Tetrahedron: *Asymmetry* 20 (2009) 892–896

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereocontrolled transformation of nitrohexofuranoses into cyclopentylamines via 2-oxabicyclo[2.2.1]heptanes. IV: Synthesis of enantiopure methyl (1*S*,2*R*,3*R*,4*R*,5*S*)-5-benzyloxycarbonylamino-2,3-isopropylidenedioxy-4-methoxycyclopentanecarboxylate

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ARTICLE INFO

Article history:
Received 4 February 2009
Accepted 4 March 2009
Available online 3 April 2009

This paper is dedicated to Professor George Fleet, on the occasion of his 65th birthday

ABSTRACT

The first total synthesis of a new enantiopure polyhydroxylated cyclopentyl β-amino acid [methyl (1*S*,2*R*,3*S*,4*R*,5*S*)-2-benzyloxy-5-benzyloxycarbonylamino-3-hydroxy-4-methoxycyclopentanecarboxylate] was achieved according to our recent novel strategy for the transformation of nitrohexofuranoses into cyclopentylamines. This approach is based on an intramolecular cyclization leading to 2-oxabicyclo[2.2.1]heptane derivatives. Epimerization of this amino acid derivative to methyl (1*S*,2*R*,3*R*,4*R*,5*S*)-2-benzyloxy-5-benzyloxycarbonylamino-3-hydroxy-4-methoxycyclopentanecarboxylate constitutes the first example of the preparation of one of the members of this family of amino acids with a stereochemistry that is not compatible with the above key cyclization step.

1. Introduction

The chemistry of nitro compounds is very wide ranging in organic synthesis due to the special properties of the nitro group.[1] In fact, nitro sugars are versatile synthons that are of interest for the preparation of richly functionalized carbo- and heterocycles because they combine the ability of the sugar pool for the generation of chemical diversity and the synthetic potential of nitro compounds for the construction of carbon–carbon bonds prior to the transformation of the nitro group into a variety of other chemical functionalities.

In connection with our current interest in nitro sugars as powerful synthetic tools for the creation of novel carba- and aza-sugar derivatives,[2] we developed a nitro sugar-based stereocontrolled route to the unexplored polyhydroxylated cyclopentane β-amino acids.[2a,e,i] Our interest in these compounds is due to their structural connection with the corresponding unsubstituted partners, the *trans*- and *cis*-2-aminocyclopentyl carboxylic acids, which proved to be ideal candidates for the replacement of amino acids in α-peptides in order to stabilize them both structurally and biologically.[3] Our work in this field is aimed at substantially increasing the current limited number of such alicyclic β-amino acids and thus to open up promising opportunities for the generation of lipo- or hydrosoluble β-peptides, while allowing the hydroxy substituents on the cyclopentane rings to be either protected or unprotected.

Our synthetic strategy for polysubstituted cyclopentyl β-amino acids was first applied to the D-glucose nitro derivative **7a** (Scheme 1) and involved the intramolecular alkylation of the nitronate of this nitro sugar lactone to give bicyclic lactone **9a**, which was easily transformed into the amino acid derivative **11a** by a route that includes the opening of the lactone ring and reduction of the nitro group to the amine.[2i]

This approach has the evident limitation that, in principle, it can provide access only to eight polyhydroxylated cyclopentyl β-amino acids, that is, just those resulting from the eight hexoses that satisfy the stereochemical requirements for the key intramolecular nitronate alkylation involved in their preparation (D-glucose, D-alose, D-idose, D-talose and the corresponding L-isomers). Herein we report how this synthetic strategy can be applied to the preparation of additional members of this family of β-amino acids. This approach is exemplified by the preparation of the enantiomerically pure cyclopentyl β-amino acid ester **13b** (Scheme 3) by inversion of the configuration of the C-4 stereogenic centre of its epimer **11b**, which in turn was easily obtained from D-glucose as shown in Scheme 1.

