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Stereocontrolled transformation of nitrohexofuranoses into cyclopentylamines via 2-oxabicyclo[2.2.1]heptanes. Part 2: Synthesis of (1*S*,2*R*,3*S*,4*S*,5*R*)-3,4,5-trihydroxy-2-aminocyclopentanecarboxylic acid

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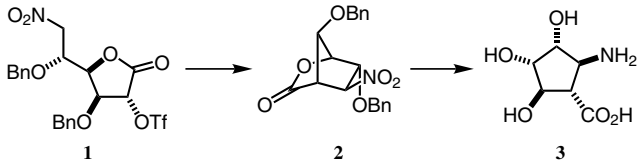
Abstract—A recent new strategy for the transformation of nitrohexofuranoses into cyclopentylamines, based on intramolecular cyclization followed by controlled opening of the resulting 2-oxabicyclo[2.2.1]heptane derivatives, allowed the first total synthesis of (1*S*,2*R*,3*S*,4*S*,5*R*)-2,3,4-trihydroxy-5-aminocyclopentanecarboxylic acid from L-idose.

1. Introduction

Although less abundant than α-amino acids, β-amino acids have been receiving considerable attention in recent years mainly due to their structural, chemical and biological properties and their utility as chiral auxiliaries and building blocks.[1] Moreover, β-amino acids have been easily incorporated into peptides, which proved to be more stable metabolically[2] and to have more tendency to fold than their α-amino counterparts.[3] In particular, peptides incorporating cyclic β-amino acids exhibit a strong tendency to adopt very stable secondary structures in short peptide sequences, due to the limited conformational mobility of the cyclic monomers.

Among the known carbocyclic β-amino acids, the four isomers of 2-aminocyclopentanecarboxylic acids have been the most commonly investigated.[3] Thus (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin) is a natural compound isolated independently by two groups from *Bacillus cereus* and *Streptomyces setonii*, which has been shown to exhibit potent antifungal activity in vivo against *Candida albicans*.[4] This amino acid was used to replace the proline subunit in the tetrapeptide morphiceptin resulting in a peptidomimetic pharmacologically more active than the former.[5] β-Oligopeptides consisting of *trans*-2-aminocyclopentanecarboxylic acid have a high propensity to adopt a 12-helical folding pattern.[6] *cis*-2-aminocyclopentanecarboxylic acid oligomers were later shown to be unnatural foldamers more suitable for rational design of new peptides showing novel tertiary structures, because they can adopt sheet like structures by switching from helix to nonpolar strands.[7]

Several methods have been described for the synthesis of cyclopentane β-amino acids.[1c] However, very few syntheses of polyhydroxylated derivatives have been reported.[8] We have recently reported the synthesis of the polyhydroxylated *trans*-2-aminocyclopentanecarboxylic acid **3** from a D-glucose derivative **1** by a novel route including a key step consisting of an stereoselective preparation of bicyclic sugarnitrolactone **2** (Scheme 1).[9]



1 2 3

Scheme 1.

The extension of this promising novel synthetic methodology to the plethora of hexofuranoses is of evident interest in order to expand the limited range of known 2-aminocyclopentanecarboxylic acids by the

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preparation of several isomeric trihydroxylated pentacyclic β-amino acids.

2. Results and discussion

Such studies will enhance the potential impact of these novel compounds and allow the preparation of hydrophilic and hydrophobic cyclopentane β-peptides. Accordingly, we describe herein the synthesis of enantiomerically pure 3,4,5-trihydroxy-2-aminocyclopentanecarboxylic acid **16** from L-idose (Scheme 2). Selective protection of the hydroxy group at the C-6 position of known L-idofuranose derivative **4**[10] with *tert*-butyldiphenylsilyl chloride followed by benzylation of the resulting furanose **5** with benzyl bromide and sodium hydride and further treatment of fully protected furanose **6** with TBAF in THF allowed us to obtain idose derivative **7**. This compound was next converted into the desired nitrofuranose **10** via **8** and **9**, a known protocol for the replacement of hydroxyl groups by nitro groups.[11] The acetonide of the nitroidofuranose **10** was removed with trifluoroacetic acid and water and the anomeric position of the resulting derivative **11** was selectively oxidized to idonolactone **12** by treatment with bromine and barium carbonate. Reaction of this lactone **12** with triflic anhydride and pyridine allowed us to obtain the key compound **13**, which when directly reacted with TBAF in THF readily underwent the expected intramolecular C-alkylation of the initially formed nitronate. The resulting bicyclic compound **14**, which was obtained in moderate yield, was easily identified from its spectroscopic and analytical data. Additionally, this assignment was supported by the X-ray crystal structure of closely related bicyclic nitrolactol **21** (Fig. 1).[12]

