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Stereocontrolled transformation of nitrohexofuranoses into cyclopentylamines via 2-oxabicyclo[2.2.1]heptanes. III: synthesis of enantiopure methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-amino-3,4,5-trihydroxycyclopentanecarboxylate

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ABSTRACT

The first total synthesis of enantiopure methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-amino-3,4,5-trihydroxycyclopentanecarboxylate was carried out according to our recent novel strategy for the transformation of nitrohexofuranoses into cyclopentylamines, which is based on an intramolecular cyclization leading to 2-oxabicyclo[2.2.1]heptane derivatives. Differences in reactivity for this key step were rationalized by using molecular mechanism-based calculations.

1. Introduction

Carbohydrates[1] and 'naked sugars'[2] provide abundant sources of versatile synthons of great usefulness for the stereoselective synthesis of natural products. These powerful synthetic strategies are well-established tools of special interest for the preparation of richly functionalized carbo- and heterocycles. Two approaches have been applied to carbohydrate-based cyclizations. One of them involves cyclization of an open chain carbohydrate derivative, and the other includes the generation of a bicyclic derivative consisting of the original sugar ring and the new ring, which is followed by the opening of the sugar ring. Although several synthetic applications of this approach have been developed,[3] the variant involved in the intramolecular alkylation of the nitronate of the D-glucose derivative **4** to give the bicyclic lactone **6a** had not been explored until our recent synthesis of β-peptide **7a**,[4] that includes a polyhydroxylated cyclopentane β-amino acid (see Scheme 1). This approach takes advantage of the sugar pool for the generation of chemical diversity and the synthetic potential of nitroalkanes to form carbon–carbon bonds ahead of transformations of the nitro group into a variety of functionalities, including its reduction to an amino group.[5]

Herein, we report two slight modifications of this route that allowed us to prepare enantiomerically pure 3,4,5-trihydroxy-*trans*-2-aminocyclopentanecarboxylic acid derivative **8a** from D-glucose. Both modifications allowed us to substantially improve the yield of the key nitronate based intramolecular cyclization steps **5**→**6a** and **11**→**12**, respectively. The results indicated that the latter cyclization is more efficient than the former, an outcome that could be explained by molecular mechanics-based calculations.

2. Results and discussion

The reaction of the easily prepared nitroglucofuranose derivative **1** with trifluoroacetic acid and water, followed by anomeric oxidation of the resulting hydroxy lactol **2** with bromine and barium carbonate afforded the lactone **3** as a yellow oil (94% yield from **1**). Reaction of **3** with triflic anhydride in pyridine furnished the corresponding triflate **4**, which when treated with TBAF in THF readily underwent an intramolecular displacement of the triflate group by the carbanion α to the nitro group to afford the bicyclic β-nitrolactone **6a** in 75% yield for the last two steps (previous yield, 41%). This substantial yield improvement was achieved when the concentration of triflate **4** in the reaction mixture was raised from 0.10 M to 0.11 M; this compound was also allowed to stand in vacuo for 12 h just before its transformation.

The stereochemical outcome of this key step leading to compound **6a** was explained by assuming that both bicyclic compounds **6a** and **6b** could be formed from the nitronate of compound **5** (Scheme 2). Under these reaction conditions, compounds **6a** and **6b** should be in equilibrium with their common nitronate **6c.** At equilibrium, the thermodynamically more stable compound **6a** should be favored with respect to compound **6b**, where the NO_2 and the OBn substituents are eclipsed. This explains the remarkable stereoselectivity of the cyclization.

In a modification of our previous synthetic route leading to **7a**, the reaction of this bicyclic lactone with sodium methoxide in