2. Chemical results and discussion

Treatment of D-glucose derivative **1**[4] with sodium hydride and methyl iodide provided *O*-methoxy derivative **2** in 99% yield. Removal of the *tert*-butyldiphenylsilyl group using tetrabutylammonium

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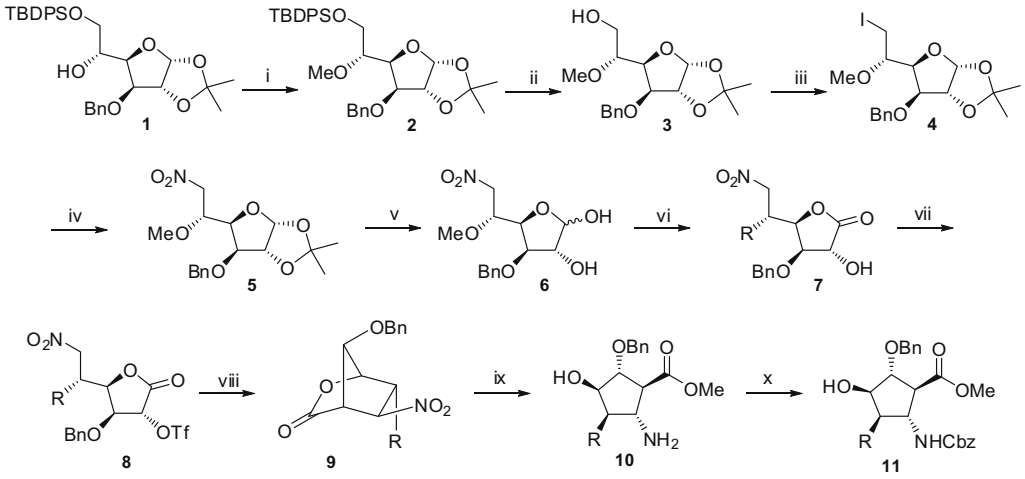
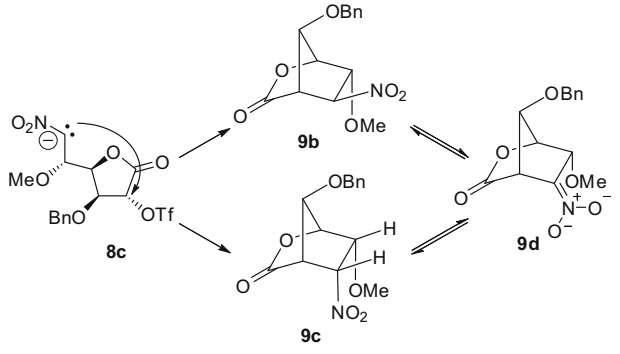
doi:10.1016/j.tetasy.2009.03.004



Scheme 1. Compounds **7**, **8**, **9**, **10** and **11**: (a) R = OBn, (b) R = OMe. Reagents and conditions: (i) NaH, NBu_4Br, MeI, THF, rt, 16 h, 99%; (ii) TBAF, THF, rt, 19 h, 96%; (iii) Imidazole, Ph_3P, I_2, toluene, 85 °C, 3 h, 93%; (iv) $NaNO_2$, phloroglucinol, rt, DMSO, 72 h, 75%; (v) TFA/H_2O (1:1), rt, 15 h; (vi) Br_2, $BaCO_3$, dioxane/H_2O (2:1), rt, 29 h (88% from **5**); (vii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (viii) TBAF, THF, rt, 4 h (54% from **7**); (ix) H_2, Raney-Ni, citric acid, MeOH, rt, 24 h; (x) CbzCl, $NaHCO_3$, MeOH, rt, 6 h (60% from **9b**).

fluoride[5] was followed by treatment of the resulting compound **3** with iodine, triphenylphosphine and imidazole[6] to give iodo-derivative **4**, from which our key nitro sugar derivative **5** was easily derived by treatment with sodium nitrite and phloroglucinol,[7] as a scavenger to avoid the nitrite ester formation. Reaction of **5** with trifluoroacetic acid and water, followed by anomeric oxidation of the resulting hydroxy lactol **6** with bromine and barium carbonate, afforded lactone **7b** as a yellow oil (88% yield from **5**). Treatment of **7b** with triflic anhydride in pyridine furnished the desired triflate **8b**, which was maintained in vacuo for 12 h and then directly reacted with TBAF in THF to promote its intramolecular cyclization to the desired bicyclic β-nitrolactone **9b**, which was obtained in 54% yield from **7**. The yield for this cyclization is substantially lower that that obtained for the previously described cyclization of **8a**.[2a] This suggests that this key reaction is markedly influenced by the steric effect of the substituents at the C-5 position of key compounds **7**.

