated. For this purpose, 2,3-*O*-isopropylidene-D-lyxofuranose **8**, readily available from D-lyxofuranolactone[27] was treated with methyl (triphenylphosphoranylidene) acetate to afford *C*-glycofuranoside **9** as a mixture of α- and β-anomers (69% yield, Scheme 2). Mesylation of the primary alcohol of **9** followed by heating of the obtained mesylate **10** with NaN_3 and NaOMe in DMF led to the formation of compound **11** albeit in a rather poor (27%) yield.

Treatment of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **12** with methyl (triphenylphosphoranylidene) acetate afforded manno-*C*-glycoside **13** as an anomeric mixture in 96% yield. Acidic removal of the 5,6-isopropylidene group ($AcOH/H_2O$ 7:3),[28] followed by selective silylation (TBDPSCl, imidazole) of the primary hydroxyl group afforded compound **14** (71% over 2 steps). Submission of the mesylate of **14** to the above described basic reaction conditions only afforded elimination products. The

[a]Sodium methoxide in DMF gave the best results in this transformation as compared to several other bases (DiPEA, KO^{t}Bu) in several solvent systems (DMF, NMP, DMPU).
[b]We thank the referee for this observation.

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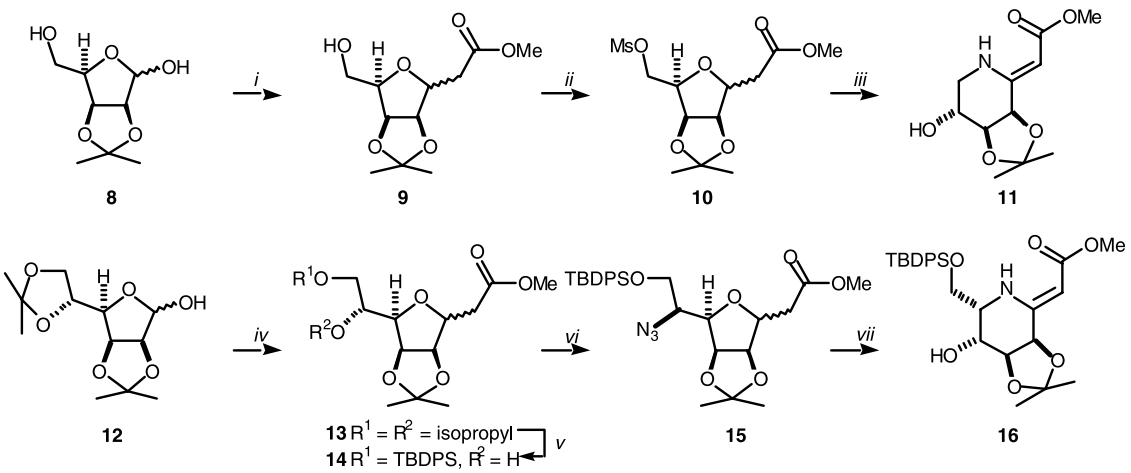

Scheme 2. Reagents and conditions: *i*. $Ph_3P{=}CHCO_2Me$, CH_3CN. *ii*. MsCl, pyridine. *iii*. NaN_3, NaOMe (0.3 equiv), DMF, Δ. *iv*. $Ph_3P{=}CHCO_2Me$, CH_3CN. *v*. a. aq AcOH, Δ. b. TBDPS-Cl, imidazole. *vi*. a. Tf_2O, pyridine. b. NaN_3, DMF. *vii*. NaOMe (0.3 equiv), DMF, Δ.

formation of the latter unwanted products may be due to the fact that the initially required azide substitution reaction of the secondary mesylate proceeded sluggishly. We therefore first synthesized the azide **15** from the corresponding triflate of **14**. Heating of **15** in the presence of sodium methoxide afforded the expected piperidine **16** in a yield of 35%.

