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Stereocontrolled transformation of nitrohexofuranoses into cyclopentylamines via 2-oxabicyclo[2.2.1]heptanes. Part 6: synthesis and incorporation into peptides of the first reported 2,3-dihydroxycyclopentanecarboxylic acid

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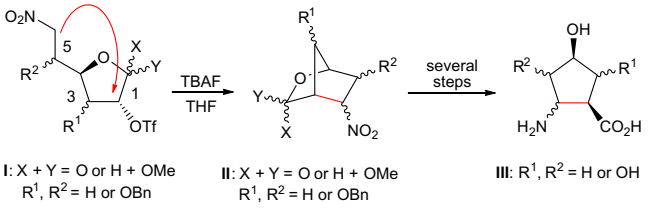
ABSTRACT

Herein we report the intramolecular alkylation of nitronates of methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-β-D-glucofuranoside and methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-α-D-glucofuranoside into the corresponding 2-oxabicyclo[2.2.1]heptane derivatives. Similarly, methyl-3-*O*-benzyl-5-deoxy-5-nitromethyl-β-D-xylofuranoside and methyl-3-*O*-benzyl-5-deoxy-5-nitromethyl-α-D-xylofuranoside were cyclized to (1*R*,3*R*,4*S*,5*R*,7*R*)-7-benzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane and (1*R*,3*S*,4*S*,5*R*,7*R*)-7-benzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane, respectively. These 2-oxabicyclo[2.2.1]heptane derivatives were eventually transformed into enantiopure methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-amino-2,3-dihydroxycyclopentanecarboxylate and this novel β-amino acid was incorporated into peptides.

1. Introduction

The design and synthesis of new amino acids and peptidomimetics has attracted considerable attention in recent times, due to the pharmacological limitations of bioactive peptides, which have been related to their conformational flexibility and their metabolic instability.[1] Particular attention has been devoted to β-amino acids, on account of the metabolic and conformational stability of β-peptides.[2] Among them, cyclopentane β-amino acids have become attractive candidates for the stabilization of bioactive peptides, due to the high tendency of their homopolymers to fold in rigid secondary structures in short peptide sequences.[3]

Carbohydrates are an abundant source of useful scaffolds for the stereoselective synthesis of functionalized carbo- and heterocycles.[4] One of the approaches developed for this purpose involves the generation of a bicyclic derivative constituted by the original sugar ring and a new ring, followed by the opening of the sugar ring (*approach a*). Alternatively, a new ring results from the cyclization of an open chain carbohydrate derivative (*approach b*). Among the variants of the *approach a* that have been developed, the one involving an intramolecular alkylation of nitronates of sugar derivatives **I** to give bicyclic compounds **II** has allowed us to develop the first approach for the synthesis of polyhydroxylated cyclopentane β-amino acids **III** (Scheme 1).[5] Stereocontrolled access to these richly functionalized alicyclic β-amino acids is limited to hexoses that fit the stereochemical requirements for the intramolecular displacement of –OTf leaving groups at C-2 by nitronates at C-6 (D-glucose, D-idose, D-allose, D-talose, and their respective L-hexose enantiomers). Moreover, our previous studies in this field allowed us to recognize that the efficiency of the key cyclization leading to compounds **II** depends on a number of structural factors of their precursors **I**: the sp^2 or sp^3 character of the carbon atom at C-1, the configuration of the stereogenic centers at C-1(sp^3), C-3 and C-5, and the nature of the substituents at C-3 and C-5.[5]



I: X + Y = O or H + OMe
R^1, R^2 = H or OBn

II: X + Y = O or H + OMe
R^1, R^2 = H or OBn

III: R^1, R^2 = H or OH

Scheme 1.

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In order to gain more insight into the factors influencing the key cyclization involved in this synthesis of polysubstituted cyclopentane β-aminoacids, we herein report its extension to additional nitro sugars **I**.

2. Results and discussion

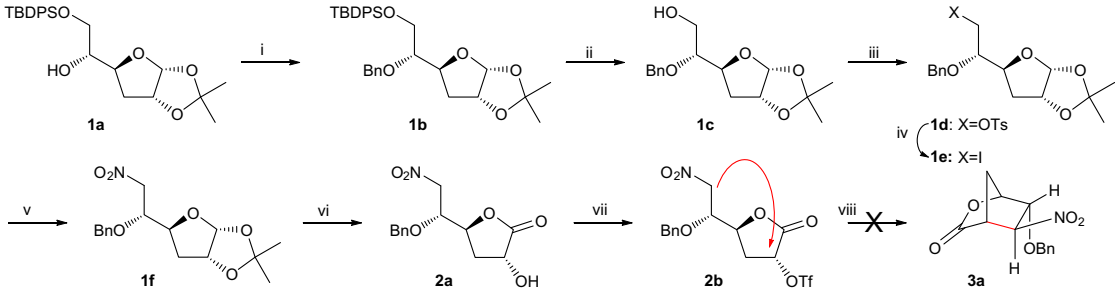
At first, we studied the cyclization of 6-nitro-3,6-dideoxy-2-*O*-triflyl-D-gluconolactone **2b**, which was obtained in seven steps and 17.3% overall yield from the known D-glucose derivative **1a**,[7] following a protocol previously developed in our group for the preparation of 6-nitro-6-dehydro-D-hexofuranosides (Scheme 2).[5a]

Benzylation of the free OH group of **1a** by treatment with NaH and BnBr was followed by a TBAF mediated removal of the TBDPS protecting group of the resulting derivative **1b**. This afforded compound **1c**, which in turn easily provided its *O*-tosyl derivative **1d** upon treatment with TsCl for 10 h, in the presence of pyridine.[6] The reaction of this compound with NaI resulted in the efficient formation of iodo derivative **1e**,[6] which yielded the key nitrosugar **1f**, after reaction with $NaNO_2$ and trihydroxybenzene (phloroglucinol),[5a] a scavenger that avoids nitrite ester formation. Removal of the isopropylidene protecting group of **1f** with aqueous TFA, followed by oxidation of the anomeric position of the resulting 3-deoxy furanose with Br_2 and $BaCO_3$, furnished the expected sugar lactone **2a**, which was directly converted into its –OTf derivative **2b**, when reacted with Tf_2O and pyridine (Scheme 2).[5c] Finally, compound **2b** was directly allowed to react with TBAF in dry THF, but the expected cyclization leading the bicyclic lactone **3a** did not occur. This unsuccessful result allowed us to confirm that a substituent at the C-3 position of type **2b** substrates is required for the success of these cyclizations.[5c]

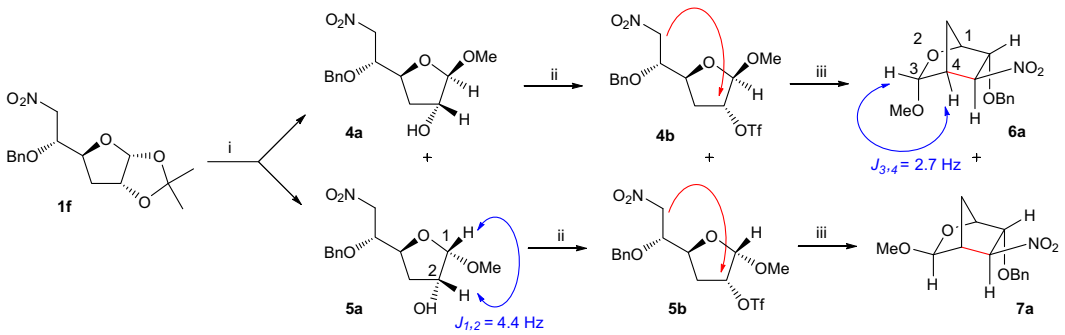
However, satisfactory results were achieved when we explored the alternative nitronate alkylation route depicted in Scheme 3.[5c] Thus, when nitroglucofuranose derivative **1f** was now reacted with AcCl in MeOH, a 6:1 ratio of an inseparable anomeric mixture of **4a** and **5a** was obtained. This ratio was established from the relative intensities of the two singlets that appear in its ^1H NMR at 3.34 ppm and 3.46 ppm, due to the anomeric methoxy substituents of **4a** and **5a**, respectively. On the other hand, the configuration at the anomeric stereogenic center of **5a** was deduced from a doublet at 4.83, ppm due to its anomeric proton, which is coupled with the proton at C-2. The coupling constant value ($J_{1,2}$ = 4.4 Hz) requires a *cis*-configuration of both protons. This is in accordance with the configuration proposed for anomer **4a**. As expected, its anomeric proton showed a singlet (δ = 4.78 ppm), due to a *trans*-configuration of the protons H_1 and H_2.