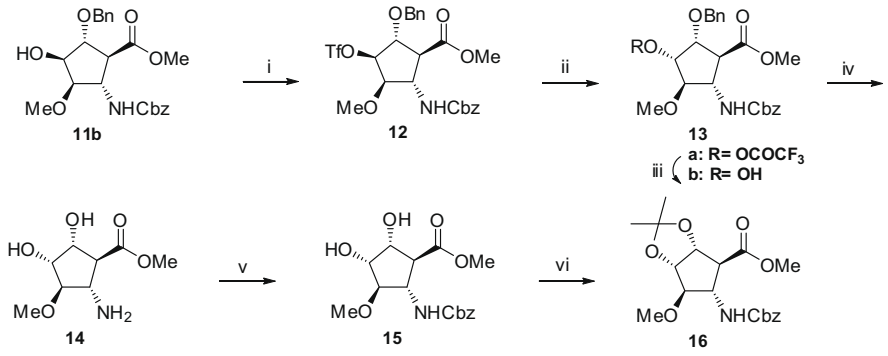


Scheme 2.

The stereochemical outcome of this key step to compound **9b** was explained on the assumption that, as in previous similar cases, both bicyclic compounds **9b** and **9c** should be formed from nitronate **8c** (Scheme 2). Under the reaction conditions, however, compounds **9b** and **9c** should be in equilibrium with their common nitronate **9d**. At equilibrium, the thermodynamically more stable compound **9b** should be favoured over compound **9c**, where the NO_2 and the OMe substituents are eclipsed. This explains the remarkably high stereoselectivity of the cyclization.

Hydrogenation of bicycle **9b**, using Raney-Ni as the catalyst and MeOH as the solvent, resulted in the opening of its lactone ring and the reduction of the nitro group to the amino group in the new D-glucose-derived cyclopentane β-amino acid ester **10b**. This compound was finally reacted with CbzCl to give derivative **11b**, in which the amino group is protected by a Cbz moiety.

The reaction of β-amino acid derivative **11b** with triflic anhydride in pyridine was followed by treatment of the resulting triflate derivative **12** (Scheme 3) with sodium trifluoroacetate to give the desired compound **13a**. Compound **13a** was subsequently treated with sodium methoxide to give the expected amino acid derivative **13b**.[8] This sequence allowed the programmed inversion of the



Scheme 3. Reagents and conditions: (i) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1 h; (ii) CF_3CO_2Na, DMF, 50 °C, 48 h; (iii) MeONa/MeOH (1 M), rt, 24 h (45% from **11**); (iv) H_2, Pd/C, citric acid, MeOH, rt, 5 h; (v) CbzCl, $NaHCO_3$, MeOH, rt, 4 h; (vi) 2,2-DMP, PTSA, $CuSO_4$, acetone, rt, 12 h (80% from **13b**).

configuration at the C-3 stereogenic centre of **11b**, albeit with low efficiency (45% yield)—probably due to steric hindrance.

The catalytic hydrogenation of **13b** with H_2 and Pd/C as the catalyst in an acidic medium resulted in the removal of the two benzyl-protecting groups to give amino acid ester **14**. This compound was reacted with CbzCl and sodium bicarbonate for re-protection of the amino group. The resulting compound **15** was finally transformed into methyl (1*S*,2*R*,3*R*,4*R*,5*S*)-5-benzyloxycarbonylamino-2,3-*O*-isopropylidene-4-methoxycyclopentanecarboxylate **16** by reaction with 2,2-dimethoxypropane, acetone and *p*-toluenesulfonic acid, a process that resulted in the selective protection of the *cis*-diol moiety.