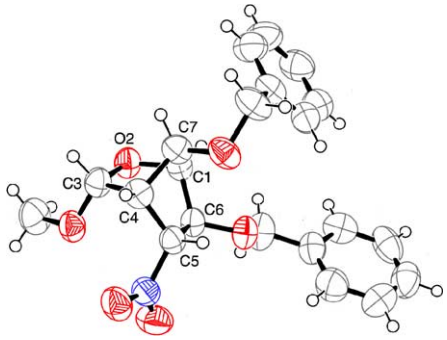
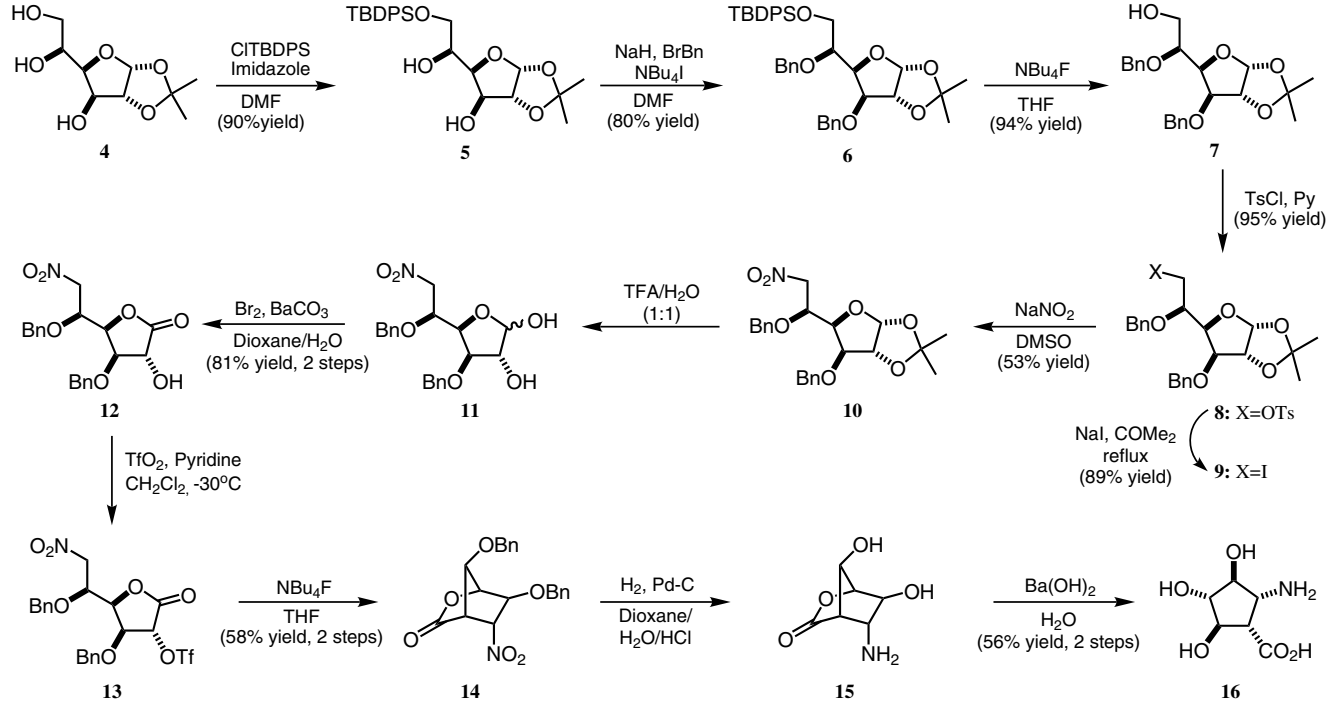


Figure 1. Molecular structure of compound **21** in the solid state.

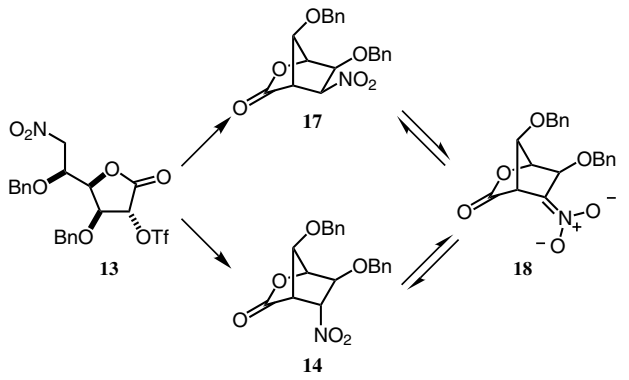
Bicyclic compounds **17** and **14** (Scheme 3) should be formed from the nitronate of compound **13**. Under the reaction conditions, however, compounds **17** and **14** should be in equilibrium with their common nitronate **18**. At equilibrium, the thermodynamically more stable compound **14** should be favoured with respect to compound **17**, where the NO_2 and the OBn substituents are eclipsed. This explains the highly remarkable stereoselectivity of the cyclization.