In conclusion, the results described in this paper demonstrate the versatility of the tandem retro-Michael-[2,3]-cycloaddition reaction as an alternative route towards the synthesis of highly functionalized piperidines. Future attention will be directed to optimization of the reaction conditions as well as application of the strategy to obtain various novel aza-*C*-saccharides. Furthermore, the obtained piperidines will be used, after transformation into suitably protected building blocks,[29] for the synthesis of oligosaccharide and oligopeptide mimetics.[c]

EXPERIMENTAL

General methods. All solvents were stored on molecular sieves 4 Å, with the exception of acetonitrile (Biosolve, p.a.) and methanol (Biosolve, p.a.), which were stored on molecular sieves 3 Å. Column chromatography was performed using Grace AB Amicon (35-70 μm) silica gel. Thin-layer chromatography (TLC) was done using Merck 60 F_{254} precoated silica plates and spots were visualized with UV or with a solution of cerium ammonium molybdate (1.5% $NH_4Mo_2O_2$, 1% Ce(IV)SO_4 and 10%

[c]Compound **5a** was hydrogenated in the presence of a palladium catalyst, treated with Boc_2O,[2a] followed by saponification of the methyl ester (for details see the Experimental) to give a novel β-amino acid building block that can, for instance, be used in the construction of carbohydrate mimetics. Ref. [29].

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H_2SO_4 in ethanol) followed by charring. NMR spectra were recorded on Bruker AC 250, AC 200 and Mercury 300 spectrometers. For the NMR spectra, the solvent peak was used as reference ($CDCl_3$: δ 7.27 for ^1H, δ 76.93 for ^{13}C). Melting points were measured on a Büchi melting point apparatus and are uncorrected. Elemental analysis was performed by the Institute of Physical Chemistry, University of Vienna. Mass spectra were recorded using a PE/SCIEX API 165 instrument with electron spray interface.

General procedure for the synthesis of *C*-glycosides using the Wittig reaction. Reaction was carried out according to Ref. [25]; the isopropylidene protected carbohydrate was dissolved in acetonitrile (0.2 M) and treated with the Wittig reagent (1.5 equiv) at rt. The reaction mixture was heated at 80°C until TLC analysis indicated full conversion.

Methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*galacto/talo*-heptaonate (9). Compound **9** was prepared according to the general procedure, with compound **8** (0.96 g, 5 mmol) and carbomethoxymethylene triphenylphosphorane (2.0 g, 6 mmol). After heating for 22 h, the reaction mixture was concentrated under reduced pressure and the residue redissolved in methanol (30 mL) and treated with NaOMe (0.5 equiv). After 1 hour, the mixture was neutralized with Dowex X10 50W (H^+), the ion exchange resin was removed by filtration, and the filtrate was concentrated under reduced pressure. Flash chromatography with diethyl ether as eluent gave **9** (0.85 g, 69%), a slightly yellow syrup, as a mixture of anomers. The compound was used without further purification in the next step. ^1H NMR (200 MHz, $CDCl_3$): δ 4.68 (dd, 1H, H^5), 4.45 (dd, 1H, H^4), 4.21 (ddd, 1H, H^3), 4.02 (ddd, 1H, H^6), 3.62 (s, 3H, OMe), 3.55-3.75 (m, 2H, 2 × H^7), 2.52-2.72 (m, 2H, 2 × H^2), 1.48, 1.40, 1.27 (s, 6H, Me iPr). ^{13}C NMR (200 MHz, $CDCl_3$): δ 171.1, 170.5 (C^1), 112.6, 112.1 (C iPr), 84.5, 84.0, 83.8, 82.4, 81.5, 81.2, 80.5 (C^3, C^4, C^5, C^6), 62.3, 61.8 (C^7), 51.6, 51.5 (OMe), 37.5, 34.2 (C^2), 27.1, 25.9 (Me iPr), 25.2, 24.7 (Me iPr).