3. Conclusion

In conclusion, only eight hexoses (D-glucose, D-idose, D-alose, D-talose and the corresponding L-hexoses) satisfy the stereochemical requirements of our strategy for the preparation of polyhydroxylated cyclopentyl β-amino acids involving an intramolecular alkylation of nitronates of 6-deoxy-6-nitro-2-trifluoromethanesulfonyl-gluconolactones. We have reported here that the synthetic potential of this strategy is not strictly limited to the eight polyhydroxylated cyclopentyl β-amino acids derived from the panel of hexoses. Further transformation of these amino acids, via inversion of the configuration of their stereogenic centres, opens up the opportunity to substantially increase the number of such amino acids that can be obtained by this synthetic strategy.

We have also reported the first example of this expanded methodology, which corresponds to the synthesis of methyl (1*S*,2*R*,3*R*,4*R*,5*S*)-2-benzyloxy-5-benzyloxycarbonylamino-3-hydroxy-4-methoxycyclopentanecarboxylate (**13b**) by inversion of the configuration of the C-3 of its epimer **11b**, which is easily obtained from D-glucose by the intramolecular nitronate alkylation.[2a]

Further transformations of amino acid **13b**, including the selective protection of its *cis*-diol moiety as the acetonide, allowed us to prepare the new amino acid **16**, which is of interest for the preparation of conformationally restricted β-peptides on account of the extra conformational rigidity provided by the presence of the dioxolane ring.

Work is currently in progress which is aimed at extending these synthetic protocols to the preparation of a wide panel of polyhydroxylated cyclopentyl β-amino acids as an initial stage for the study of the structural, physical and biological properties of their β-peptides.

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 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 eluants; TLC spots were visualized with Hanessian mixture. Column chromatography was carried out using Merck type 9385 silica gel.

4.1. 3-*O*-Benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-*O*-methyl-α-D-glucofuranose 2

To a cooled (0 °C) suspension of NaH (0.83 g, 34.42 mmol, 60% dispersion in mineral oil) in dry THF (60 mL) was added dropwise a solution of compound **1** (3.78 g, 6.89 mmol) in dry THF (300 mL). When the evolution of hydrogen had ceased, NBu_4Br (0.02 g, 0.07 mmol) and MeI (1.3 mL, 20.66 mmol) were added. The mixture was allowed to warm up to room temperature and was stirred at room temperature for 16 h. TLC (EtOAc/hexane 1:4) showed that the starting material had been consumed and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and was washed with H_2O (50 mL) and saturated aq NH_4Cl (50 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:11) to afford compound **2** (3.82 g, 6.79 mmol, 99% yield) as a yellow oil: $[\alpha]_D^{24} = -18.7$ (*c* 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 1.05 (s, 9H, ^{t}Bu); 1.30 (s, 3H, CH_3); 1.46 (s, 3H, CH_3); 3.37 (s, 3H, OCH_3); 3.64 (ddd, 1H, $J_{5,4}$ = 9.4 Hz, $J_{5,6}$ = 4.4 Hz, $J_{5,6'}$ = 1.9 Hz, H-5); 3.80 (dd, 1H, $J_{6,6'}$ = 11.3 Hz, $J_{6,5}$ = 4.4 Hz, H-6); 4.00 (dd, 1H, $J_{6',6}$ = 11.3 Hz, $J_{6',5}$ = 1.9 Hz, H-6′); 4.10 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 4.36 (dd, 1H, $J_{4,5}$ = 9.4 Hz, $J_{4,3}$ = 3.0 Hz, H-4); 4.58 (d, 1H, $J_{H,H'}$ = 11.7 Hz, CH_2Ph); 4.59 (d, 1H, $J_{2,1}$ = 3.7 Hz, H-2); 4.68 (d, 1H, $J_{H,H'}$ = 11.7 Hz, CH_2Ph); 5.90 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1); 7.30–7.44 (m, 10H, H-ar); 7.67–7.68 (m, 5H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 19.24, 26.38, 26.71, 26.79, 57.79, 62.81, 72.13, 78.19, 78.31, 81.90, 82.15, 105.11, 111.61, 127.57, 127.68, 127.78, 128.40, 129.45, 129.48, 133.54, 133.69, 135.68, 135.72, 137.76. IR (NaCl, ν_{max}, cm^{-1}): 1112 (st, Si–O–C). MS (CI, *m*/*z*, %): 563 (22, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{33}H_{42}O_6Si$: C, 70.43; H, 7.52. Found: C, 70.37; H, 7.57.