Hydrogenation of nitrolactone **14** in an acidic medium allowed the reduction of the nitro group to the amine and the removal of the benzyl protecting groups to be carried out in a single step. Finally, the resulting aminolactone **15** was directly opened to the desired amino acid **16** by treatment with barium hydroxide.

A slight modification of the above route to amino acid **16** allowed the formation of the expected bicyclic nitrolactol derivative **21** (Scheme 4). Reaction of nitroidofuranose derivative **10** with acetyl chloride and



Scheme 2.



Scheme 3.

methanol provided derivative **19** as a 1:1 epimeric mixture, which was treated with triflic anhydride in pyridine to convert its hydroxyl group at C-2 into an OTf leaving group, as before.

Treatment of the resulting mixture **20** with TBAF provided the nitrolactol derivative **21**, its stereochemistry being firmly established by X-ray crystallography (Fig. 1).[12] The selectivity of the formation of compound **21** from furanose **20** can be explained in a similar way to the stereoselectivity of the formation of compound **14** (Scheme 3).

3. Conclusion

The β-amino acid **16** now obtained has the same configuration as cispentacin at its amino acid moiety, making it a serious candidate for pharmacological studies in order to establish if its antifungal activity is greater than that of cispentacin. This is now under investigation.

Work is also in progress to test the incorporation of this new β-amino acid into peptides in order to study the folding properties of its homopolymer.

The preparation of the isomer of β-amino acid **16** resulting from similar synthesis on D-idose is also under investigation.

4. Experimental

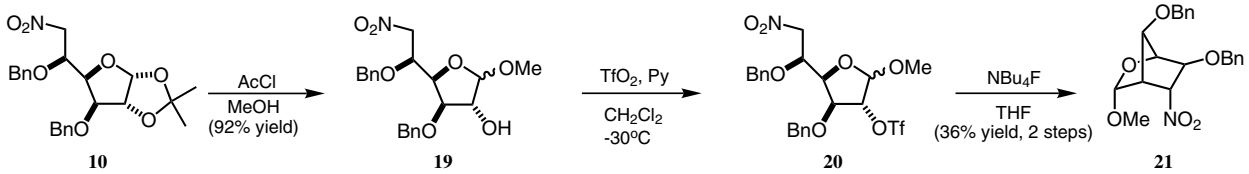
Melting points were determined using a Kofler Thermogerate apparatus and are uncorrected. Specific rotations were recorded on a JASCO DIP-370 optical polarimeter. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker WM-250 apparatus or a Bruker AMX-500. Mass spectra were obtained on a Kratos MS 50 TC 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 eluants; the TLC spots were visualized with Hanessian mixture. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 13. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

4.1. 6-*O*-*t*-Butyldiphenylsilyl-1,2-*O*-isopropyl-β-L-idofuranose 5

tert-Butyldiphenylsilyl chloride (2.40 mL, 9.05 mmol) and imidazole (1.23 g, 10.10 mmol) were sequentially added to a solution of 1,2-*O*-isopropyl-β-L-idofuranose **4** (2.00 g, 9.05 mmol) in dry DMF (18 mL) at −20 °C under argon. The reaction mixture was stirred at this temperature for 2 h and then the solvent was eliminated under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). The resulting solution was washed with water (3 × 20 mL) and the organic layers were dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluant 1:3 ethyl acetate/hexane) to yield 6-*O*-*t*-butyldiphenylsilyl-1,2-*O*-isopropyl-β-L-idofuranose **5** (3.741 g, 90%) as a pale yellow oil: $[\alpha]_D^{22} = -7.0$ (*c*, 2.8 in $CHCl_3$); IR (NaCl, cm^{-1}) 3425 (–OH); ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (s, 9H, 3 × –CH_3), 1.33, 1.48 (2 × s, 6H, –CH_3), 2.76 (d, 1H, J = 5.2 Hz, –OH), 3.68–4.23 (m, 4H), 4.32–4.34 (m, 1H), 4.55 (d, 1H, $J_{1,2}$ = 3.6 Hz, H_2), 6.00 (d, 1H, $J_{1,2}$ = 3.6 Hz, H_1), 7.38–7.64 (m, 10H, 10 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 19.57, 26.65, 27.22, 65.43, 71.56, 78.02, 79.68, 85.77, 105.25, 112.15, 128.33, 130.42, 135.94, 135.99, 132.97, 133.02; MS (EI) *m*/*z* 428 (M^+−2 × –CH_3, 1%), 323 (10%), 221 (100%).