The reaction of this mixture of compounds **4a** and **5a** with Tf_2O and pyridine, under the same conditions as for **2a**, provided the corresponding mixture of compounds **4b** and **5b**, which was treated directly with TBAF in THF. The intramolecular displacement of the triflate group at C-2 by the nitronate at C-6 resulted in the formation of a 20:1 mixture of bicyclic anomers **6a** and **7a**, which was separated by column chromatography and identified from their analytical and spectroscopic properties. The anomeric proton at 5.17 ppm of anomer **6a** showed a doublet with a coupling constant of $J_{3,4}$ = 2.7 Hz, due to an *endo* disposition of its methoxy group. On the other hand, the *exo* disposition of the methoxy group of its isomer **7a** was easily deduced from a singlet at 4.67 ppm, due to its anomeric proton.

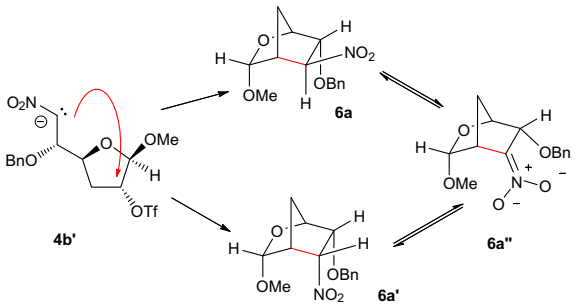
The stereochemical outcome of the key step to compound **6a** can be explained by assuming that both bicyclic compounds **6a** and **6a′** should be formed from nitronate **4b′** (Scheme 4). Under the reaction conditions, however, compounds **6a** and **6a′** should be in equilibrium with their common nitronate **6a″**. At equilibrium, the thermodynamically more stable compound **6a** should be favoured over compound **6a′**, where the NO_2 and the OBn substituents are eclipsed. This explains the remarkably high stereoselectivity of the cyclization. A similar behavior could explain the selective transformation of compound **5b** into bicyclic compound **7a.**



Scheme 2. Reagents and conditions: (i) (a) NaH, NBu_4I, BnBr, DMF, 50 °C, 1 h; (b) MeOH, 50 °C, 2 h; (ii) TBAF, THF, rt, 4 h; (iii) TsCl, Py, rt, 10 h; (iv) NaI, acetone, reflux, 15 h; (v) $NaNO_2$, phloroglucinol, DMSO, rt, 96 h; (vi) (a) TFA, H_2O, rt, 12 h; (b) Br_2, $BaCO_3$, dioxane, H_2O, rt, 14 h; (vii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (viii) TBAF, THF, rt, 1.5 h.



Scheme 3. Reagents and conditions: (i) AcCl, MeOH, 0 °C, 14 h; (ii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (iii) TBAF, THF, rt, 1.5 h.



Scheme 4.

We next considered the transformation of the C-5 unsubstituted nitrosugar **1g**[7] into its bicyclic lactone derivative **3b** (Scheme 5, *route a*). Thus, proceeding as for its analogue **1f**, compound **1g** was easily converted into the key 2-*O*-triflyl lactone **2d**, via lactone **2c**. However, unsatisfactory results were also achieved, because the nitronate of **2d** did not cyclize to the desired lactone **3b**. Accordingly, it was further confirmed that substituents were required at both the C-3 and C-5 positions of type **2** nitrosugar lactones for successful cyclization to the corresponding bicyclic nitrosugar lactones **3.**[5]

In view of the unsatisfactory results for the cyclization **2d**→**3b**, we decided to consider nitrosugar **1g** for the alternative nitronate alkylation involved in *route b* of Scheme 5, which is similar to those previously developed for its analogue **1f**. The reaction of compound **1g** with AcCl in methanol provided a 1:1 anomeric mixture of compounds **4c** and **5c**, as established by the isolation of both components by column chromatography. Treatment of this mixture of anomers **4c** and **5c** with triflic anhydride and pyridine allowed us to obtain a mixture of their *O*-Tf derivatives **4d** and **5d**, which was directly reacted with TBAF in THF. The result was the formation of a 10:10.6 anomeric mixture of bicyclic glycosides **6b** and **7b**, which were obtained in 71% overall yield for the two steps and were isolated by column chromatography. The *endo* disposition of the methoxy group at the anomeric center of **6b** was deduced from the coupling constant $J_{3,4}$ = 3.1 Hz of the doublet at 5.01 ppm present in its ^{1}H NMR spectrum. On the other hand, a singlet at 4.55 exhibited by the ^{1}H NMR spectrum of **7b** was in accordance with an *exo* disposition of its methoxy group.

Bicyclic glycosides **6b** and **7b** were converted into the disubstituted *trans*-2-aminocyclopentane carboxylic acid derivative **10b** (Scheme 6), following the protocol previously developed for the preparation of polyhydroxylated cyclopentane β-amino acids.[5c] Thus, acidic hydrolysis of the mixture of anomers **6b** and **7b** resulted in the formation of a tricomponent mixture **6c**+**8**+**7c**, which was directly subjected to an oxidation with sodium chlorite. This provided β-nitro acid **9a**, which was then reacted with trimethylsilyldiazomethane, to give the corresponding methyl ester derivative **9b**. The same results were achieved when compounds **6b** and **7b** were separately subjected to this reaction sequence. Reduction of the nitro group of **9b** by catalytic hydrogenation, followed by protection of the amino group of the resulting β-amino acid derivative **10a**, by reaction with *tert*-butoxycarbonyl anhydride, yielded the desired cyclopentane β-amino acid derivative **10b**. Its absolute configuration was confirmed by means of nOe experiments (Fig. 1). Thus, a 1.9% nOe enhancement from proton H-1 to proton H-3 confirmed the stated *cis*-disposition of both protons. Moreover, a 2.8% nOe enhancement from proton H-5 to proton H-2, confirmed the *cis*-disposition of these protons.