Methyl 3,6-anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto/glycero*-D-*talo*-octanoate (13). Compound **13** was prepared according to the general procedure with compound **12** (5.22 g, 20 mmol) and carbomethoxymethylene triphenylphosphorane (13.4 g, 40 mmol). After heating for 18 h, the reaction mixture was concentrated under reduced pressure and the residue treated with diethyl ether (50 mL). The precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography with a gradient of diethyl ether/pentane (1:1 → 2:1). Compound **13** was obtained, as a colorless oil, as an anomeric mixture. (6.11 g, 96%) and used directly in the next step. **13(β)** ^1H NMR (250 MHz, $CDCl_3$): δ 4.8 (dd), 4.77 (1H, H^5), 4.77 (1H H^4), 4.42-4.33 (m, 1H, H^7), 4.12-3.95 (m, 2H, H^8), 3.95 (bt, 1H, H^3), 3.7 (s, 3H, OMe), 3.51 (ddd, 1H H^6), 2.77 (t, 2H, H^2), 1.5 (s, 3H, Me iPr), 1.44 (s, 3H, Me iPr), 1.38 (s, 3H, Me iPr), 1.33 (s, 3H, Me iPr). **13(α)**: ^1H NMR (250 MHz, $CDCl_3$): 4.77 (m, 1H, H^5), 4.65 (dd, 1H, H^4), 4.49 (t, 1H, H^3), 4.42-4.33 (m, 1H, H^7), 4.12-3.95 (m, 2H, 2 × H^8), 3.8 (dd, 1H, H^6), 3.7 (s, 3H, OMe), 2.5 (dd, 2H, 2 × H^2), 1.48 (s, 3H, Me iPr), 1.44 (s, 3H, Me iPr), 1.38 (s, 3H, Me iPr), 1.33 (s, 3H, Me iPr). **(13α/β)** ^{13}C NMR (250 MHz, $CDCl_3$): δ 171.2, 170.4 (C^1), 112.7, 112.3, 109.0, 108.8 (C iPr), 84.7, 81.4, 80.8, 80.73, 80.69, 80.6, 80.5, 77.5 (C^3, C^4, C^5, C^6), 73.1, 72.9 (C^7),66.73, 66.67 (C^8), 51.7, 51.5 (OMe), 36.0, 33.1 (C^2), 26.7, 25.9, 25.5, 25.1, 25.0, 24.52, 24.46 (Me iPr).

General mesylation procedure. Mesylation was carried out according to a literature procedure.[30] The alcohol (0.15 M) in dry pyridine was treated with methanesulfonyl chloride (1.1 equiv) at 0°C. After 10 min the reaction mixture was allowed to warm to room temperature and stirring was continued for 1 h. The reaction mixture was cooled (0°C), quenched with water (50 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were washed with 10% citric acid (3×10 mL), sat $NaHCO_3$ (2×10 mL), brine (1×10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was coevaporated with toluene (2×10 mL) to remove traces of pyridine.

4,7-Anhydro-1,3-dideoxy-5,6-*O*-isopropylidene-8-*O*-methanesulfonyl-D-*allo/altro*-oct-2-ulose (7b). The reaction was carried out according to the general procedure, using 4,7-anhydro-1,3-dideoxy-5,6-*O*-isopropylidene-D-*allo/altro*-oct-2-ulose[a] (0.69 g, 3.0 mmol). Purification by flash chromatography with diethyl ether as eluent, yielded **(7b)** (0.74 g, 80%) as a clear oil (α/β ration 1/5.5). The product was directly used in the next step. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.75 (dd, 1H, $H^5\beta$), 4.7 (dd, 1H, $H^6\beta$), 4.6 (dd, 1H, $H^6\alpha$), 4.45 (dd, 1H, $H^5\alpha$), 4.40-4.05 (m, 4H, H^4, H^7, $2 \times H^8$ for both α and β), 3.05 (s, 3H, OMs β), 3.03 (s, 3H, OMs α), 2.85 (d, 2H, $2 \times H^3$ β), 2.75 (dd, 2H, $2 \times H^3$ α), 2.15 (s, 3H, CH_3), 1.52 (s, 3H, CH_3 iPr α), 1.45 (s, 3H, CH_3 iPr β), 1.31 (s, 3H, CH_3 iPr α), 1.30 (s, 3H, CH_3, iPr β). ^{13}C NMR (200 MHz, $CDCl_3$): δ 206.0, 205.6 (C=O), 114.9, 112.7 (C iPr), 84.1, 82.1, 81.7, 81.3, 81.1, 81.0, 80.6, 77.2 (C^4, C^5, C^6, C^7), 69.0, 68.5 (C^8), 46.6, 43.0 (C^3), 37.5 (OMs), 30.5, 30.5 (C^1), 27.2, 26.1, 25.3, 24.7 ($2 \times CH_3$ iPr).

3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-8-*O*-methanesulfonyl-D-*glycero*-D-*allo/altro*-heptononitrile (7c). The reaction was carried out according to the general procedure, using 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*glycero*-D-*allo/altro*-heptononitrile[a] (0.94 g, 4.4 mmol). Flash chromatography with a gradient of EtOAc/hexane (1:4 → 4:1) gave compound **7c** (1.2 g, 93%, α/β 1/10). The product was directly used in the next step. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.72 (dd, J=3.5, 6.5, 1H, H^5), 4.55 (dd, J=4.4, 6.5, 1H, H^4), 3.38 (m, 2H, H^3, H^6), 4.25 (dd, J=3.5, 7.4, 1H, H^7), 4.14 (dd, J=10.3, 3.5, 1H, H^7), 3.09 (s, 3H, OMs), 2.73 (dd, J=16.6, 4.7, 5.3, 2H, $2 \times H^2$), 1.55 (s, 3H, CH_3 iPr), 1.17 (s, 3H, CH_3 iPr). ^{13}C NMR (200 MHz, $CDCl_3$): δ 116.5 (C^1), 114.9 (C iPr), 83.0, 81.7, 80.8, 79.4 (C^3, C^4, C^5, C^6), 68.5 (C^7), 37.2 (OMs), 26.9, 25.0 ($2 \times CH_3$ iPr), 21.6 (C^2).

Methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-7-*O*-methanesulfonyl-D-*galacto*- and D-*talo*-heptonate (10). Compound **10** was prepared according to the general procedure, using compound **9** (1.44 g, 5.8 mmol). Flash chromatography with diethyl ether:pentane (8:2) afforded compound **10** (1.7 g, 91%, α/β 1/1) as a clear syrup. **10α** ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.83 (dd, J = 6.25, 4.1, 1H, H^4), 4.69 (dd, J = 6.25, 1.25, 1H, H^5), 4.55 (bt, J = 6.9, 4.1, 1H, H^3), 4.49 (dd, J = 4.4, 11.25, 1H, H^7), 4.39 (dd, J = 7.2, 11.25, 1H, H^7), 4.2 (dt, J = 7.2, 1.25, 4.4, 1H, H^6), 3.72 (s, 3H, OMe), 3.06 (s, 3H, OMs), 2.54 (dd, J = 6.9, 3.0, 2.2, 2H, H^2), 1.5 (s, 3H, Me iPr), 1.32 (s, 3H, Me iPr). **10α** ^{13}C NMR (250 MHz, $CDCl_3$): δ 171.1 (C^1), 112.8 (iPr), 80.9, 78.5, 77.9, 77.7 (C^3,C^4,C^5,C^6), 67.8 (C^7), 51.8 (OMe), 37.4 (OMs), 33.1 (C^2), 25.7, 24.6 (Me iPr). **10β** ^{13}C NMR (250 MHz, $CDCl_3$): δ 170.5 (C^1), 113.4 (C iPr), 84.7,

80.8, 80.6, 78.1 (C^3, C^4, C^5, C^6), 68.2 (C^7), 51.9 (OMe), 37.5 (OMs), 36.2 (C^2) 26.1, 24.7 (Me iPr).

Anal. calcd for $C_{12}H_{20}O_8S$ (324.35): C 44.43, H 6.21, S 9.88. Found; C 44.51, H 6.21, S 9.88.

General retro-Michael-[2 + 3]-cycloaddition procedure: A. The azide (0.4 M) in dry DMF was treated with NaOMe (0.3 equiv) and heated under reflux, using a heating mantle. After 2 h, the reaction mixture was allowed to cool to rt, diluted with water (0.2 M), extracted with diethyl ether (3 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. **B**. The mesylate (0.3 M) in dry DMF was treated with NaN_3 (1.7 equiv) and NaOMe (0.3 equiv) and heated under reflux for 1 h, using a heating mantle. The reaction mixture was diluted with methanol (until 0.15 M) and neutralized with Dowex 50W X8 (H^+). The ion exchange resin was removed by filtration and the filtrate treated with activated charcoal, filtered and concentrated under reduced pressure.

Methyl (3*R*, 4*S*, 5*R*)-2-(5-hydroxy-3,4-*O*-isopropylidene) piperidylidene carboxylate (5a). Retro-Michael cyclo-addition was carried out according to general procedure **B**, using compound **7a**[22] (1.43 g, 4.4 mmol). Flash chromatography (Et_2O) and recrystallization of the pale yellow solid from ethanol gave **5a** (0.64 g, 60%) as white needles. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.23 (s, 1H, NH), 4.77 (s, 1H, H^2), 4.58-4.49 (m, 1H, H^4), 4.58-4.49 (m, 1H, H^6), 3.80-3.78 (m, 1H, H^5), 3.51 (s, 3H, OMe), 3.29-3.18 (m, 2H, 2 × H^7), 2.57 (d, 1H, OH), 1.54 (s, 3H, Me iPr), 1.43 (s, 3H, Me iPr). ^{13}C NMR (250 MHz, $CDCl_3$): δ 170.6 (C^1), 155.5 (C^3), 110.3 (C iPr), 84.4 (C^2), 75.0 (C^5), 73.1 (C^4), 66.9 (C^6), 50.3 (OMe), 41.5 (C^7), 25.9 (Me iPr), 24.1 (Me iPr). Mp. 157.5-158°C. IR (DCM, cm^{-1}): 3559 (OH), 3330 (NH), 2993, 2939 (CH), 1662 (C═O), 1615 (C═C).