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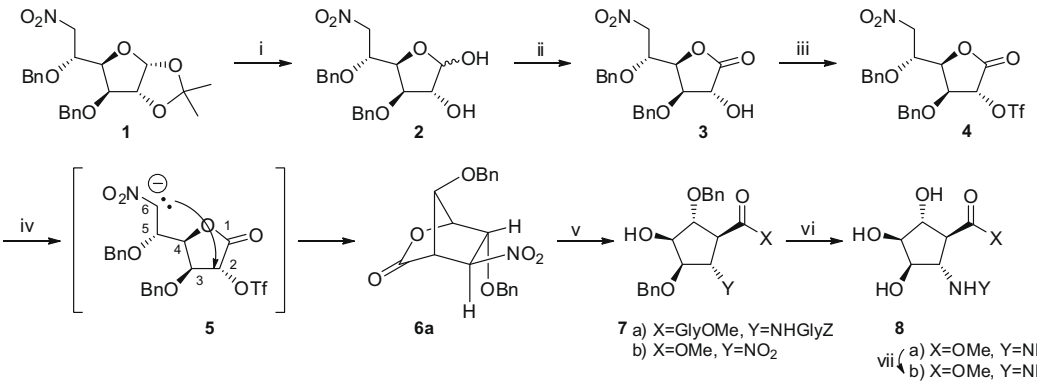
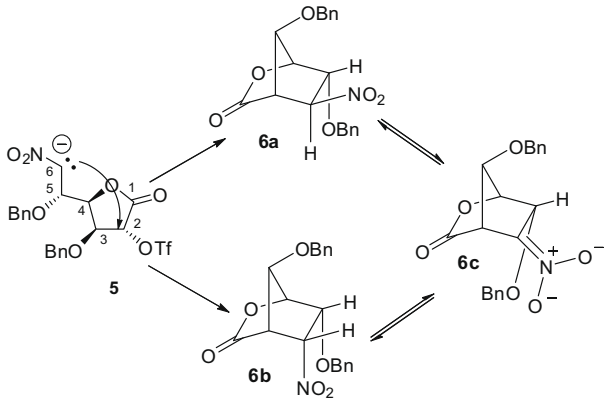


Scheme 1. Reagents and conditions: (i) TFA/H_2O (1:1), rt, 19 h; (ii) Br_2, $BaCO_3$, dioxane/H_2O (2:1), rt, 36 h (94% from **1**); (iii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (iv) TBAF, THF, rt, 6 h (75% from **3**); (v) MeONa/MeOH (0.5 M), rt, 1.5 h, 65%; (vi) H_2, Pd/C, MeOH, citric acid, 50 h; (vii) CbzCl, $NaHCO_3$, MeOH, rt, 6 h (60% from **7b**).



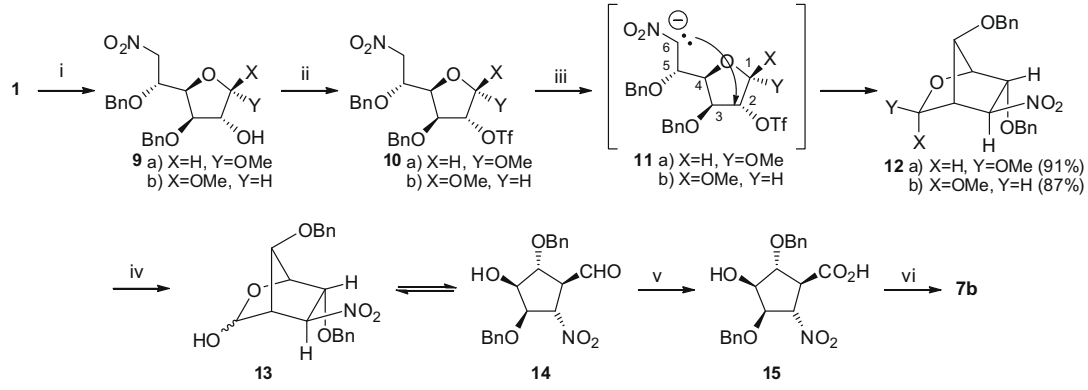
Scheme 2.

MeOH followed by hydrogenation of the resulting methyl 5-nitrocyclopentane carboxylate **7b** in an acidic medium provided the desired β-amino acid ester **8a**, as a result of the reduction of the nitro group to the amine and simultaneous removal of the benzyl-protecting groups. Finally, **8a** was directly reacted with CbzCl in order to transform it into its derivative **8b**, with its amino group protected by a Cbz moiety.

Over the course of our previous work in this field, we obtained a cyclopentylamine-based glycosidase inhibitor from D-glucose via the bicyclic pyranoside **12b** (Scheme 3).[4a] A salient aspect of this approach is that the nitronate-based cyclization of the epimeric mixture **11a** and **11b** led to the isolation of a single compound **12b** in moderate yield (46%). Here, we describe further studies on this route, which allowed us to clarify and improve the yield of this key cyclization, and to apply it to a new, longer but more efficient preparation of the above-mentioned cyclopentane β-amino acid derivative **8a**.