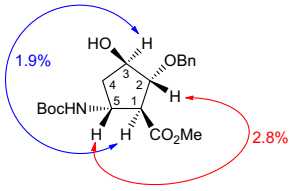
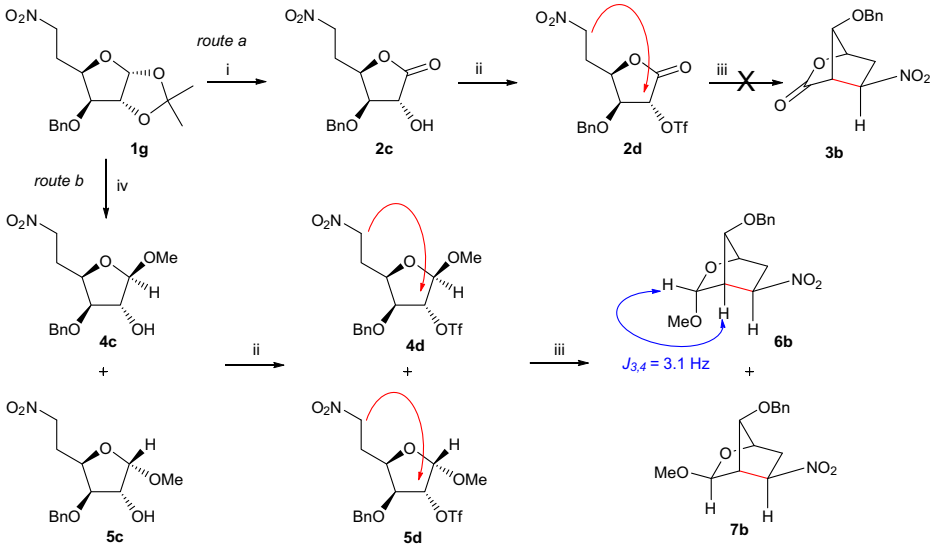
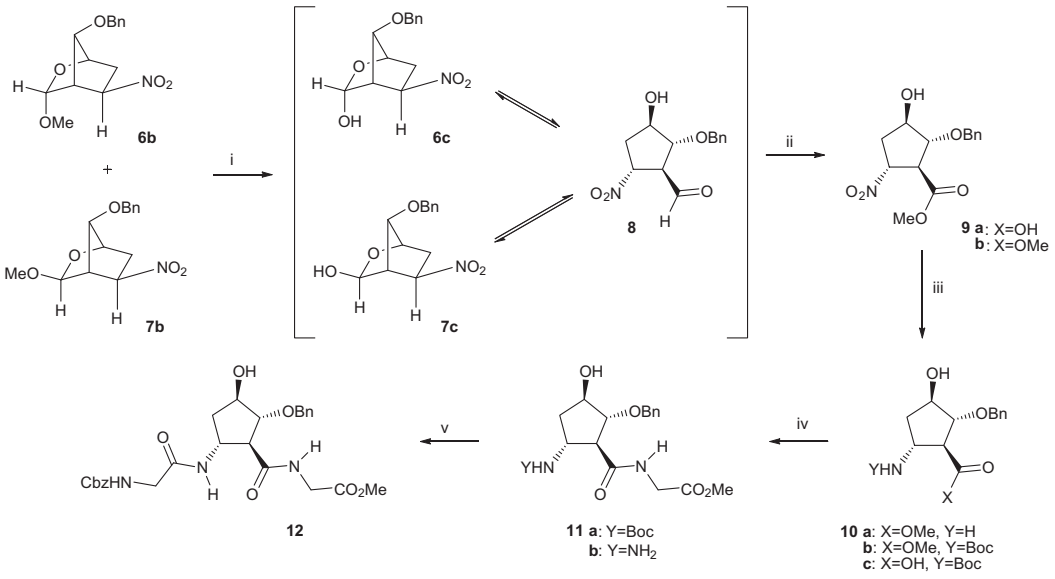


Figure 1. nOe enhancements observed for amino acid derivative **10b**.

Finally, the incorporation of amino acid derivative **10b** into peptides was studied, by means of the incorporation of glycine subunits to either the *N*- or the *C*-terminal position of this amino acid.[5d] Basic hydrolysis of the methoxycarbonyl moiety of **10b** (Scheme 6) afforded the corresponding carboxylic acid **10c**, which upon treatment with HCl-Gly-OMe, in the presence of DIEA and TBTU, gave dipeptide **11a** in 61% yield. Removal of the



Scheme 5. Reagents and conditions: (i) (a) TFA, H_2O, rt, 19 h; (b) Br_2, $BaCO_3$, dioxane, H_2O, rt, 6 h; (ii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (iii) TBAF, THF, rt; (iv) AcCl, MeOH, 0 °C, 14 h.



Scheme 6. Reagents and conditions: (i) (a) TFA/H_2O 3:1, rt, 3 h; (b) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O 1:1, 1 h; (ii) $TMSCHN_2$, Et_2O/MeOH 7:2, 15 min; (iii) (a) 1 M HCl, 10% Pd/C, H_2 (1 atm), MeOH, rt, 48 h; (b) $NaHCO_3$, $(Boc)_2O$, rt, 16 h; (iv) (a) $Ba(OH)_2$, THF/H_2O, 1 h; (b) HCl-Gly-OMe, TBTU, DIEA, 12 h; (v) (a) TFA, THF, rt, 1 h; (b) Cbz-Gly-OH, TBTU, DIEA, 6 h.

tert-butoxycarbonyl protecting group of **11a** under acidic conditions resulted in the formation of dipeptide derivative **11b**, which when reacted with Cbz-Gly-OH, DIEA and TBTU, provided the expected tripeptide **12** in 45% overall yield for the two steps. The presence of its two glycine subunits was confirmed by its ^{13}C NMR spectrum, which showed at 41.5 and 44.4 ppm the signals due to its methylene groups and at 170.0 and 170.3 ppm the signals corresponding to their amide carbonyls.

3. Conclusion

In conclusion, we have studied the synthesis of 5-nitro-2-oxabicyclo[2.2.1]heptan-3-ones **3a** and **3b** by intramolecular alkylation of nitronates of 6-deoxy-6-nitro-2-*O*-trifluoromethanesulfonyl-hexonolactones **2b** and **2d**, respectively. The results reported here, combined with results from previous similar studies,[5] allowed us to establish that these cyclizations take place only when substituents are present at both their C-3 and C-5 positions of the starting 2-*O*-triflyl-hexonolactones **2**. On the other hand, the successful cyclizations of **4b→6a**, **5b→7a**, **4d→6b,** and **5d→7b** constitute further confirmation of our previous findings that the above limitation regarding the cyclization of 2-*O*-trifluoromethanesulfonyl-hexonolactones **2** can be easily overcome when starting from the corresponding glycofuranosides. Finally, as a further application of this chemistry, we have reported the synthesis of the novel cyclopentane β-amino acid derivative **10b** and a protocol for its incorporation into peptides.

Work is currently in progress aimed at extending these studies to sugar-based 3-nitropropionic acids and sugar-based 4-nitrobutyric acids.

4. Experimental

4.1. General

Melting points were determined using a Kofler Thermogerate apparatus and are uncorrected. Specific rotations were recorded on a JASCO DIP-370 optical polarimeter. Infrared spectra were recorded on a MIDAC Prospect-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DPX-250 apparatus. Mass spectra were obtained on a Hewlett Packard 5988A mass spectrometer and high resolution mass spectra on a VG Autospect 20-250 spectrometer. Elemental analyses were obtained from the Elemental Analysis Service at the University of Santiago de Compostela. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and ethyl acetate/hexane mixtures as eluents; the TLC spots were visualized with Hanessian mixture. Column chromatography was carried out using Merck type 9385 silica gel.

4.2. 5-*O*-Benzyl-6-*O*-*tert*-butyldiphenyl-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 1b

To a suspension of sodium hydride (120 mg, 3.06 mmoles) and tetrabutylammoniun iodide (10 mg, 0.03 mmoles) in DMF cooled at 0 °C, a solution of 3-deoxy-1,2-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-α-D-glucofuranose **1a** (151 mg, 7.38 mmol) in dry DMF (8 mL), was added and the resulting mixture was stirred at rt for 1 h. Benzyl bromide (0.4 mL, 3.31 mmol) was then added and the resulting mixture was stirred at 50 °C for 1 h. Next, methanol (2 mL) was added and the mixture was stirred at 50 °C under argon for 2 h. The reaction mixture was cooled to rt, the solid was filtered off through Celite and the solution was concentrated to dryness under reduced pressure. The resulting residue was purified by flash column chromatography (ethyl acetate/hexane 1:9), to give compound **1b** (830 mg, 63% yield) as a yellow oil. $[\alpha]_D^{25} = -13.8$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz, ppm): 1.07 (s, 9H, $-^t$BuSi); 1.28 (s, 3H, $-CH_3$); 1.49 (s, 3H, $-CH_3$); 1.78–1.90 (m, 1H, H-3); 2.00 (dd, 1H, $J_{3',4}$ = 4.4 Hz, $J_{3',3}$ = 13.5 Hz, H-3′); 3.69–3.83 (m, 3H, H–5, H-6, H-6′); 4.45–4.52 (m, 1H, H–4); 4.61–4.68 (m, 3H, H–2, $-CH_2Ph$); 5.75 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 7.10–7.42 (m, 9H, 9 × Ar–H); 7.50–7.75 (m, 6H, 6 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 19.2 (C); 26.0 (CH_3); 26.6 (CH_3); 26.8 (3 × CH_3); 33.5 (CH_2); 63.8 (CH_2); 73.1 (CH_2); 78.2 (CH); 79.4 (CH); 80.4 (CH); 105.0 (CH); 110.8 (C); 127.3 (CH); 127.4 (2 × CH); 127.6 (3 × CH); 128.0 (2 × CH); 129.5 (CH); 129.6 (CH); 133.0 (2 × C); 134.7 (CH); 135.4 (2 × CH); 135.5 (2 × CH); 138.6 (C); MS-CI (*m*/*z*, %): 533 (5, $[M+H]^+$); 517 (15, $[M-CH_3]^+$); 417

(30, $[M-C_6H_{11}O_2]^+$); 288 (95, $[M-C_{12}H_{10}]^+$); 91 (100, $[PhCH_2]^+$); Anal. Calcd for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57. Found: C, 72.00; H, 7.78.