Anal. calcd for $C_{11}H_{17}O_5N$ (243.25): C 54.31, H 7.04, N 5.76. Found: C 54.56, H 6.93, N 5.69.

Acetyl (3*S*, 4*R*, 5*R*)-2-(5-hydroxy-3,4-*O*-isopropylidene) piperidylidene (5b). The reaction was carried out according to general procedure **B**, using compound **7b**[22] (0.31 g, 1.0 mmol). Purification by flash chromatography with a gradient of EtOAc/pentane (1:1 → 1:0) gave compound **5b** as an amorphous white solid (0.143 g, 63%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.35 (s, 1H, NH), 5.25 (s, 1H, H^3), 4.50 (m, 2H, H^5, H^6), 3.82 (m, 1H, H^7), 3.15-3.40 (m, 2H, 2 × H^7), 2.90 (d, 1H, OH), 2.05 (s, 3H, CH_3), 1.55 (s, 3H, CH_3 iPr), 1.40 (s, 3H, CH_3 iPr). ^{13}C NMR (200 MHz, $CDCl_3$): δ 195.5 (C═O), 156.7 (C^4), 110.4 (C iPr), 95.4 (C^3), 74.2, 73.1 (C^5, C^6), 66.3 (C^7), 41.2 (C^8), 29.0 (C^1), 25.9, 24.1 (2 × CH_3 iPr). IR (DCM, cm^{-1}): 3561 (OH), 3055, 2990 (CH), 1629 (C═O), 1572 (C═C). HRMS (H^+): Calcd 228.1236. Found 228.1233.

Cyano (3*S*, 4*R*, 5*R*)-2-(5-hydroxy-3,4-*O*-isopropylidene) piperidylidene (5c). Compound **5c** was prepared according to general procedure **B**, using compound **7c** (0.30 g, 1.02 mmol). Flash chromatography with diethyl ether yielded **5c** as an oil (0.090 g, 41%) in an *E/Z* ratio of 2/1. The two products could not be separated by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48 (s, 1H, NH (9Z)), 5.42 (s, 1H, NH (9E)), 5.19 (dd, 1H, H^4 (9E)), 4.57 (d, J = 7.4, 1H, H^4 (9Z)), 4.50 (m, 1H, H^5 (9E)),

4.48 (dd, J = 4.1, 7.4, 1H, H^5 (9Z)), 4.19 (s, 1H, H^2 (9E)), 4.04 (s, 1H, H^2 (9Z)), 3.86 (dt, J = 4.4, 4.1, 8.6, 1H, H^6 (9Z)), 3.35 (m, 1H, H^6 (9E)), 3.05-3.18 (m, 2H, 2 × H^7 (9Z), 2 × H^7 (9E)), 2.63 (s, 1H, OH), 1.55 (s, 3H, CH_3 iPr (9E)), 1.53 (s, 3H, CH_3 iPr (9Z)), 1.46 (s, 3H, CH_3 iPr (9E)), 1.41 (s, 3H, CH_3 iPr (9Z)). ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.8 (C^3), 118.8 (C^1), 110.7 (C iPr), 73.9 (C^4 (9Z)), 73. (C^5 (9Z)), 72.7 (C^4 (9E)), 72.0 (C^5 (9E)), 67.3 (C^6 (9E)), 66.3 (C^2 (9E)), 66.1 (C^6 (9E)), 63.0 (C^2 (9E)), 42.1 (C^7 (9Z)), 41.8 (C^7 (9E)), 26.0, 24.3 (2 × CH_3 iPr (9Z)), 25.8, 24.0 (2 × CH_3 iPr (9E)). IR (DCM, cm^{-1}): 3685, 3561 (OH), 3413 (NH(E)), 3055, 2989 (CH), 2195 (CN), 1675 (C═C(E)), 1623 (C═C(Z)). HRMS (H^+): Calcd 211.1083. Found 211.1088.