When nitroglucofuranose derivative **1** (the common starting material for routes in Schemes 1 and 3) was reacted with acetyl chloride in methanol, it provided a 90% yield of a 1.2:1 epimeric mixture **9a** and **9b**, from which anomers **9a** and **9b** were isolated carefully by column chromatography. Reaction of **9a** with triflic anhydride and pyridine, allowed us to obtain the key compound **10a**, which when directly treated with TBAF in THF readily underwent the expected C-alkylation of the starting nitronate **11a**. The resulting bicylic compound **12a**, which was obtained in 91% yield (not previously isolated), was easily identified by its spectroscopic and analytical data. Additionally, its structure was confirmed by X-ray crystallography.[6] On the other hand, anomer **9b** was similarly converted into bicyclic pyranoside **12b** (87% yield, previous yield 46%), via compound **10b**. A remarkable aspect of this route is that the intramolecular cyclization leading to **12a** was slightly more efficient than that leading to its anomer **12b**. On the other hand, when the anomeric mixture of **9a** and **9b** was subjected to this reaction sequence, a 89% yield of a 1.3:1 anomeric mixture of **12a** and **12b** was obtained as seen from the ^1H NMR spectrum of this mixture.[7] This anomeric ratio, which differs from those of the starting mixture of **9a** and **9b**, additionally confirms the different cyclization efficiencies of their derivatives **10a** and **10b**.

According to our plan, hydrolysis of the mixture **12a** and **12b** followed by their immediate oxidation with sodium chlorite provided the desired 5-nitrocyclopentane-carboxylic acid **15**, which



Scheme 3. Reagents and conditions: (i) AcCl, MeOH, 0 °C to rt, 13 h (49% for **9a**, 41% for **9b**); (ii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (iii) TBAF, THF, rt, 14 h (91% for **12a** from **9a**, 87% for **12b** from **9b**); (iv) TFA/H_2O (3:1), rt, 4 h; (v) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (1:1); (vi) $TMSCHN_2$, Et_2O/MeOH (7:2), rt, 15 min (75% from **12a** + **12b**).

was directly converted into the previously obtained methyl ester derivative **7b** when it was allowed to react with trimethylsilyldiazomethane. We assumed that the hydrolysis of the bicyclic glycoside mixture **12a** and **12b** produced the expected mixture of hemiacetals **13**, which is in equilibrium with its open aldehyde form **14**. Treatment of this mixture **13** and **14** with sodium chlorite resulted in the oxidation of **14** to **15**, a process that promotes the displacement of this equilibrium to compound **14**. This hypothesis was supported by the ^{1}H NMR of the mixture **13** and **14**.[8]

3. Structural rationale for the reactivity difference

The only structural difference between compound **4** and compounds **10a** or **10b** is the presence of a C=O group at the C-1 position in the former reactant instead of the OMe group at the same position in the latter reactants. As aforementioned, compounds **10a** and **10b** cyclize more efficiently than compound **4**. The opposite behavior would be expected, based on the premise that the positive charge induced at the C-2 position of lactone **4** by the carbonyl group should promote a nucleophilic attack on that atom by the negatively charged carbon atom C-6. Therefore, one would expect that the replacement of the carbonyl group by a methoxy substituent would decrease the reactivity. Since electronic effects do not seem to explain these reactivity differences, we searched for an alternative explanation based on steric allowance afforded by the substituents.

To shed some light into this option, we have carried out Molecular Dynamic calculations aimed at explaining the reaction yields, assuming that they could be rationalized in terms of the steric effects that govern the cyclations of nitrosugars **4** and **10**.

The main working hypothesis for our calculations was that the central role of the substituents at C-1 is to act as 'steering groups' on the reaction, influencing it through their steric and/or electrostatic effects, rather than substantially altering the electronic structure of these compounds. These modulators can facilitate or impede the generation of what has been called 'near attack conformations' (or NAC's),[9,10] that is, those in which the reacting centers C-2 and C-6 in compounds **4, 10a** or **10b** are brought closer to a distance equal or below to the sum of their van der Waals radii. The molecular dynamics (MDs)-based methodology utilized herein is described in the Section 5.

In order to estimate the effect of replacing the carbonyl at position C-1 of nitrolactone **4** by a OMe group, we have compared the C-2–C-6 distance distribution functions of lactone **4** with those of compounds **10a** and **10b**. The results are shown in Figure 1. A study of this figure indicates that compound **4** has very few reactive conformations (around 20 at around 3.5 Å), which increase substantially in the OMe-containing compounds **10** regardless of group configuration, in qualitative agreement with experimental results.

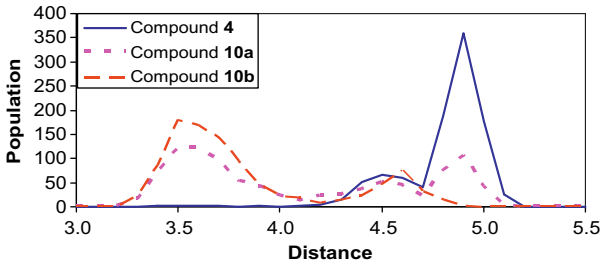


Figure 1. Distribution of distances between reactive atoms C-2 and C-6 for compounds **4**, **10a**, and **10b** as obtained from MD production trajectories.