4.3. 5-*O*-Benzyl-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 1c

To a solution of 5-*O*-benzyl-3-deoxy-1,2-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-α-D-glucofuranose **1b** (830 mg, 1.58 mmol) in dry THF (52 mL), TBAF (3.5 mL, 1 M in THF) was added and the resulting mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (50 mL). The solution was washed with water (3 × 30 mL), dried (sodium sulfate), filtered, and concentrated to dryness in vacuo. The resulting residue was purified by flash column chromatography (ethyl acetate/hexane 1:2), to give compound **1c** (440 mg, 95% yield) as a yellow oil. $[\alpha]_D^{27} = -0.2$ (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 1.23 (s, 3H, $-CH_3$); 1.42 (s, 3H, $-CH_3$); 1.67–1.78 (m, 1H, H-3); 2.00 (dd, 1H, $J_{3',4}$ = 4.4 Hz, $J_{3',3}$=13.5 Hz, H-3′); 2.19 (br s, 1H, –OH); 3.47–3.66 (m, 3H, H-5, H-6, H-6′); 4.21 (dt, 1H, $J_{4,3'} = J_{4,5}$ = 4.4 Hz, $J_{4,3}$ = 10.7 Hz, H–4); 4.58–4.65 (m, 3H, H-2, $-CH_2Ph$); 4.69 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 7.18–7.27 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 26.0 (CH_3); 26.6 (CH_3); 34.5 (CH_2); 62.3 (CH_2); 73.2 (CH_2); 78.6 (CH); 79.7 (CH); 80.3 (CH); 104.9 (CH); 111.1 (C); 127.7 8 (3 × CH); 128.35 (2 × CH); 138.21 (C); IR (*v*, cm^{-1}): 3484 (b, OH); MS-CI (*m*/*z*, %): 295 (15, $[M+H]^+$); 279 (25, $[M-CH_3]^+$); 237 (60, $[M-C_3H_5O]^+$); 181 (55, $[M-C_6H_9O_2]^+$); 91 (100, $[PhCH_2]^+$); Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.90; H, 7.45.

4.4. 5-*O*-Benzyl-3-deoxy-1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulphonyl-α-D-glucofuranose 1d

Tosyl chloride (0580 mg, 3.02 mmol) was added to a solution of 5-*O*-benzyl-3-deoxy-α-D-glucofuranose **1c** (440 mg, 1.51 mmol) in dry pyridine (91 mL), and the resulting mixture was stirred at rt for 10 h and filtered over Celite. The liquids were evaporated off under reduced pressure, the residue was dissolved in dichloromethane (50 mL), and the solution was washed with a 2 M aq solution of hydrochloric acid (20 mL), water (2 × 20 mL) and brine (2 × 20 mL), dried (sodium sulfate), and filtered. After removal of the solvents under reduced pressure, the residue was purified by flash column chromatography (ethyl acetate/hexane 1:4), to give compound **1d** (660 mg, 98% yield) as a yellow oil. $[\alpha]_D^{20} = -12$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 1.30 (s, 3H, $-CH_3$); 1.47 (s, 3H, $-CH_3$); 2.04–2.12 (m, 2H, H-3, H-3′); 2.44 (s, 3H, $-CH_3$); 3.72–3.79 (m, 1H, H-5); 3.98–4.09 (m, 1H, H-6); 4.11–4.25 (m, 2H, H-6′, H-4); 4.55–4.69 (m, 3H, H-2, $-CH_2Ph$); 5.72 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 7.24–7.34 (m, 7H, 7 × Ar–H), 7.75–7.80 (m, 2H, 2 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 21.5 (CH_3); 26.0 (CH_3); 26.6 (CH_3); 34.8 (CH_2); 70.0 (CH_2); 73.4 (CH_2); 77.3 (2 × CH); 80.2 (CH); 105.2 (CH); 111.1 (C); 127.6 (CH); 127.7 (2 × CH); 127.8 (2 × CH); 128.2 (2 × CH); 129.8 (2 × CH); 132.5 (C); 137.6 (C); 144.8 (C); IR (*v*, cm^{-1}): 1598 (SO_2); MS-CI (*m*/*z*, %): 449 (40, $[M+H]^+$); 433 (45, $[M-CH_3]^+$); 373 (65, $[M-C_3H_7O_2]^+$); 299 (75, $[M-C_9H_9O_2]^+$); 91 (100, $[PhCH_2]^+$).

4.5. 5-*O*-Benzyl-3,6-dideoxy-6-iodo-1,2-*O*-isopropylidene-α-D-glucofuranose 1e

Sodium iodide (523 mg, 35.0 mmol) was added to a solution of 5-*O*-benzyl-3-deoxy-6-*O*-*p*-toluenesulphonyl-α-D-glucofuranose **1d** (520 mg, 1.16 mmol) in acetone (29 mL), and the resulting mixture was refluxed for 15 h. After cooling to rt, the mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was dissolved in diethyl ether (75 mL) and the solution was washed with water (75 mL) and a 1 M aqueous solution of sodium thiosulfate (75 mL), dried (sodium sulfate), and filtered. Removal of the solvent in vacuo was followed by purification of the residue by flash column chromatography (ethyl acetate/hexane 1:7), and compound **1e** (420 mg, 90% yield) was isolated as a yellow oil. $[\alpha]_D^{20} = -11$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 1.32 (s, 3H, $-CH_3$); 1.51 (s, 3H, $-CH_3$); 1.71–1.82 (m, 1H, H-3); 2.20 (dd, 1H, $J_{2,3'}$ = 4.6 Hz, $J_{3,3'}$ = 13.5 Hz, H-3′); 3.31–3.34 (m, 2H, H-5, H-6); 3.45 (dd, 1H, $J_{6',5}$ = 4.6 Hz, $J_{6',6}$ = 10.7 Hz, H-6′); 4.31–4.39 (m, 1H, H-4); 4.57 (d, 1H, $J_{7,7}$ = 6.5 Hz, –C*H*HPh); 4.70–4.76 (m, 2H, H-2, –CH*H*Ph); 5.76 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 7.25–7.39 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 6.3 (CH_2); 26.1 (CH_3); 26.7 (CH_3); 34.3 (CH_2); 72.4 (CH_2); 78.4 (CH); 79.1 (CH); 80.2 (CH); 105.0 (CH); 111.2 (C); 127.6 (CH); 127.7 (2 × CH); 128.1 (2 × CH); 137.5 (C); MS-ESI (*m*/*z*, %): 405 (30, $[M+H]^+$); 389 (50, $[M-CH_3]^+$); 347 (80, $[MH-C_3H_6O]^+$); 277 (15, $[M-I]^+$); 91 (100, $[PhCH_2]^+$); Anal. Calcd for $C_{16}H_{21}IO_4$: C, 47.54; H, 5.24; encontrado C, 47.77; H, 5.48.