4.2. 3,5-Di-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-1,2-*O*-isopropyl-β-L-idofuranose 6

A solution of 6-*O*-*t*-butyldiphenylsilyl-1,2-*O*-isopropyl-β-L-idofuranose **5** (2.60 g, 5.68 mmol) in DMF (26 mL) was added to a mixture of sodium hydride (60% in mineral oil, 0.57 g, 14.2 mmol) in dry DMF (4 mL) under argon. The reaction mixture was stirred at rt for 1 h and benzyl bromide (2.00 mL, 17.03 mmol) and tetrabutylammonium iodide (0.53 g) were added. The resulting mixture was stirred at rt for 24 h, when methanol was added. After stirring the reaction mixture for 20 min, the solvent was evaporated in vacuo and the



Scheme 4.

residue was dissolved in diethyl ether (100 mL) and filtered through Celite. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (eluant 1:5 ethyl acetate/hexane) to yield 3,5-di-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-1,2-*O*-isopropyl-β-L-idofuranose **6** (2.90 g, 80%) as a pale yellow oil: $[\alpha]_D^{22} = -15.0$ (*c* 3.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (s, 9H, 3 × –CH_3), 1.33, 1.51 (2 × s, 6H, –CH_3), 3.68–3.94 (m, 4H), 4.19 (d, 1H, $J = 11.6$ Hz), 4.50–4.79 (m, 5H), 5.99 (d, 1H, $J_{1,2} = 3.9$ Hz, H_1), 7.15–7.69 (m, 20H, 20 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 19.75, 27.01, 27.33, 64.28, 72.13, 73.33, 79.52, 81.30, 82.51, 83.33, 105.44, 112.15, 127.66, 128.11, 128.36, 128.63, 128.92, 136.21, 133.93, 133.99, 137.70, 139.70; MS (EI) *m/z* 520 ($M^+ - 2 \times$ –CH_3–Ph, 1%), 355 (10%), 91 (100%).

4.3. 3,5-Di-*O*-benzyl-1,2-*O*-isopropyl-β-L-idofuranose 7

A 1 M solution of tetrabutylammonium fluoride in THF (9 mL) was added to a solution of 3,5-di-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-1,2-*O*-isopropyl-β-L-idofuranose **6** (2.90 g, 4.54 mmol) in dry THF (30 mL) and the mixture was stirred at rt for 38 h under argon. The solvent was eliminated under reduced pressure and the residue was dissolved in dichloromethane (120 mL), washed with water (3 × 60 mL) and the organic layer was dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluant: 1:3 ethyl acetate/hexane) and the 3,5-di-*O*-benzyl-1,2-*O*-isopropyl-β-L-idofuranose **7** (1.71 g, 94%) was isolated as a yellow oil: $[\alpha]_D^{22} = -53.0$ (*c* 2.3, $CHCl_3$); IR (NaCl, cm^{-1}) 3474 (–OH); ^1H NMR (250 MHz, $CDCl_3$) δ 1.33, 1.50 (2 × s, 6H, –CH_3), 2.13 (t, 1H, $J = 6.2$ Hz, –OH), 3.60–3.68 (m, 1H), 3.85–3.94 (m, 2H), 4.32 (dd, 1H, $J = 3.4$ Hz, $J = 8.2$ Hz), 4.45 (d, 1H, $J = 11.6$ Hz), 4.58–4.70 (m, 3H), 4.92 (d, 1H, $J = 11.6$ Hz), 6.01 (d, 1H, $J_{1,2} = 4.0$ Hz, H_1), 7.28–7.40 (m, 10H, 10 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 26.77, 27.19, 62.34, 72.13, 73.91, 79.19, 81.87, 82.05, 82.49, 105.41, 112.16, 128.13, 128.42, 128.63, 128.86, 129.03, 137.32, 139.11; MS (EI) *m/z* 402 [$(M+H)^+$, 3%], 401 (M^+, 2%), 181 (85%), 91 (100%).