As pointed out above, one would expect that the replacement of the carbonyl group by a methoxy substituent would decrease the reactivity. The opposite behavior predicted by our calculations and validated by our reaction yields could be explained by the preponderance of the ring flexibility over the electronic withdrawing effect brought about by the presence of the OMe group. It would be expected that bringing the reactant atoms to a value around the van der Waals contact will distort the ring, a process that is more favored when a OMe group is present at position C-1. To verify this hypothesis, we have calculated the fluctuations of the ring dihedral angles in compounds **4** and **10a**. The time evolution of torsion angle around C-2–C-3 bond for these compounds is displayed in Figure 2. As seen from this figure, the OMe-containing compound **10a** has larger amplitude oscillations than the C=O counterpart, a result that supports our explanation for the difference in reactivity amongst these compounds.

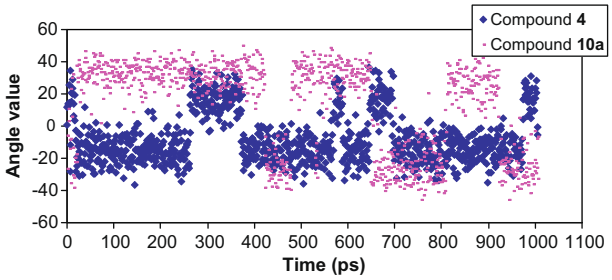


Figure 2. Time evolution of the dihedral angle centered around the C-2–C-3 bond, as obtained from our MD simulations.

4. Conclusion

In conclusion, we have adapted our strategy for the transformation of nitrosugars into carbasugars[4] to the development of two efficient alternative stereocontrolled transformations of D-glucose into (1*S*,2*S*,3*R*,4*S*,5*R*)-2-amino-3,4,5-trihydroxycyclopentanecarboxylic acid derivative **8a**. The alternative via nitrosugarlactone **3** (Scheme 1), which consists of 13 steps, allowed us to obtain this polyhydroxylated cyclopentane β-amino acid **8b** in 15% overall yield. On the other hand, the alternative via nitroglycosides **9a** and **9b** is longer but more efficient, because target **8b** is obtained in 20% yield after 14 steps (Scheme 3).

Molecular dynamic simulations performed on the cyclization substrates **4** and **10** allowed us to elaborate a hypothesis for the increased reactivity of the latter compounds based on the larger flexibility of their rings.

Work that is currently in progress is aimed at extending these studies to hexoses other than D-glucose, in order to prepare a range of polyhydroxylated cyclopentane β-amino acids prior the study of the structural, physical, and biological properties of their β-peptides. We will also apply our simulation protocols to the above-mentioned hexoses, in order to determine whether the substituent effects on the reactivity are due to steric effects, like in the case presented here.

5. Experimental

5.1. Computer-based simulations

To determine the influence of the nature and stereochemical conformation of the substituents, we subjected all molecules to a molecular mechanics protocol that started with a 100-step steepest descent energy minimization stage to alleviate steric clashes. In a second phase, these molecules underwent a molecular dynamics (MD) protocol, starting with a 5-ps equilibration stage and ending in a 1 ns production phase. The parameters utilized in our MD calculations resembled those employed in the synthetic route.

Hence, we use a temperature value of 300 K and a dielectric constant of 7.6, the value that corresponds to THF, the solvent used in the synthesis. The molecular mechanic simulations were performed with the DISCOVER module in the INSIGHTII suite of programs.[11] The force field used throughout these calculations was CVFF,[12] in a NVT ensemble regime. The present algorithm is far less time consuming than quantum mechanical calculations, and does not require parameter calibration that is needed for the transition state molecular mechanics-based calculations.[13]

5.2. Synthetic procedures

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. 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.

5.3. 3,5-Di-*O*-benzyl-6-deoxy-6-nitro-D-glucono-1,4-lactone 3

3,5-Di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose **1** (2.04 g, 4.76 mmol) was dissolved in a mixture of trifluoroacetic acid/water (1:1, 120 mL), and the reaction mixture was stirred at room temperature until the starting material had been consumed (TLC, ethyl acetate/hexane 1:5) (19 h). The solvent was evaporated in vacuo, and the residue was coevaporated with toluene (3 × 50 mL) to give 3,5-di-*O*-benzyl-6-deoxy-6-nitro-D-glucofuranose **2** as a clear gum, which was used in the next step without further purification.