4.6. 5-*O*-Benzyl-3,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose 1f

1,3,5-Trihydroxybenzene (phloroglucinol) (380 mg, 2.36 mmol) and sodium nitrite (230 mg, 3.29 mmol) were added to a solution of 5-*O*-benzyl-3-deoxy-6-iodo-α-D-glucofuranose **1e** (380 mg, 0.94 mmol) in dry DMSO (9 mL), and the resulting mixture was stirred at rt for 96 h. Next, water was added (15 mL) and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:3), to give compound **1f** (240 mg, 80% yield) as a yellow oil. $[\alpha]_D^{20} = -12$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 1.30 (s, 3H, $-CH_3$); 1.48 (s, 3H, $-CH_3$); 1.68–1.79 (m, 1H, H-3); 2.14 (dd, 1H, $J_{3',4}$ = 4.4 Hz, $J_{3',3}$ = 13.5 Hz, H-3′); 4.17–4.25 (m, 1H, H-5); 4.28–4.34 (m, 1H, H-4); 4.48–4.61 (m, 2H, H-2, H-6); 4.63 (s, 2H, $-CH_2$-Ph); 4.70–4.75 (m, 1H, H-6′); 5.75 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 7.23–7.35 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 25.7 (CH_3); 26.3 (CH_3); 35.0 (CH_2); 73.8 (CH_2); 76.6 (CH_2); 77.0 (CH); 77.2 (CH); 79.9 (CH); 105.0 (CH); 111.2 (C); 127.6 (2 × CH); 127.7 (CH); 128.1 (2 × CH); 136.8 (C); IR (*v*, cm^{-1}): 1554 (s, NO_2); 1376 (s NO_2); MS-CI (*m*/*z*, %): 324 (27, $[M+H]^+$); 266 (100, $[M-C_3H_6O]^+$); 250 (62, $[MH-C_3H_6O_2]^+$); 91 (100, $[PhCH_2]^+$); Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.24; H, 6.42; N, 4.15.

4.7. 5-*O*-Benzyl-3,6-dideoxy-6-nitro-D-glucono-1,4-lactone 2a

5-*O*-Benzyl-3,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-D-glucofuranose **1f** (180 mg, 0.54 mmol) was dissolved in a 1:1 trifluoroacetic acid/water mixture (20 mL) and the reaction mixture was stirred at rt for 12 h. The solvent was evaporated in vacuo and the residue was coevaporated with toluene (3 × 10 mL) to give 5-*O*-benzyl-3,6-dideoxy-6-nitro-D-glucofuranose as a clear gum. This crude product was dissolved in a 2:1 dioxane/water mixture (10 mL), barium carbonate (150 mg, 0.75 mmol) and then bromine (0.08 mL, 0.75 mmol) were added, after which the reaction mixture was stirred at rt in darkness for 6 h. The reaction mixture was then quenched with saturated aq sodium thiosulfate solution (until colorless) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexane 1:2), to give **2a** (60 mg, 41% yield) as a clear oil. $[\alpha]_D^{25} = +39.6$ (*c* 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 2.02–2.34 (m, 2H, H-3, H-3′); 3.59 (br s, 1H, –OH); 4.16–4.51 (m, 7H, H-2, H-4, H-5, H-6, H-6′,

–CH_2Ph); 7.01–7.22 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 31.0 (CH_2); 66.8 (CH); 74.7 (CH_2); 75.4 (CH_2); 76.3 (CH); 76.8 (CH); 128.3 (2 × CH); 128.5 (CH); 128.6 (2 × CH); 136.1 (C); 177.0 (C); IR (ν, cm^{-1}): 3445 (b, OH); 1798 (CO); 1555 (s, NO_2); 1380 (s, NO_2); MS-CI (*m*/*z*, %): 282 (10, $[M+H]^+$); 237 (25, $[M-CO_2]^+$); 207 (56, $[M-C_2H_2O_3]^+$); 91 (100, $[PhCH_2]^+$); Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.72; H, 5.43; N, 5.02.

4.8. 5-*O*-Benzyl-3,6-dideoxy-6-nitro-2-*O*-trifluoromethanesulphonyl-D-glucono-1,4-lactone 2b

5-*O*-Benzyl-3,6-dideoxy-6-nitro-D-glucono-1,4-lactone **2a** (60 mg, 0.21 mmol) was dissolved in dry dichloromethane (1.4 mL) and the solution was then cooled down to −30 °C under argon. Dry pyridine (0.05 mL, 0.63 mmol) and trifluoromethanesulphonic anhydride (0.06 mL, 0.27 mmol) were added and the mixture was stirred at −30 °C for 1.5 h. The reaction was diluted with dichloromethane (10 mL), and washed with dilute aq hydrochloric acid (10 mL) and brine (10 mL). The organic layer was dried (sodium sulfate) and concentrated to dryness to give lactone **2b** as a clear gum, which was used in the next step without further purification, after keeping it in vacuo overnight.

4.9. Methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-β-D-glucofuranoside-4a and methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-α-D-glucofuranoside 5a

Acetyl chloride (0.31 mL, 4.44 mmol) was added to a cooled (0 °C) solution of **1f** (240 mg, 0.74 mmol) in dry methanol (5 mL) and the resulting mixture was stirred at 0 °C for 14 h. After neutralization with Na_2CO_3, the mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. Flash column chromatography (ethyl acetate/hexane 1:1) of the residue afforded a chromatographically pure 6:1 mixture of anomers **4a** and **5a** (150 g, 70% yield), which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 2.00–2.08 (m, 4H, H-3a, H-3b, H-3′a, H-3′b); 2.22 (br s, 2H, –OHa, –OHb); 3.34 (s, 3H, –CH_3a); 3.46 (s, 3H, –CH_3b); 4.07–4.17 (m, 2H, H-5a, H-5b); 4.19–4.25 (m, 2H, H-2a, H-2b); 4.48–4.65 (m, 9H, H-6a, H-6b, H-6a′, H-6b′, H-4a, H-4b, –*CH*HPha, –CH_2Phb); 4.74 (d, 1H, *J* = 13.2 Hz, –*CH*HPha); 4.78 (s, 1H, H-1a); 4.83 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1b); 7.25–7.37 (m, 10H, 5 × Ar–Ha, 5 × Ar–Hb); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 34.4 (CH_2b); 36.1 (CH_2a); 55.5 (CH_3a); 56.0 (CH_3b); 74.0 (CH_2a); 74.6 (CH_2b); 76.0 (CHa); 76.9 (CHb); 77.0 (CH_2b); 77.7 (CH_2a); 78.5 (CHb); 78.8 (CHa); 80.5 (CHa, CHb); 102.9 (CHb); 110.0 (CHa), 128.4 (2 × CHa); 128.5 (2 × CHb); 128.6 (CHa); 128.7 (CHb); 128.9 (2 × CHa); 129.0 (2 × CHb); 136.1 (Ca); 136.2 (Cb); IR (ν, cm^{-1}): 3443 (b, OH); 1553 (s, NO_2); 1375 (s, NO_2); MS-CI (*m*/*z*, %): 298 (76, $[M+H]^+$); 280 (80, $[MH-H_2O]^+$); 207 (61, $[MH-C_7H_7]^+$); 91 (100, $[PhCH_2]^+$). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.39; H, 6.30; N, 4.67.

4.10. Methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-2-*O*-trifluoromethanesulfonyl-β-D-glucofuranoside 4b and methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-2-*O*-trifluoromethanesulfonyl-α-D-glucofuranoside 5b

A mixture of compounds **4a** and **5a** (0.13 g, 0.47 mmol) was subjected to the same procedure as for the transformation of compound **2a** into compound **2b**, for a period of 25 min. The reaction was quenched with 2 M HCl (2 mL), diluted with water (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (sodium sulfate) and concentrated to dryness under reduced pressure to a mixture of **4b** and **5b**, which was used without further purification.