4.4. 3,5-Di-*O*-benzyl-6-*O*-*p*-toluenesulfonyl-1,2-*O*-isopropyl-β-L-idofuranose 8

p-Toluenesulfonyl chloride (1.35 g, 7.01 mmol) was added to a solution of 3,5-di-*O*-benzyl-1,2-*O*-isopropyl-β-L-idofuranose **7** (1.41 g, 3.53 mmol) dry pyridine (14 mL) and the mixture was stirred at rt for 10 h under argon. The reaction mixture was then concentrated in vacuo and the residue was dissolved in dichloromethane (150 mL). The resulting solution was washed with hydrochloric acid 2 M (1 × 60 mL) and water (2 × 60 mL) and the organic layers were dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluant: 1:4 ethyl acetate/hexane) to give 3,5-di-*O*-benzyl-6-*O*-*p*-toluenesulfonyl-1,2-*O*-isopropyl-β-L-idofuranose **8** (1.86 g, 95%) as a white solid: mp 102–104 °C (ethyl acetate/hexane); $[\alpha]_D^{23} = -23.9$ (*c* 1.1, $CHCl_3$); IR (NaCl, cm^{-1}) 1363 (–SO_2–); ^1H NMR (250 MHz, $CDCl_3$) δ 1.31, 1.46 (2 × s, 6H, –CH_3), 2.40 (s, 1H, –CH_3), 3.94–3.99 (m, 2H), 4.14 (ABq, 2H, $J = 4.2$ Hz), 4.25–4.30 (m, 1H), 4.41 (d, 1H, $J = 11.5$ Hz), 4.53–4.70 (m, 4H), 5.92 (d, 1H, $J_{1,2} = 3.9$ Hz, H_1), 7.21–7.36 (m, 12H, 12 × H–Ph), 7.71 (ABq, 2H, $J = 7.7$ Hz); ^{13}C NMR (62.8 MHz, $CDCl_3$) 22.08, 26.83, 27.28, 70.59, 72.20, 73.88, 76.51, 80.59, 82.43, 82.54, 105.35, 112.42, 128.01, 128.20, 128.26, 128.44, 128.52, 128.67, 129.02, 130.22, 133.09, 137.36, 138.61, 145.18; MS (EI) *m/z* 554 (M^+, 0.2%), 277 (15%), 107 (54%), 91 (100%); found C 64.62, H 6.28, S 5.64 $C_{30}H_{34}O_8S$ requires C 64.96, H 6.18, S 5.78.

4.5. 3,5-Di-*O*-benzyl-6-deoxy-6-iodo-1,2-*O*-isopropyl-β-L-idofuranose 9

Sodium iodide (8.87 g, 59.21 mmol) was added to a solution of 3,5-di-*O*-benzyl-6-*O*-*p*-toluenesulfonyl-1,2-*O*-isopropyl-β-L-idofuranose **8** (1.64 g, 2.96 mmol) in acetone (92 mL) and the resulting mixture was refluxed for 15 h. The reaction mixture was cooled down to rt and then filtered and the filtrate was concentrated in vacuo. The residue was dissolved in diethyl ether (180 mL) and washed with water (180 mL). The aqueous layer was extracted with diethyl ether (2 × 70 mL) and the combined organic layers were washed with 1 N aqueous sodium thiosulfate solution (180 mL), dried with anhydrous sodium sulfate, filtered and the solvent eliminated under reduced pressure. The residue was purified by flash column chromatography (eluant: 1:9 ethyl acetate/hexane) to give 3,5-di-*O*-benzyl-6-deoxy-6-iodo-1,2-*O*-isopropyl-β-L-idofuranose **9** (1.34 g, 89%) as a yellow amorphous solid: $[\alpha]_D^{20} = -38.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.34, 1.49 (2 × s, 6H, –CH_3), 3.07–3.11 (m, 2H), 3.71–3.73 (m, 1H), 4.44 (d, 1H, $J = 11.8$ Hz), 4.58–4.85 (m, 3H), 6.00 (d, 1H, $J_{1,2} = 3.9$ Hz, H_1), 7.26–7.45 (m, 10H, 10 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) 5.99, 26.92, 27.29, 72.07, 74.95, 77.65, 82.26, 83.73, 105.53, 112.44, 128.02, 128.13, 128.48, 128.60, 128.69, 128.76, 128.95, 129.16, 137.10, 138.76; MS (EI) *m/z* 511 (M^++1, 2%), 510 (M^+, 3%), 509 ($M^+ - 1$, 5%), 345 (20%), 181 (76%), 91 (100%); found 509.0834. HRMS (EI) calcd for: $C_{23}H_{26}O_5I$ $(M-H)^+$ 509.0825.