This crude reaction (1.85 g, 4.75 mmol) was dissolved in dioxane/water (2:1, 90 mL). Barium carbonate (1.03 g, 5.23 mmol) and then bromine (0.6 mL, 11.88 mmol) were added, and the reaction mixture was stirred for 36 h at room temperature with the exclusion of light. The reaction mixture was quenched with saturated aqueous sodium thiosulfate solution (until the mixture was colorless), and the mixture was then extracted with ethyl acetate (3 × 200 mL). The combined ethyl acetate extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The crude residue was purified by flash column chromatography (ethyl acetate/hexane 1:2) to give 3,5-di-*O*-benzyl-6-deoxy-6-nitro-D-glucono-1,4-lactone **3** (1.74 g, 4.49 mmol, 94% from **1**) as a clear oil: $[\alpha]_D^{25} = +17.9$ (*c* 2.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 4.10–4.17 (m, 1H); 4.38–4.87 (m, 10H); 7.08–7.36 (m, 10H, 10 × CH_{ar}). ^{13}C NMR ($CDCl_3$, ppm): 71.68, 72.52, 74.39, 75.12, 75.92, 78.18, 79.82, 127.88, 128.08, 128.27, 128.51, 128.62, 136.39, 136.47, 174.83. IR (NaCl, ν_{max}, cm^{-1}): 3442 (br, OH); 1791 (st, CO) 1555, 1380 (st, NO_2). MS (CI, *m/z*, %): 386 (2, $[M-H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.77; H, 5.53; N, 3.52.

5.4. 3,5-Di-*O*-benzyl-6-deoxy-6-nitro-2-*O*-trifluoro-methanesulfonyl-D-glucono-1,4-lactone 4

Compound **3** (1.91 g, 4.93 mmol) was dissolved in dry dichloromethane (40 mL), and the solution was then cooled down to −30 °C under argon. Pyridine (1.5 mL) and trifluoromethanesulfonic anhydride (1.20 mL, 7.40 mmol) were added, and the mixture was stirred at −30 °C for 1.5 h. The reaction mixture was diluted with dichloromethane (100 mL), washed with dilute hydrochloric acid (100 mL) and brine (100 mL). The organic layer was dried (anhydrous sodium sulfate) and concentrated to dryness to give 3,5-di-*O*-benzyl-6-deoxy-6-nitro-2-*O*-trifluoro-methanesulfonyl-D-glucono-1,4-lactone **4** as a clear gum, which was used in the next step without further purification after keeping it in vacuo overnight.

5.5. (1*S*,4*S*,5*S*,6*R*,7*R*)-6,7-Dibenzyloxy-5-nitro-2-oxabicyclo [2.2.1]-heptan-3-one 6a

A 1 M solution of tetrabutylammonium fluoride in THF (4.93 mL) was added to a solution of triflate **4** in THF (44 mL), and the resulting mixture was stirred under argon for 6 h. The solvent was evaporated, and the residue dissolved in dichloromethane (100 mL). The solution was washed with water (3 × 100 mL), and the organic layer was dried (anhydrous sodium sulfate) and concentrated in vacuo. The resulting gum was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give the (1*S*,4*S*,5*S*,6*R*,7*R*)-6,7-dibenzyloxy-5-nitro-2-oxabicyclo[2.2.1]heptan-3-one **6a** (1.36 g, 3.68 mmol, 75% from **3**) as a yellow oil. $[\alpha]_D^{21} = -35.0$ (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 4.03 (s, 1H, H-1); 4.28–4.30, 4.51–4.54 (2 × m, 4H, CH_2Ph, H-6, H-7); 4.67 (dd, 1H, $J_{5,6}$ = 4.0 Hz, $J_{5,4}$ = 2.3 Hz, H-5); 4.79 (d, 1H, $J_{H,H'}$ = 11.9 Hz, CH_2Ph); 4.81 (d, 1H, $J_{H,H'}$ = 11.9 Hz, CH_2Ph); 5.05 (d, 1H, $J_{4,5}$ = 2.3 Hz, H-4); 7.17–7.40 (m, 10H, 10 × CH_{ar}). ^{13}C NMR ($CDCl_3$, ppm): 50.29, 72.57, 72.66, 80.22, 81.42, 82.19, 84.78, 127.97, 128.21, 128.31, 128.63, 128.71, 128.79, 135.39, 136.60, 169.33. IR (NaCl, ν_{max}, cm^{-1}): 1804 (st, CO); 1554, 1361 (st, NO_2). MS (CI, *m/z*,%): 370 (6, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.07; H, 5.36; N, 3.51.