4.11. (1*S*,3*R*,4*R*,5*S*,6*R*)-6-(Benzyloxy)-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane 6a and (1*S*,3*S*,4*R*,5*S*,6*R*)-6-(benzyloxy)-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane 7a

A 1 M solution of tetrabutylammonium fluoride in THF (1.1 mL) was added to a solution of a recently obtained mixture of **4b** and **5b** in THF (5 mL) and the resulting mixture was stirred at rt under argon for 1.5 h. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (10 mL). The solution was washed with water (3 × 10 mL), and the organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting gum was purified by flash column chromatography (ethyl acetate/hexane 1:5) to give bicycle **6a** (100 mg, 97% yield from **4a**), as an orange oil, and bicycle **7a** (5 mg 28% yield from **5a**), as a yellow oil. Data for **6a**: $[\alpha]_D^{27} = +58$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 1.88–2.07 (m, 2H, H-7, H-7′); 3.17 (m, 1H, H-4); 3.52 (s, 3H, –OCH_3); 4.29–4.33 (m, 2H, H-1, H-6); 4.75 (ABq, 2H, *J* = 12.3 Hz, –CH_2Ph); 5.10 (t, 1H, $J_{5,4} = J_{5,6}$ = 2.5 Hz, H-5); 5.17 (d, 1H, $J_{3,4}$ = 2.7, H-3); 7.26–7.44 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 34.4 (CH_2), 47.1 (CH), 56.6 (CH_3), 71.8 (CH_2), 78.4 (CH), 84.2 (CH), 84.7 (CH); 104.5 (CH); 127.9 (3 × CH); 128.4 (2 × CH); 137.1 (C); MS-CI (*m*/*z*, %): 280 (5, $[M+H]^+$); 248 (25, $[M-OCH_3]^+$); 233 (10, $[M-NO_2]^+$); 91 (100, $[PhCH_2]^+$); IR (ν, cm^{-1}): 1552 (s, NO_2), 1373 (s, NO_2); Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.47; H, 6.32; N, 5.17. Data for **7a**: $[\alpha]_D^{25} = +32$ (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 1.81–1.84 (m, 1H, H-7); 2.09–2.12 (m, 1H, H-7′); 3.05 (m, 1H, H-4); 3.41 (s, 3H, –OCH_3); 4.26–4.31 (m, 2H, H-1, H-6); 4.42–4.44 (m, 1H, H-5); 4.67 (s, 1H, H-3); 4.69 (m, 2H, –CH_2Ph); 7.26–7.39 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 34.2 (CH_2), 47.0 (CH), 56.5 (CH_3), 71.6 (CH_2), 78.2 (CH), 84.0 (CH), 84.5 (CH); 104.3 (CH); 127.7 (3 × CH); 128.2 (2 × CH); 136.7 (C); MS-CI (*m*/*z*, %): 280 (5, $[M+H]^+$); 248 (17, $[M-OCH_3]^+$); 233 (30, $[M-NO_2]^+$); 91 (100, $[PhCH_2]^+$); IR (ν, cm^{-1}): 1551 (s, NO_2), 1372 (s, NO_2); Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.31; H, 6.04; N, 5.24.

4.12. 3-*O*-Benzyl-5-deoxy-5-nitromethyl-D-xylono-1,4-lactone 2c

When compound **1g** (0.18 g, 0.56 mmol) was subjected to the conditions used for the preparation of **2a**, D-xylono-1,4-lactone **2c** (0.09 g, 0.32 mmol, 57%) was obtained as a yellow oil. $[\alpha]_D^{23} = +32$ (*c* 1.8, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 2.21–2.34 (m, 1H, H-5); 2.55–2.67 (m, 1H, H-5′); 3.00 (br s, 1H, –OH); 4.31–4.84 (m, 7H, H-2, H-3, H-4, H-6, H-6′, –CH_2Ph); 7.28–7.43 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 27.4 (CH_2); 71.5 (CH_2); 71.6 (CH); 72.5 (CH_2); 76.4 (CH); 79.6 (CH_2); 127.9 (2 × CH); 128.3 (CH); 128.7 (2 × CH); 174.7 (C); IR (ν, cm^{-1}): 3413 (b, OH); 1786 (s, CO); 1554 (s, NO_2); 1376 (s, NO_2); MS-CI (*m*/*z*, %): 264 (1, $[M-OH]^+$); 145 (25, $[M-CH_3]^+$); 91 (100, $[PhCH_2]^+$). Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.63, H, 5.43, N, 5.04.

4.13. 3-*O*-Benzyl-5-deoxy-5-nitromethyl-2-*O*-trifluoromethanesulphonyl-D-xylono-1,4-lactone 2d

Applying the conditions used for the preparation of compound **2b**, lactone **2c** was transformed into its 2-*O*-triflyl derivative **2d**, which was used without further purification after keeping it in vacuo overnight.

4.14. Methyl-3-*O*-benzyl-5-deoxy-5-nitromethyl-β-D-xylofuranoside 4c and methyl-3-*O*-benzyl-5-deoxy-5-nitromethyl-α-D-xylofuranoside 5c

5-Nitromethyl-α-D-xylofuranose **1g** (370 mg, 1.15 mmol), under the conditions used for the transformation of compound **1f**

to give a mixture of **4a** and **5a**, provided a residue that was purified by flash column chromatography (ethyl acetate/hexane 1:2), to give compound **4c** (150 mg, 44% yield) and its anomer **5c** (160 mg, 45% yield), both as colorless oils. Data for **4c**: $[\alpha]_D^{27} = -59$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz, ppm): 2.28–2.38 (m, 2H, H-5, H-5′), 2,54 (s, 1H, –OH), 3.38 (s, 3H, $-OCH_3$), 3.91 (dd, 1H, $J_{3,2} = J_{3,4} = 3.3$ Hz, H-3), 4.20–4.33 (m, 2H, H-2, H-6), 4.47–4.51 (m, 2H, H-4, H-6′), 4.52 (d, 1H, *J* = 12.1 Hz, –C*H*HPh), 4.68 (d, 1H, *J* = 12.1 Hz, –CH*H*Ph), 4.75 (d, 1H, $J_{1,2} = 1.9$ Hz, H-1), 7.29–7.39 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 28.4 (CH_2), 55.9 (CH_3), 72.3 (CH_2), 72.6 (CH_2), 74.4 (CH), 77.2 (CH), 83.5 (CH), 104.5 (CH), 127.8 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 137.3 (C); IR (*v*, cm^{-1}): 3445 (b, OH); 1555 (s, NO_2); 1374 (s, NO_2); MS-CI (*m*/*z*, %): 298 (47, $[M+H]^+$); 280 (95, $[MH-H_2O]^+$); 207 (73, $[MH-C_7H_7]^+$); 91 (100, $[PhCH_2]^+$); Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.64; H, 6.52; N, 4.77. Data for **5c**: $[\alpha]_D^{27} = -15$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz, ppm): 2.27–2.39 (m, 2H, H-5, H-5′), 2,80 (d, 1H, *J*=6.9 Hz, –OH), 3.44 (s, 3H, $-OCH_3$), 3.91 (dd, 1H, $J_{3,2} = J_{3,4} = 3.3$ Hz, H-3), 4.18–4.28 (m, 2H, H-2, H-6), 4.56–4.64 (m, 3H, H-4, H-6′, –C*H*HPh), 4.76 (d, 1H, *J* = 6.8 Hz, –CH*H*Ph), 4.93 (d, 1H, $J_{1,2} = 4.7$ Hz, H-1), 7.26–7.39 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 27.3 (CH_2), 55.6 (CH_3), 71.5 (CH_2), 72.5 (CH_2), 74.8 (CH), 77.9 (CH), 83.6 (CH), 101.4 (CH), 127.6 (2 × CH), 127.8 (CH), 128.4 (2 × CH), 137.5 (C), IR (*v*, cm^{-1}): 3442 (b, OH), 1557 (s, NO_2), 1374 (s, NO_2), MS-CI (*m*/*z*, %): 298 (63, $[M+H]^+$), 280 (80, $[MH-H_2O]^+$), 207 (65, $[MH-C_7H_7]^+$), 91 (100, $[PhCH_2]^+$); Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.69; H, 6.57; N, 4.80.