4.6. 3,5-Di-*O*-benzyl-6-deoxy-6-nitro-1,2-*O*-isopropyl-β-L-idofuranose 10

Sodium nitrite (0.40 g, 5.36 mmol) and 1,3,5-trihydroxybenzene (0.82 g, 4.67 mmol) were added to a solution of 3,5-di-*O*-benzyl-6-deoxy-6-iodo-1,2-*O*-isopropyl-β-L-idofuranose **9** (1.29 g, 2.52 mmol) in dry DMSO (16 mL) and the resulting mixture was stirred at rt for 4 days under argon. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (30 mL) and extracted with ethyl acetate (4 × 60 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and the solvent eliminated under reduced pressure. The residue was purified by flash column chromatography (eluant: 1:7 → 1:5 ethyl acetate/hexane) to give 3,5-di-*O*-benzyl-6-deoxy-6-nitro-1,2-*O*-isopropyl-β-L-idofuranose **10** (0.58 g, 53%) as a yellow solid: mp

85–87 °C (diethyl ether/hexane); $[\alpha]_D^{23} = -51.0$ (*c* 1.0, $CHCl_3$); IR (NaCl, cm^{-1}) 1557, 1376 (–NO_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.33, 1.45 (2 × s, 6H, –CH_3), 3.91 (d, 1H, $J = 3.4$ Hz), 4.22–4.25 (m, 2H), 4.30–4.80 (m, 7H), 5.97 (d, 1H, $J_{1,2} = 3.8$ Hz, H_1), 7.25–7.35 (m, 10H, 10 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) 26.77, 27.26, 72.12, 74.73, 75.84, 80.46, 81.84, 82.14, 105.59, 112.52, 128.40, 128.52, 128.73, 128.89, 129.22, 137.03, 137.23; MS (EI) *m/z* 429 (M^+, 4%), 428 (M^+-1, 15%), 271 (25%), 181 (82%), 91 (100%); found C 64.64, H 6.55, N 3.29 $C_{23}H_{27}NO_7$ requires C 64.32, H 6.34, N 3.26.

4.7. 3,5-Di-*O*-benzyl-6-deoxy-6-nitro-β-L-idono-1,4-lactone 12

A solution of 3,5-di-*O*-benzyl-6-deoxy-6-nitro-1,2-*O*-isopropyl-β-L-idofuranose **10** (0.25 g, 0.58 mmol) in a 1:1 mixture of trifluoroacetic acid/water (10 mL) was stirred at rt for 16 h. The solvent was concentrated in vacuo and coevaporated with toluene (3 × 5 mL) in order to remove traces of trifluoroacetic acid. The residue was dissolved in a mixture 2:1 of dioxane and water (12 mL) and stirred with barium carbonate (0.13 g, 0.64 mmol) and bromine (0.08 mL, 1.45 mmol) for 6 h. The resulting mixture was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were dried with anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (eluant: 2:5 ethyl acetate/hexane) to give 3,5-di-*O*-benzyl-6-deoxy-6-nitro-1,2-*O*-isopropyl-β-L-idono-1,4-lactone **12** (0.18 g, 81%) as a yellow oil: IR (NaCl, cm^{-1}) 3443 (–OH), 1791 (C=O), 1555, 1380 (–NO_2); ^1H NMR (250 MHz, $CDCl_3$) δ 2.64 (d, 1H, $J = 3.1$ Hz, –OH), 3.91 (d, 1H, $J = 3.4$ Hz), 4.44–4.73 (m, 9H), 4.89 (d, 1H, $J = 11.6$ Hz), 7.16–7.41 (m, 10H, 10 × H–Ph); MS (EI) *m/z* 388 [$(M+H)^+$, 3%], 386 [$(M-H)^+$, 2%], 296 (36%), 181 (59%), 91 (100%).

4.8. 3,5-Di-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-6-deoxy-6-nitro-β-L-idofurano-1,4-lactone 13

Trifluoromethanesulfonyl anhydride (0.11 mL, 0.68 mmol) was slowly added to a solution of 3,5-di-*O*-benzyl-6-deoxy-6-nitro-1,2-*O*-isopropyl-β-L-idono-1,4-lactone **12** (0.17 g, 0.45 mmol) and pyridine (0.11 mL, 1.36 mmol) in dry dichloromethane (3 mL) at −30 °C under argon. The reaction mixture was stirred at this temperature for 1.5 h and then diluted with dichloromethane (25 mL). The resulting solution was washed with 2 N aqueous hydrochloric acid solution (12 mL), which was further extracted with dichloromethane (2 × 19 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated in vacuo and the residue was used in the next step without further purification.