5.6. Methyl (1*S*,2*R*,3*S*,4*R*,5*S*)-2,4-Dibenzyloxy-3-hydroxy-5-nitrocyclopentanecarboxylate 7b

Bicyclolactone **6a** (0.20 g, 0.54 mmol) was added over a solution of MeONa in MeOH (1 mL, 0.5M), and the mixture was stirred under argon at rt for 1.5 h. This mixture was then concentrated to dryness and purified by flash column chromatography (ethyl acetate/hexane 1:2) to give methyl ester **7b** (0.13 g, 0.32 mmol, 65% yield) as a yellow oil. $[\alpha]_D^{21} = +67.0$ (*c* 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 2.50 (br s, 1H, H-1); 3.64–3.68 (m, 1H, H-4); 3.75 (s, 3H, OCH_3); 4.07–4.09 (m, 1H, H-2); 4.18–4.20 (m, 1H, H-3); 4.53–4.79 (m, 5H, 2 × CH_2Ph, OH); 5.41 (t, 1H, *J* = 6.6 Hz, H-5); 7.25–7.36 (m, 10H, 10 × CH_{ar}). ^{13}C NMR ($CDCl_3$, ppm): 51.34, 52.87, 71.77, 73.10, 74.00, 82.89, 83.19, 88.68, 127.73, 127.81, 127.85, 128.31, 128.42, 128.64, 136.46, 136.92, 170.17. IR (NaCl, ν_{max}, cm^{-1}): 3381 (br, OH); 1796 (st, CO); 1578, 1386 (st, NO_2). MS (CI, *m/z*, %): 402 (2, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 63.02; H, 5.94; N, 3.61.

5.7. Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-Benzyloxycarbonyl-amino-3,4,5-trihydroxycyclopentanecarboxylate 8b

Compound **7b** (0.35 g, 0.87 mmol) was dissolved in methanol (7.2 mL), and the solution was deoxygenated by bubbling argon through it. Next, Pd–C (0.10 g, 10% w/w) and citric acid (0.20 g, 1.04 mmol) were added, and the suspension was stirred at rt under a hydrogen atmosphere of 1 atm for 50 h. The reaction mixture was filtered through Celite, eluted with methanol, and the filtrate evaporated in vacuo to give the corresponding amine **8a** (0.16 g, 0.87 mmol) that was directly dissolved in MeOH (7.2 mL). After saturated aqueous sodium bicarbonate solution (4.5 mL) and benzyl chloroformate (0.14 mL, 1.01 mmol) were added, the resulting

mixture was stirred at rt for 6 h, and then concentrated to dryness. The residue was partitioned between ethyl acetate and water, and the aqueous portion extracted with ethyl acetate (4 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol 9:1) to give methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-benzyloxycarbonylamino-3,4,5-trihydroxycyclopentane-carboxylate **8b** (0.17 g, 0.52 mmol, 60% from **7b**) as a colorless oil. $[\alpha]_D^{26} = +125.5$ (*c* 2.0, $CHCl_3$). ^1H NMR (acetone-d_6, ppm): 2.65–2.71 (br s, 1H, H-1); 2.97 (br s, 1H, OH); 3.60 (s, 3H, OCH_3); 3.81–3.86 (m, 1H, H-2); 4.00–4.06 (m, 2H, H-4, H-5); 4.15–4.21 (m, 2H, H-3, -OH); 4.55 (br s, 1H, OH); 5.03 (d, 1H, $J_{H,H'}$ = 12.6 Hz, CH_2Ph); 5.09 (d, 1H, $J_{H,H'}$ = 12.6 Hz, CH_2Ph); 6.75 (br s, 1H, NH); 7.27–7.37 (m, 5H, 5 × CH_{ar}). ^{13}C NMR (acetone-d_6, ppm): 53.04, 55.40, 60.69, 67.56, 76.43, 77.96, 79.43, 129.56, 129.59, 130.12, 139.13, 158.07, 174.87. IR (NaCl, ν_{max}, cm^{-1}): 3465 (br, NH, OH); 1731 (st, CO); 1683 (st, NCO). MS (CI, *m/z*, %): 326 (1, $[M+H]^+$); 315 (62, $[M-CH_3]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.89; N, 4.31. Found: C, 55.42; H, 5.77; N, 4.21.

5.8. Methyl 3,5-di-*O*-benzyl-6-deoxy-6-nitro-D-glucofuranosides 9a and 9b

Acetyl chloride (0.74 mL, 10.34 mmol) was added to a cooled (0 °C) solution of 3,5-di-*O*-benzyl-6-deoxy-6-nitro-D-glucofuranose **1** (0.74 g, 1.72 mmol) in dry methanol (11.2 mL) and the resulting mixture was allowed to warm to rt and stirred for 13 h. The mixture was concentrated to dryness, to give a (1.2:1) mixture of epimers **9a** and **9b**. The residue was subjected to flash column chromatography (ethyl acetate/hexane 1:3) to give the α-anomer **9a** (0.34 g, 0.84 mmol, 49%) as a colorless oil and the β-anomer **9b** (0.29 g, 0.72 mmol, 41%) as a crystalline solid.