4.15. (1*R*,3*R*,4*S*,5*R*,7*R*)-7-Benzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane 6b and (1*R*,3*S*,4*S*,5*R*,7*R*)-7-benzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane 7b

Proceeding as for the mixture of **4a** and **5a**, a mixture of anomers **4c** and **5c** (310 mg, 1.05 mmol) was transformed into a mixture of their *O*-triflyl derivatives **4d** and **5d**, which were directly converted into a mixture of their respective bicylic glycosides **6b** and **7b** (220 mg, 71% yield) The residue was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give bicycle **6b** (107 mg) and bicycle **7b** (113 g), as yellow oils. Data for **6b**: $[\alpha]_D^{27} = -40.5$ (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz, ppm): 2.41 (dd, 1H, $J_{6,5} = 8.7$ Hz, $J_{6,6'} = 14.7$ Hz, H-6), 2.72–2.92 (m, 1H, H-6′), 3.38 (s, 3H, $-OCH_3$), 3.64–3.74 (m, 1H, H-4), 4.00–4.10 (m, 1H, H-7), 4.20–4.28 (m, 1H, H-1), 4.41 (ABq, 2H, *J* = 6.7 Hz, $-CH_2$-Ph), 4.86–5.00 (m, 1H, H-5), 5.01 (d, 1H, $J_{3,4} = 3.1$ Hz, H-3), 7.17–7.40 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 34.7 (CH_2), 47.7 (CH), 56.0 (CH_3), 71.8 (CH_2), 77.9 (CH), 78.4 (CH), 81.1 (CH), 101.4 (CH), 127.6 (2 × CH), 127.9 (CH), 128.4 (2 × CH), 136.8 (C); MS-CI (*m*/*z*, %): 280 (50, $[M+H]^+$); 248 (65, $[M-OCH_3]^+$); 233 (70, $[M-NO_2]^+$); 91 (100, $[PhCH_2]^+$); IR (*v*, cm^{-1}): 1552 (s, NO_2), 1373 (s, NO_2). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.37; H, 6.18; N, 5.14. Data for **7b**: $[\alpha]_D^{25} = -14.8$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz, ppm): 2.29 (dd, 1H, $J_{6,5} = 8.8$ Hz, $J_{6,6'} = 14.5$ Hz, H-6), 2.77 (m, 1H, H-6′); 3.35 (s, 3H, $-OCH_3$), 3.52 (s, 1H, H-4), 4.25 (s, 1H, H-7), 4.29–4.40 (m, 2H, $-CH_2Ph$); 4.49 (d, 1H, *J* = 11.4 Hz, $-CHNO_2$), 4.55 (s, 1H, H-3), 7.15–7.39 (m, 5H, 5 × Ar–H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 35.2 (CH_2), 48.2 (CH), 55.1 (CH_3), 72.0 (CH_2), 75.7 (CH), 80.3 (CH), 81.2 (CH), 103.3 (CH), 127.7 (2 × Ar–H), 127.9 (Ar–H), 128.4 (2 × Ar–H), 137.0 (C). MS-CI (*m*/*z*, %): 280 (50, $[M+H]^+$); 248 (53, $[M-OCH_3]^+$); 233 (85, $[M-NO_2]^+$); 91 (100, $[PhCH_2]^+$); IR (*v*, cm^{-1}): 1551 (s, NO_2), 1372 (s, NO_2). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.12; H, 6.26; N, 4.94.

4.16. (1*S*,2*R*,3*R*,5*R*)-Methyl 2-(benzyloxy)-3-hydroxy-5-nitrocyclopentanecarboxylate 9b

A solution of a mixture of bicycles **6b** and **7b** (120 mg, 0.432 mmol) in a 3:1 TFA/H_2O mixture (1.38 mL) was stirred at rt for 4 h. The reaction mixture was evaporated to dryness and coevaporated with toluene (3 × 2 mL). Next, 2-methyl-2-butene (1.05 mL, 9.92 mmol), $NaClO_2$ (280 mg), and $NaH_2PO_4{\cdot}H_2O$ (240 mg) were added to a solution of the resulting residue in 1:1 *t*-BuOH/H_2O (2.30 mL) and the resulting mixture was stirred at rt for 1 h. After the addition of water (2 mL), the mixture was extracted with ethyl acetate (4 × 4 mL), and the combined organic layers were dried (sodium sulfate), filtered, and concentrated to dryness under reduced pressure. To a solution of the resulting crude acid **9a** in 7:2 Et_2O/MeOH (1 mL), $TMSCHN_2$ (0.025 mL/2 M in hexane) was added and the mixture was stirred at rt for 15 min and then evaporated to dryness. The resulting residue was purified by flash column chromatography (ethyl acetate/hexane 1:1) to give methyl 5-nitrocyclopentanecarboxylate **9b** (85 mg, 87% yield) as a clear yellow oil. $[\alpha]_D^{23} = +113.0$ (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz, ppm): 2.01 (br s, 1H, OH), 2.41 (ddd, 1H, $J_{4,5} = 3.2$ Hz, $J_{4,3} = 7.6$ Hz, $J_{4,4'} = 13.9$ Hz, H-4), 2.64 (ddd, 1H, $J_{4',3} = 5.2$ Hz, $J_{4',5} = 7.6$ Hz, $J_{4',4} = 13.9$ Hz, H-4′), 3.72–3.75 (m, 1H, H-1), 3.76 (s, 3H, $-OCH_3$), 4.09–4.12 (m, 1H, H-2), 4.29–4.33 (m, 1H, H-3), 4.55 (d, 1H, *J* = 11.8 Hz, –CHPh), 4.68 (d, 1H, *J* = 11.8 Hz, –CHPh); 5.63–5.45 (m, 1H, H-5), 7.30–7.37 (m, 5H, 5 × Ar–H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 37.5 (CH_2), 52.8 (CH), 53.0 (OCH_3), 71.7 (CH_2), 75.0 (CH), 84.5 (CH), 86.6 (CH), 127.7 (2 × CH), 128.0 (CH), 128.4 (2 × CH), 137.1 (C), 171.3 (C═O); MS-CI (*m*/*z*, %): 296 [$(M+H)^+$, 72], 295 [$(M)^+$, 20], 294 [$(M-H)^+$, 80], 181 (99), 91 [$(PhCH_2)^+$, 100]; IR (*v*, cm^{-1}): 3467 (OH); 1737 (CO); 1552, 1373 (NO_2). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94, H, 5.80, N, 4.74. Found: C, 56.99; H, 5.71; N, 4.63.

4.17. (1*S*,2*R*,3*R*,5*R*)-Methyl 2-(benzyloxy)-5-(*tert*-butoxycarbonylamino)-3-hydroxy-cyclopentanecarboxylate 10b