Methyl (3*R*, 4*S*, 5*R*)-2-(5-hydroxy-3,4-*O*-isopropylidene) piperidylidene carboxylate (11). Compound 11 was prepared according to general procedure **B**, using compound **10** (1.46 g, 4.5 mmol). Flash chromatography with diethyl ether gave compound **11** (0.3 g, 27%) as an colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 8.25 (s, 1H, NH), 4.82 (s, 2H, H^2), 4.55 (dd, J = 7, 1H, H^4), 4.27 (ddd, J = 7.3, 1.4, 3.0, 1H, H^5), 3.88 (m, J = 2.5, 1H, H^6), 3.63 (s, 3H, OMe), 3.51 (dt, 1H, H^7), 3.20 (ddt, 1H, H^7), 1.48 (s, 3H, Me iPr), 1.38 (s, 3H, Me iPr). ^{13}C NMR (250 MHz, $CDCl_3$): δ 170.6 (C^1), 156.3 (C^3), 109.3 (C iPr), 83.9 (C^2), 76.0 (C^5), 73.0 (C^4), 67.4 (C^6), 50.0 (OMe), 41.7 (C^7), 26.1, 23.6 (Me iPr). HRMS (H^+): Calcd 244.1185. Found 244.1592.

Methyl (3*R*, 4*S*, 5*R*, 6*S*)-2-{5-hydroxy-3,4-*O*-isopropylidene-6-[(*O-tert*-butyldiphenylsilyl)methyl]} piperidylidene carboxylate (16). Compound 16 was prepared according to general procedure **A**, using compound **15** (1.3 g, 2.4 mmol). Purification by flash chromatography with a gradient of EtOAc/hexanes (1/9 → 2/3) yielded compound **16** (0.4 g, 33%) as an oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H, NH), 7.36-7.76 (m, 10H, 2 × Ph), 4.85 (s, 1H, H^2), 4.55 (d, J = 7, 1H, H^4), 4.31 (dd, J = 2.5, 7, 1H, H^5), 4.02 (m, 1H, H^6), 3.96 (m, J = 4.4, 4, 15.6, 2H, H^8), 3.66 (s, 3H, OMe), 3.30 (dt, J = 3.4, 1H, H^7), 1.45 (s, 3H, Me iPr), 1.38 (s, 3H, Me iPr), 1.1 (s, 9H, 3 × Me *tBu*). ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.5 (C^1), 156.2 (C^3), 135.7, 135.4, 130.1, 127.9 (2 × Ph), 109.7 (C iPr), 86.1 (C^2), 76.0 (C^5), 74.1 (C^4), 70.7 (C^6), 65.2 (C^8), 50.5 (C^7), 50.0 (OMe), 27.0 (3 × Me *tBu*), 26.2, 24.1 (Me iPr), 19.3 (Si-C). HRMS ($C_{28}H_{38}NO_6Si$): Calcd 512.2468. Found 512.2449.

Methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-8-*O-tert*-butyldiphenylsilyl-D-*glycero*-D-*galacto*/D-*glycero*-D-*talo*-octanoate (14). Compound **14** was prepared according to a literature procedure.[28] Compound **13** (6.11 g, 19.3 mmol) in a 1:1 mixture of $AcOH/H_2O$ (40 mL) was stirred at room temperature for 43 h. The reaction mixture was concentrated under reduced pressure at 28°C bath temperature. The residue was purified by flash chromatography with diethyl ether to give methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*glycero*-D-*galacto*/D-*glycero*-D-*talo*-octanoate (3.94 g, 74%). ^{13}C NMR (200 MHz, CD_3OD): δ 172.8 (C^1), 112.7, 112.4 (C iPr), 84.2, 80.6, 80.5, 80.1, 80.0, 77.3 (C^3, C^4, C^5, C^6), 69.5, 69.1 (C^7), 63.6 (C^8), 51.9 (OMe), 35.2, 33.1 (C^2), 25.2, 24.9, 23.7 (Me iPr). Adapted from Ref. [31], methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*glycero*-D-*galacto*/D-*glycero*-D-*talo*-octanoate (1.389 g, 5.03 mmol) dissolved in dry DMF (20 mL) was treated with imidazole (1.03 g, 15