4.9. (5*R*,6*S*,7*R*)-6,7-Dibenzyloxy-5-nitro-2-oxabicyclo-[2.2.1]heptan-3-one 14

A 1 M solution of tetrabutylammonium fluoride in THF (0.45 mL) was added to a solution of the triflate **13** in dry THF (4 mL) and the mixture was stirred at rt for 4 h under argon. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (25 mL). The resulting solution was washed with water (3 × 13 mL) and the organic layers were dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluant: 1:5 ethyl acetate/hexane) to give the (5*R*,6*S*,7*R*)-6,7-dibenzyloxy-5-nitro-2-oxabicyclo[2.2.1]heptan-3-one **14** (0.10 g, 58%) as a yellow oil: $[\alpha]_D^{22} = -2.0$ (*c* 0.90, $CHCl_3$); IR (NaCl, cm^{-1}) 1811 (C=O), 1554, 1363 (–NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ 3.42–3.44 (m, 1H, H_7), 3.42–3.44 (m, 1H, H_7), 4.37 (m, 1H, H_1), 4.48–4.52, 4.65–4.79 (2 × m, 6H, 2 × –OCH_2Ph, H_5, H_6), 5.45 (dd, 1H, $J_{4,7} = 3.4$ Hz, $J_{4,5} = 3.4$ Hz, H_4), 7.26–7.37 (m, 10H, 10 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) 49.79, 72.20, 73.37, 78.94, 81.32, 82.20, 87.46, 128.04, 128.10, 128.46, 128.55, 128.63, 128.67, 135.77, 136.15, 167.95; MS (EI) *m/z* 370 [$(M+H)^+$, 6%], 369 (M^+, 15%), 368 [$(M-H)^+$, 8%], 278 (52%), 181 (66%), 91 (100%); found C 65.03, H 5.18, N 3.79 $C_{20}H_{19}NO_6$ requires C 64.63, H 5.42, N 3.70.

4.10. (1*S*,2*R*,3*S*,4*S*,5*R*)-2,3,4-Trihydroxy-5-aminocyclopentanic acid 16

Palladium–carbon (10%, 20 mg) was added to a solution of (5*R*,6*S*,7*R*)-6,7-dibenzyloxy-5-nitro-2-oxabicyclo[2.2.1]heptan-3-one **14** (34 mg, 0.09 mmol) in a 2:1 mixture of dioxane and water (1.5 mL) and one drop of hydrochloric acid was added. The mixture was stirred at rt for 36 h under hydrogen, filtered through Celite and the filtrate was concentrated in vacuo. The residue was stirred with 0.1 N aqueous solution of barium hydroxide (3 mL) at rt for 3 h and the resulting mixture was acidified with an acidic resin (Amberlite IR-120) to pH = 1 and stirred with the resin for 24 h. The mixture was then filtered and the resin washed with water until the filtrate remained colourless on addition of silver nitrate. The resin was stirred with a 1N aqueous solution of ammonia (6 mL), filtered and the filtrate concentrated in vacuo to give the (1*S*,2*R*,3*S*,4*S*,5*R*)-2,3,4-trihydroxy-5-aminocyclopentanic acid **16** (9 mg, 56%) as an amorphous white solid: $[\alpha]_D^{22} = -27.8$ (*c* 0.3, water); ^1H NMR (250 MHz, D_2O) δ 3.42–3.44 (m, 1H, H_7), 3.42–3.44 (m, 1H, H_7), 4.37 (m, 1H, H_1), 4.48–4.52, 4.65–4.79 (2 × m, 6H, 2 × –OCH_2Ph, H_5, H_6), 5.45 (dd, 1H, $J_{4,7} = 3.4$ Hz, $J_{4,5} = 3.4$ Hz, H_4), 7.26–7.37 (m, 10H, 10 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) 49.79, 72.20, 73.37, 78.94, 81.32, 82.20, 87.46, 128.04, 128.10, 128.46, 128.55, 128.63, 128.67, 135.77, 136.15, 167.95; MS (EI) *m/z* 370 [$(M+H)^+$, 6%], 369 (M^+, 15%), 368 [$(M-H)^+$, 8%], 278 (52%), 181 (66%), 91 (100%); found C 65.03, H 5.18, N 3.79 $C_{20}H_{19}NO_6$ requires C 64.63, H 5.42, N 3.70.

4.11. Methyl-3,5-di-*O*-benzyl-6-deoxy-6-nitro-α,β-L-idofuranoside 19

Acetyl chloride (0.30 mL, 4.01 mmol) was added to a solution of 3,5-di-*O*-benzyl-6-deoxy-6-nitro-1,2-*O*-isopropyl-β-L-idofuranose **10** (0.29 g, 0.67 mmol) in dry

methanol (10 mL) at 0 °C under argon. The reaction mixture was stirred at rt for 13 h and sodium carbonate was added to pH = 8. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in dichloromethane (20 mL) and washed with water (20 mL), which was further extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (5 mL), dried with anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (eluant: 2:5 ethyl acetate/hexane) to give methyl-3,5-di-*O*-benzyl-6-deoxy-6-nitro-α,β-L-idofuranoside **19** (0.25 g, 92%) as a mixture of both anomers: IR (NaCl, cm^{-1}) 3454 (–OH), 1555, 1380 (–NO_2); ^1H NMR (250 MHz, $CDCl_3$) δ 3.46, 3.49 (2 × s, 6H, 2 × –OCH_3), 3.90–3.93 (m, 1H), 3.97–4.00 (m, 2H), 4.19–4.86 (m, 19H), 5.02 (d, 1H, J = 4.9 Hz), 7.28–7.36 (m, 20H, 20 × H–Ph); MS (EI) *m/z* 402 [$(M-H)^+$, 1%], 370 (6%), 181 (65%), 91 (100%).