Spectroscopic data for ***9a***: $[\alpha]_D^{22} = -6.0$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 2.84 (d, 1 H, $J_{OH,2}$ = 5.9 Hz, OH); 3.48 (s, 3H, OCH_3); 4.04–4.06 (m, 1H, H-5); 4.21–4.31 (m, 3H, H-2, H-3, H-4); 4.53–4.82 (m, 6H, 2 × CH_2Ph, H-6, H-6′); 5.01 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1); 7.18–7.35 (m, 10H, 10 × CH_{ar}). ^{13}C NMR ($CDCl_3$, ppm): 55.66, 71.35, 72.73, 74.23, 75.94, 76.78, 77.29, 82.94, 101.97, 127.40, 127.50, 128.22, 128.27, 137.05, 137.08. IR (NaCl, ν_{max}, cm^{-1}): 3455 (br, OH); 1558, 1376 (st, NO_2). MS (CI, *m/z*,%) = 403 (8, $[M]^+$); 402 (23, $[M-H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.51; H, 6.24; N, 3.50.

Spectroscopic data for ***9b***: mp 91–93 °C. $[\alpha]_D^{22} = -77.0$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 2.84 (br s, 1H, OH); 3.39 (s, 3H, OCH_3); 3.93 (d, 1H, $J_{3,4}$ = 4.2 Hz, H-3); 4.22 (s, 1H, H-2); 4.40–4.55 (m, 1H, H-4); 4.50 (m, 1H, CH_2Ph); 4.55–4.58 (m, 2H, CH_2Ph); 4.59–4.69 (m, 3H, CH_2Ph, H-5, H-6′); 4.80 (s, 1H, H-1); 4.89 (dd, 1H, $J_{6,6'}$ = 13.2 Hz, $J_{6,5}$ = 2.8 Hz, H-6); 7.20–7.38 (m, 10H, 10 × CH_{ar}). ^{13}C NMR ($CDCl_3$, ppm): 55.89, 71.83, 72.67, 75.02, 77.19, 77.29, 80.53, 82.35, 109.92, 127.55, 127.58, 128.09, 128.12, 136.97. IR (NaCl, ν_{max}, cm^{-1}): 3448 (br, OH); 1551, 1379 (st, NO_2). MS (CI, *m/z*, %) = 403 (5, $[M]^+$); 402 (11, $[M-H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.55; H, 6.30; N, 3.47.

5.9. (1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-6,7-Dibenzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane 12a

Compound **9a** (0.20 g, 0.50 mmol) was dissolved in dry dichloromethane (4.0 mL), and the solution cooled to −30 °C under nitrogen. Pyridine (0.15 mL) and trifluoromethanesulfonic anhydride (0.12 mL, 0.74 mmol) were added, and the mixture was stirred for 1.5 h at −30 °C. The reaction mixture was diluted with dichloromethane (10 mL), washed with dilute hydrochloric acid (10 mL) and brine (10 mL). The organic layer was dried (anhydrous sodium sulfate) and concentrated to dryness to give the corresponding triflate **10a** as a clear gum, which was used in the next step without further purification.

A 1 M solution of tetrabutylammonium fluoride in THF (0.5 mL) was added to a solution of the previously obtained triflate in THF (4.5 mL), and the resulting mixture was stirred under argon for 14 h. The solvent was evaporated, and the residue dissolved in dichloromethane (10 mL). The solution was washed with water (3 × 10 mL), and the organic layer was dried (anhydrous sodium sulfate) and concentrated in vacuo. The resulting gum was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give compound **12a** (0.17 g, 0.45 mmol, 91% from **9a**) as a yellow oil. $[\alpha]_D^{22} = -23.7$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 3.41 (s, 3H, OCH_3); 3.52 (m, 1H, H-4); 4.20 (m, 1H, H-7); 4.40 (m, 1H, H-1); 4.48 (2 × d, 1H, $J_{H,H'}$ = 11.5 Hz, CH_2Ph); 4.74–4.78 (m, 3H, CH_2Ph, H-6); 5.03 (s, 1H, H-1); 5.26 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 7.25–7.36 (m, 10H, 10 × CH_{ar}). ^{13}C NMR ($CDCl_3$, ppm): 48.26, 55.15, 72.06, 72.23, 76.49, 81.20, 83.01, 87.27, 103.18, 126.77, 127.36, 127.62, 127.68, 136.48, 137.17. IR (NaCl, ν_{max}, cm^{-1}): 1550, 1378 (st, NO_2). MS (CI, *m/z*, %): 386 (3, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.58; H, 6.09; N, 3.78.