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mmol) and *tert*-butyldiphenylchlorosilane (1.4 mL, 5.5 mmol). After 30 min the reaction mixture was neutralized with pH 7 acetate buffer (10 mL) and extracted with DCM (3 × 20 mL). The combined organic phases were washed with brine (2 × 15 mL), dried (Na_2SO_4) and purified by flash chromatography with a gradient of diethyl ether/pentane (1:4 → 3:1). Compound **14** (2.5 g, 96.5%) was obtained as a slightly yellow oil. **14β** ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3-7.7 (m, 10H, 2 × Ph), 4.82 (dd, J = 3.4, 6.1, 1H, H^5), 4.75 (dd, J = 3.8, 6.1, 1H, H^4), 3.75-4.13 (m, 4H, H^3, H^6, H^7, H^8), 3.50 (s, 3H, OMe), 3.54 (dd, J = 1H, H^8), 2.88 (d, H, H^2), 2.76 (dd, 1H, H^2), 1.47 (s. 3H, Me iPr), 1.33 (s, 3H, Me iPr), 1.08 (s, 9H, 3 × Me, *tBu*). ^{13}C NMR (200 MHz, $CDCl_3$): δ 171.3 (C^1), 135.5, 133.1, 129.7, 127.6 (Ph), 112.3 (C iPr), 81.2, 80.7, 80.3, 77.6 (C^3, C^4, C^5, C^6), 69.5 (C^7), 65.5 (C^8), 51.6 (OMe), 33.2 (C^2), 26.8 (3 × Me *tBu*), 25.7, 24.7 (Me iPr), 18.2 (Si-C). **14α** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.69 (m, 10H, 2 × Ph), 4.86 (dd, J = 3.9, 6, 1H, H^5), 4.63 (dd, J = 1.1, 6, 1H, H^4), 4.47 (dt, J = 1.1, 7.2, 1H, H^3), 4.04 (m, 1H, H^7), 3.78-3.91 (m, 3H, H^6, 2 × H^8), 3.64 (s, 3H, OMe), 2.48 (m, J = 5.1, 7.2, 2H, 2 × H^2), 1.50 (s. 3H, Me iPr), 1.35 (s, 3H, Me iPr), 1.09 (s, 9H, 3 × Me, *tBu*). ^{13}C NMR (200 MHz, $CDCl_3$): δ 170.6 (C^1), 135.4, 133.0, 129.7, 127.6 (Ph), 112.7 (C iPr), 84.5, 81.3, 80.6, 79.3 (C^3, C^4, C^5, C^6), 69.8 (C^7), 65.3 (C^8), 51.7 (OMe), 36.0 (C^2), 26.7 (3 × Me *tBu*), 26.1, 24.7 (Me –iPr), 19.2 (Si-C). HRMS ($C_{28}H_{38}NaO_7Si$): Calcd 537.2284. Found 537.2288.

Methyl 3,6-anhydro-2-deoxy-7-azido-4,5-*O*-isopropylidene-8-*O*-*tert*-butyldiphenylsilyl-L-*glycero*-D-*galacto*- and L-*glycero*-D-*talo*-octanoate (15). Compound 15 was prepared according to a literature procedure,[32] compound **14** (2.18 g, 4.2 mmol) in dry DCM (20 mL) at –15°C under argon was treated with dry pyridine (0.5 mL, 6.5 mmol) and trifluoromethanesulfonic anhydride (0.8 mL, 4.9 mmol). After 10 min, the reaction mixture was allowed to warm to room temperature and water (10 mL) was added. The organic layer was separated and washed with water (10 mL) and with pH 7 acetate buffer (10 mL). The aqueous phases were extracted with DCM (3 × 10 mL) and the combined organic phases were dried (Na_2SO_4), concentrated under reduced pressure and the residue coevaporated with toluene (3 × 5 mL). The triflate was redissolved in dry DMF (30 mL) and NaN_3 (0.424 g, 6.5 mmol) was added. The mixture was heated at 30°C for 1 h. Water (25 mL) was added and the reaction mixture extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography with a gradient of EtOAc/hexanes (1/4 → 1/1) to give compound **15** (1.316 g, 58%), as the α/β mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4-7.7 (m, 10H, 2 × Ph), 4.72 (dd, 1H, H^5 β), 4.62 (dd, 1H, H^5 α), 4.47 (t, 1H, H^3 α), 4.45 (dd, 1H, H^4 α), 4.41 (dd, 1H, H^4 β), 3.88-3.95 (m, 3H, H^3, H^6, H^7 β), 3.87-4.0 (m, 3H, H^6, H^7, H^8 α), 3.7-3.73 (m, 4H, H^8, OMe β), 3.7-3.73 (m, 4H, H^8, OMe α), 3.66 (dd, 1H, H^8 β), 2.83 (d, H, 2 × H^2 β), 2.45-2.63 (ddd, 2H, 2 × H^2 α), 1.45 (s, 3H, Me –iPr α), 1.41 (s, 3H, Me –iPr β), 1.23 (s, 3H, Me –iPr α), 1.22 (s, 3H, Me –iPr β), 1.10 (s, 9H, 3 × Me, *tBu* α), 1.09 (s, 9H, 3 × Me, *tBu* β). ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.2, 170.6 (C^1), 135.6, 129.8, 129.5, 127.7 (Ph), 112.8, 112.4 (C iPr), 85.0, 81.0, 80.5, 80.3, 79.3, 77.6 (C^3, C^4, C^5, C^6), 64.0, 63.8, 62.7, 62.4 (C^7 + C^8), 51.9, 51.7 (OMe), 36.2, 33.1 (C^2), 26.7 (3 × Me *tBu*), 26.2, 25.7, 24.8, 24.7 (Me iPr), 19.2 (Si-C). HRMS ($C_{28}H_{37}N_3NaO_6Si$): Calcd 562.2349. Found 562.2315.