4.12. Methyl-3,5-di-*O*-benzyl-6-deoxy-6-nitro-2-*O*-trifluoromethanesulfonyl-α,β-L-idofuranoside 20

Trifluoromethanesulfonyl anhydride (0.13 mL, 0.79 mmol) was slowly added to a solution of methyl-3,5-di-*O*-benzyl-6-deoxy-6-nitro-α,β-L-idofuranoside **19** (0.25 g, 0.61 mmol) and pyridine (0.15 mL, 1.82 mmol) in dry dichloromethane (5 mL) at −30 °C under argon. The reaction mixture was stirred at this temperature for 1.5 h and then diluted with dichloromethane (40 mL). The resulting solution was washed with 2 N aqueous hydrochloric acid solution (20 mL), which was further extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated in vacuo and the residue was used in the next step without further purification.

4.13. (3*R*,5*R*,6*S*,7*R*)-6,7-Dibenzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane 21

A 1 M solution of tetrabutylammonium fluoride in THF (1.2 mL) was added to a solution of the triflate **20** in dry THF (6 mL) and the mixture was stirred at rt for 14 h under argon. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (40 mL). The resulting solution was washed with water (3 × 20 mL) and the organic layers were dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluant: 1:8 → 1:6 ethyl acetate/hexane) to give the (3*R*,5*R*,6*S*,7*R*)-6,7-dibenzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane **21** (85 mg, 36%) as a white solid: mp 98–100 °C (ethyl acetate/hexane); $[\alpha]_D^{24} = -45.6$ (*c* 1.5, $CHCl_3$); IR (NaCl, cm^{-1}) 1553, 1365 (–NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ 3.27 (s, 3 H, –OCH_3), 3.40–3.41 (m, 1H, H_4), 4.16 (d, 1H, $J_{1,4}$ = 3.4 Hz, H_1), 4.33 (s, 1H, H_7), 4.47 (d, 1H, J = 11.1 Hz, –OCHPh), 4.60 (d, 1H, J = 11.1 Hz, –OCHPh), 4.67–4.68 (m, 1H, H_6), 4.71 (d, 1H, J = 11.7 Hz, –OCHPh), 4.78 (d, 1H, J = 11.7 Hz, –OCHPh), 4.99 (d, 1H, $J_{3,4}$ = 2.5 Hz, H_3), 5.18 (dd, 1H, $J_{5,6}$ = 4.0 Hz, $J_{5,4}$ = 4.0 Hz, H_5), 7.26–7.36 (m, 10H, 10 × H–Ph); ^{13}C NMR (62.8 MHz, $CDCl_3$) 48.04, 56.42, 72.57, 73.00, 78.12, 80.45, 82.05, 88.85, 102.53, 128.24, 128.32, 128.50, 128.59, 128.89, 128.95, 137.33, 138.23; MS (EI) *m/z* 386 [$(M+H)^+$, 14%], 385 (M^+, 3%), 384 [$(M-H)^+$, 9%], 354 (64%), 181 (14%), 91 (100%); found C 65.44, H 6.33, N 3.62 $C_{20}H_{19}NO_6$ requires C 65.44, H 6.02, N 3.63.

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12. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 254540 **21**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK fax: (+44)1223-336-033; email: deposit@ccdc.cam.ac.uk. Crystallographic data for **21**. $C_{21}H_{23}NO_6$, M = 385.41, T = 293(2) K. Monoclinic, space group $P2$ with a = 12.2964(3), b = 12.2971(3), c = 13.6330(3) Å, α = 90°,

$\beta = 110.3710(10)°$, $\gamma = 90°$, $V = 1932.52$ Å^3, Dc ($Z = 4$) = 'not measured'. $F(0\,0\,0) = 816$, Absorption coefficient = 0.807 cm^{-1}. Data were obtained on an Enraf-Nonius CAD4-Mach3 diffractometer (graphite crystal monochromator, 1 = 1.5418 Å) using the $w = 2q$ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the nonhydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-93) using all data; $wR^2 = [Sw(F_o^2 - F_c^2)^2 / Sw(F_o^2)^2]^{1/2}$.

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