5.10. (1*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-6,7-Dibenzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane 12b

Compound **9b** (0.15 g, 0.37 mmol) was dissolved in dry dichloromethane (3.0 mL), and the solution cooled to −30 °C under nitrogen. Pyridine (0.11 mL) and trifluoromethanesulfonic anhydride (0.09 mL, 0.56 mmol) were added, and the mixture was stirred for 1.5 h at −30 °C. The reaction mixture was diluted with dichloromethane (8 mL), washed with dilute hydrochloric acid (8 mL) and brine (8 mL). The organic layer was dried (anhydrous sodium sulfate) and concentrated to dryness to give the corresponding triflate **10b** as a clear gum, which was used in the next step without further purification.

A 1 M solution of tetrabutylammonium fluoride in THF (0.37 mL) was added to a solution of the previously obtained triflate in THF (3.3 mL), and the resulting mixture was stirred under argon for 14 h. The solvent was evaporated, and the residue dissolved in dichloromethane (8 mL). The solution was washed with water (3 × 8 mL), and the organic layer was dried (anhydrous sodium sulfate) and concentrated in vacuo. The resulting gum was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give compound **12b** (0.12 g, 0.32 mmol, 87% yield from **9b**) as a yellow solid. Mp 99–101 °C. $[\alpha]_D^{19} = -47.2$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 3.49 (s, 3 H, OCH_3); 3.67 (br s, 1H, H-4); 4.12 (s, 1H, H-7); 4.22–4.24 (m, 1H, H-1); 4.29 (d, 1H, $J_{H,H'}$ = 11.5 Hz, CH_2Ph); 4.48 (d, 1H, $J_{H,H'}$ = 11.5 Hz, CH_2Ph); 4.78 (d, 1H, $J_{H,H'}$ = 12.1 Hz, CH_2Ph); 4.82 (m, 1H, H-6); 4.86 (d, 1H, $J_{H,H'}$ = 12.1 Hz, CH_2Ph); 4.99 (s, 1H, H-5); 5.16 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 7.27–7.47 (m, 10H, 10 × CH_{ar}). ^{13}C NMR ($CDCl_3$, ppm): 47.97, 56.18, 72.02, 72.16, 79.10, 81.45, 83.19, 83.57, 101.93, 127.81, 127.85, 127.89, 128.18, 128.39, 136.44, 137.83. IR (NaCl, ν_{max}, cm^{-1}): 1552, 1371 (st, NO_2). MS (CI, *m/z*, %): 386 (2, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.49; H, 6.05; N, 3.67.

5.11. Methyl (1*S*,2*R*,3*S*,4*R*,5*S*)-2,4-dibenzyloxy-3-hydroxy-5-nitrocyclopentanecarboxylate 7b

A mixture (1.3:1) of compounds **12a** and **12b** (0.52 g, 1.35 mmol) was dissolved in trifluoroacetic acid/water (3:1, 12 mL) and stirred at room temperature until the starting material had been consumed (TLC, ethyl acetate/hexane 1:2) (4 h). The sol-

vent was evaporated in vacuo and the residue was coevaporated with toluene (3 × 20 mL) to give an unstable mixture of isomers **13** and **14** (0.32 g, 0.86 mmol), which was directly dissolved in *tert*-butanol/water (1:1, 20 mL). After 2-methyl-2-butene (6.6 mL), sodium chlorite (1.76 g, 19.43 mmol), and sodium dihydrogenphosphate dihydrate (1.76 g, 9.72 mmol) were added, the mixture was stirred for 1 h. until the starting material had been consumed (TLC, ethyl acetate/hexane 1:1). Water (15 mL) was added, and the solution extracted with ethyl acetate (4 × 20mL). The combined ethyl acetate extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The resulting crude carboxylic acid **15** (0.33 g, 0.85 mmol) was directly dissolved in ethyl ether/methanol (7:2, 9 mL). A 2 M solution of trimethylsilyldiazomethane in ethyl ether (0.5 mL, 1.1 mmol) was added, and the mixture was stirred at rt for 15 min (TLC, ethyl acetate/hexane 3:1). The mixture was concentrated to dryness and purified by flash column chromatography (ethyl acetate/hexane 1:2) to give the methyl ester **7b** (0.35 g, 0.87 mmol, 75% from **12a + 12b**) as a yellow oil, with the same data as described before.

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7. The ^{1}H NMR spectrum of the epimeric mixture **12a** + **12b** displayed two singlets at 3.41 ppm and 3.49, both due to the anomeric OMe substituents, respectively. A ratio 1.1:1.0 for both anomers was deduced from these signals.
8. The ^{1}H NMR spectrum of the mixture **13**+**14** includes two signals at 4.70 ppm and at 4.85 ppm, corresponding to the H-3 protons of anomers **13**. The signal displayed at 9.45 ppm was attributed to the aldehyde proton of compound **14**.
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