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(2′*R*, 3′*S*, 4′*R*, 5′*R*)-*N*-*tert*-butoxycarbonyl-2-(5′-hydroxy-3′,4′-*O*-isopropylidene) piperidyl acetic acid. Compound **5a** (1.17 g, 4.8 mmol) suspended in absolute ethanol (60 mL) was treated with 5% Pd/C (276 mg) hydrogenated at 55 bar and 50°C for 49 h. The catalyst was removed by filtration over celite and the filtrate concentrated. The residue was redissolved in dry THF (10 mL) and treated with Et_3N (2.5 mL) and Boc_2O (1.1 g, 4.9 mmol). The solution was heated at 45°C for 20 h. The reaction mixture was concentrated and redissolved in diethyl ether (100 mL), washed with 0.25N HCl (30 mL), sat $NaHCO_3$ (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography with EtOAc/hexanes (1:1) as eluent afforded the piperidine derivative as a clear oil. Yield 0.85 g (51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (t, 1H, $H^{4'}$), 4.42 (q, 1H, $H^{3'}$), 4.34 (t, 1H, $H^{5'}$), 3.80 (dd, 1H, $H^{2'}$), 3.63 (s, 3H, OMe), 3.67 (m, 1H, $H^{6'}$), 3.00 (dd, 1H, $H^{6'}$), 2.82 (dd, 1H, H^2), 2.68 (br, 1H, H^2), 1.48 (s, 3H, CH_3 iPr), 1.41 (s, 9H, 3 × CH_3 tBu), 1.33 (s, 3H, CH_3 iPr). ^{13}C NMR (300MHz, $CDCl_3$): δ 171.6 (C═O ester), 154.5 (C═O carbamate), 108.6 (C iPr), 80.2 (C tBu), 73.2 ($C^{4'}$), 72.4 ($C^{5'}$), 65.7 ($C^{3'}$), 51.2 (OMe), 48.4 ($C^{6'}$), 41.8 ($C^{2'}$), 35.0 (C^2), 28.1 (CH_3 tBu), 25.9 (CH_3 iPr), 24.2 (CH_3 iPr). The crude product was dissolved in MeOH (6 mL) and at 0°C treated with LiOH (0.4 g) dissolved in water (6 mL), added dropwise. After 1 h, EtOAc (25 mL) was added and the solution was acidified to pH 5 with a 10% solution of $NaHSO_4$. The reaction mixture was extracted with EtOAc (3 × 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound as a white foam (0.82 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (t, 1H, $H^{4'}$), 4.42 (q, 1H, $H^{3'}$), 4.35 (t, 1H, $H^{5'}$), 3.80 (dd, 1H, $H^{2'}$), 3.67 (m, 1H, $H^{6'}$), 3.03 (dd, 1H, $H^{6'}$), 2.86 (br, 2H, 2 × H^2), 1.49 (s, 3H, CH_3 iPr), 1.43 (s, 9H, 3 × CH_3 tBu), 1.34 (s, 3H, CH_3 iPr). ^{13}C NMR (300MHz, $CDCl_3$): δ 176.8 (C═O acid), 154.9 (C═O carbamate), 108.9 (C iPr), 80.7 (C tBu), 73.2 ($C^{4'}$), 72.4 ($C^{5'}$), 65.7 ($C^{3'}$), 48.4 ($C^{6'}$), 42.0 ($C^{2'}$), 35.4 (C^2), 28.2 (CH_3 tBu), 26.0 (CH_3 iPr), 24.3 (CH_3 iPr).

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