At first, 1 M aq HCl (0.02 mL) and 10% Pd/C (50 mg) were added sequentially to a deoxygenated solution of **9b** (50 mg, 0.15 mmol) in MeOH (5 mL). After deoxygenation, the mixture was stirred at rt for 48 h under a hydrogen atmosphere (1 atm). The reaction mixture was filtered over a pad of Celite, which was then washed with MeOH. The filtrate was concentrated to dryness under reduced pressure. Saturated aq $NaHCO_3$ was added to a solution of the resulting crude amine **10a** and $(Boc)_2O$ (110 mg, 0.50 mmol) in dioxane (2 mL) until basic pH and the mixture was stirred at rt for 16 h. Next, 10% HCl (5 mL) was added and the mixture was extracted with AcOEt (3 × 5 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated to dryness under reduced pressure. The residue was subjected to flash column chromatography (AcOEt/hexane 1:1) to give **10b** (30 mg, 0.09 mmol, 57% from **9b**) as a yellow oil. $[\alpha]_D^{27} = -3.7$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz, ppm): 1.35 (s, 9H, 3 × CH_3), 1.92 (dt, 1H, $J_{4a,4b} = 13.9$ Hz, $J_{4a,3} = J_{4a,5} = 7.1$ Hz, H-4a), 2.15 (ddd, 1H, $J_{4b,4a} = 13.9$ Hz, $J_{4b,5} = 7.6$ Hz, $J_{4b,3} = 3.5$ Hz, H-4b), 2.74 (dd, 1H, $J_{1,5} = 7.1$ Hz, $J_{1,2} = 5.4$ Hz, H-1), 2.78 (br s, 1H, –OH); 3.72 (s, 3H, $-OCH_3$), 4.02–4.09 (m, 1H, H-2), 4.21 (dt, 1H, $J_{3,4a} = 7.1$ Hz, $J_{3,2} = J_{3,4b} = 3.5$ Hz, H-3), 4.37–4.45 (m, 1H, H-5), 4.55 (d, 1H, $J_{H,H'} = 11.8$ Hz, –CHPh), 4.61 (d, 1H, $J_{H,H'} = 11.8$ Hz, –CHPh), 4.90 (d, 1H, $J_{NH,5} = 8.2$ Hz, –NH), 7.28–7.40 (m, 5H, 5 × Ar–H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): (3 × CH_3), 39.7 (CH_2), 52.3 (CH_3 + CH), 56.4 (CH), 72.0 (CH_2), 75.2 (CH), 79.6 (C), 87.8 (CH), 127.7 (2 × CH-Ar); 127.8 (CH-Ar); 128.4 (2 × CH-Ar); 137.6 (C-Ar); 155.0 (C═O); 173.8 (C═O). IR (*v*, cm^{-1}): 3372 (b, OH + NH); 1715 (s, C═O); 1694 (s, N—C═O). MS-CI (*m*/*z*, %): 366 (41, $[MH]^+$); 308

(100, $[M-{}^tBu]^+$); 91 (88, $[CH_2Ph]^+$). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.71; H, 7.83; N, 3.75.

4.18. (1*S*,2*R*,3*R*,5*R*)-Methyl 2-(benzyloxy)-5-(*tert*-butoxycarbonylamino)-3-hydroxy-1-(methoxycarbonylglycylcarbamoyl)cyclopentane 11a

At first, $Ba(OH)_2{\cdot}8H_2O$ (80 mg, 0.24 mmol) was added to a solution of compound **10b** (30 mg, 0.08 mmol) in 1:2 THF/H_2O (1.5 mL), and the mixture was stirred at rt for 1 h. The reaction mixture was then neutralized with DOWEX 50WX4-50 and the resin was filtered off and washed with MeOH. Removal of the solvent under reduced pressure, provided carboxylic acid **10c**, which was directly dissolved in dry CH_2Cl_2 (1 mL). Next, TBTU (30 mg, 0.10 mmol) and DIEA (0.05 mL, 0.26 mmol) were added and the mixture was stirred at rt for 15 min, after which HCl-Gly-OMe (0.01 g, 0.08 mmol) was added and the stirring was continued for 12 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq HCl (5 mL). The organic layer was dried (sodium sulfate), filtered, and concentrated to dryness under reduced pressure. Flash column chromatography of the solid residue (AcOEt/hexane 2:1), gave dipeptide **11a** (20 mg, 0.04 mmol, 61% from **10b**), as a colorless oil. $[\alpha]_D^{20} = +21.6$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz, ppm): 1.43 (s, 9H, 3 × CH_3), 1.79–1.90 (m, 1H, H-4a), 2.15–2.26 (m, 1H, H-4b), 2.87 (br s, 1H, H-1), 3.32 (br s, 1H, –OH), 3.74 (s, 3H, –OCH_3), 4.03–4.05 (m, 2H, 2 × CH-Gly), 4.20–4.35 (m, 3H, H-2 + H-3 + H-5), 4.57 (2 × d, 2H, $J_{H,H'}$ = 12.7 Hz, 2 × CHPh), 4.97 (br s, 1H, N-H), 7.28–7.34 (m, 5H, 5 × Ar–H), 8.05 (br s, 1H, –NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 28.3 (3 × CH_3), 39.8 (CH_2), 41.5 (CH_2), 52.3 (CH_3), 54.4 (CH), 58.3 (CH), 71.9 (CH_2), 75.1 (CH), 80.2 (C), 85.9 (CH), 127.7 (2 × CH–Ar), 127.8 (CH–Ar), 128.4 (2 × CH–Ar), 137.8 (C–Ar), 156.2 (C═O), 170.1 (C═O), 174.2 (C═O). IR (ν, cm^{-1}): 3310 (s NH + OH), 1737 (s, C═O), 1678 (s, N—C═O), 1629 (s, N—C═O). MS-CI (*m*/*z*, %): 423 (24, $[MH]^+$); 365 (64, $[M-{}^tBu]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{21}H_{30}N_2O_7$: C, 59.70; H, 7.16; N, 6.63. Found: C, 59.59; H, 7.31; N, 6.89.

4.19. 1*S*,2*R*,3*R*,5*R*)-Methyl 2-(benzyloxy)-5-(benzyloxycarbonylglycylamino)-3-hydroxy-1-(methoxycarbonylglycylcarbamoyl)cyclopentane 12

At first, TFA (0.2 mL) was added to a solution of dipeptide **11a** (20 mg, 0.05 mmol) in THF (0.5 mL) and the mixture was stirred at rt for 1 h. The liquids were coevaporated with toluene (3 × 2 mL) in a rotary evaporator and the remaining crude amine **11b** was used directly without any further treatment.

A solution of TBTU (30 mg, 0.09 mmol) and DIEA (0.03 mL, 0.14 mmol) in dry CH_2Cl_2 (0.5 mL) was stirred at rt for 15 min, then Cbz-Gly-OH (0.01 g, 0.08 mmol) was added and the stirring was continued for 15 min. Next, a solution of crude **11b** in dry CH_2Cl_2 (1 mL) was added and the new mixture was stirred at rt for 6 h. The reaction mixture was washed with 10% aq HCl (3 mL) and the organic layer was dried (sodium sulfate) and concentrated to dryness in a rotary evaporator. Flash column chromatography ((AcOEt) of the resulting residue gave tripeptide **12** (20 g, 45% yield from **11a**) as a colorless oil. $[\alpha]_D^{20} = +6.0$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz, ppm): 1.87–2.00 (m, 1H, H-4a); 2.13–2.23 (m, 1H, H-4b); 2.86 (br s, 1H, H-1); 3.71 (s, 3H, –OCH_3); 3.75 (br s, 1H, –OH) 3.80 (2 × d, 2H, $J_{H,H'}$ = 5.2 Hz, 2 × CH-Gly); 4.00 (2 × d, 2H, $J_{H,H'}$ = 5.2 Hz, 2 × CH-Gly); 4.20–4.32 (m, 2H, H-2 + H-3); 4.40–4.51 (m, 1H, H-5); 4.52–4.60 (m, 2H, –CH_2Ph); 5.06–5.12 (m, 2H, –CH_2Ph); 5.63 (br s, 1H, –NH); 6.84 (br s, 1H, –NH); 7.27–7.37 (m, 10H, 10 × Ar–H); 8.07 (br s, 1H, –NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 39.3 (CH_2), 41.5 (CH_2), 44.4 (CH_2), 52.3 (CH_3), 53.3 (CH), 57.6 (CH), 67.3 (CH_2), 72.0 (CH_2), 75.1 (CH), 86.0 (CH), 127.9 (4 × CH–Ar), 128.1 (2 × CH–Ar), 128.3 (4 × CH–Ar), 128.5 (CH–Ar), 128.6 (C–Ar), 135.9 (C–Ar), 137.8 (C–Ar), 156.7 (C═O), 170.0 (C═O), 170.3 (C═O), 173.8 (C═O); IR (ν, cm^{-1}): 3299 (s, NH + OH), 1728 (s, C═O), 1692 (s, N—C═O), 1656 (s, N—C═O). MS-CI (*m*/*z*, %): 515 (31, $[MH]^+$); 457 (79, $[M-{}^tBu]^+$); 91 (100, $[CH_2Ph]^+$); Anal. Calcd for $C_{26}H_{31}N_3O_8$: C, 60.81; H, 6.08; N, 8.18. Found: C, 60.60; H, 5.80; N, 7.94.

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