4.2. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-methyl-α-D-glucofuranose 3

Compound **2** (2.56 g, 4.54 mmol) was dissolved in dry THF (150 mL) and was stirred with TBAF (10 mL, 10 mmol, 1 M solution in THF) at room temperature for 19 h. TLC (EtOAc/hexane 1:2) showed that the starting material had been consumed and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (60 mL) and washed with H_2O (3 × 60 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:2) to afford compound **3** (1.41 g, 4.34 mmol, 96% yield) as a yellowish oil. $[\alpha]_D^{23} = -28.5$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 1.31 (s, 3H, CH_3); 1.49 (s, 3H, CH_3); 2.26 (br, 1H, OH); 3.37 (s, 3H, OCH_3); 3.64 (ddd, 1H, $J_{5,4}$ = 8.8 Hz, $J_{5,6}$ = 3.9 Hz, $J_{5,6'}$ = 3.6 Hz, H-5); 3.74 (dd, 1H, $J_{6',6}$ = 11.9 Hz, $J_{6',5}$ = 3.6 Hz, H-6′); 3.91 (dd, 1H, $J_{6,6'}$ = 11.9 Hz, $J_{6,5}$ = 3.9 Hz, H-6); 4.06 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 4.22 (dd, 1H, $J_{4,5}$ = 8.8 Hz, $J_{4,3}$ = 3.0 Hz, H-4); 4.56 (d, 1H, $J_{H,H'}$ = 11.7 Hz, CH_2Ph); 4.62 (d, 1H, $J_{2,1}$ = 3.9 Hz, H-2); 4.70 (d, 1H, $J_{H,H'}$ = 11.7 Hz, CH_2Ph); 5.90 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1); 7.29–7.37 (m, 5H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 26.23, 26.69, 57.49, 61.04, 71.93, 77.15, 79.44, 81.63, 81.82, 104.92, 111.79, 127.62, 127.88, 128.42, 137.37. IR (NaCl, ν_{max}, cm^{-1}): 3487 (br, OH). MS (CI, *m*/*z*, %): 325 (8, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.74; H, 7.67.

4.3. 3-*O*-Benzyl-6-deoxy-6-iodo-1,2-*O*-isopropylidene-5-*O*-methyl-α-D-glucofuranose (4)

Imidazole (0.77 g, 11.32 mmol), Ph_3P (2.13 g, 8.16 mmol) and I_2 (2.09 g, 8.16 mmol) were added to a stirred solution of compound **3** (1.02 g, 3.15 mmol) in toluene (mL) and the mixture was stirred at 85 °C for 3 h. TLC (EtOAc/hexane 1:2) showed that the starting material had been consumed. The reaction mixture was allowed to cool to room temperature, concentrated in vacuo and then partitioned between CH_2Cl_2 (30 mL) and saturated aq $NaHCO_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column

chromatography (EtOAc/hexane 1:14) to afford compound **4** (1.27 g, 2.92 mmol, 93% yield) as a yellowish oil. $[\alpha]_D^{25} = -55.6$ (*c* 2.2, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 1.32 (s, 3H, CH_3); 1.51 (s, 3H, CH_3); 3.34 (s, 3H, OCH_3); 3.16 (ddd, 1H, $J_{5,4}$ = 8.5 Hz, $J_{5,6}$ = 3.2 Hz, $J_{5,6'}$ = 3.0 Hz, H-5); 3.49 (dd, 1H, $J_{6,6'}$ = 11.2 Hz, $J_{6,5}$ = 3.2 Hz, H-6); 3.62 (dd, 1H, $J_{6',6}$ = 11.2 Hz, $J_{6',5}$ = 3.0 Hz, H-6′); 4.08 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 4.12 (dd, 1H, $J_{4,5}$ = 8.5 Hz, $J_{4,3}$ = 3.0 Hz, H-4); 4.56 (d, 1H, $J_{H,H'}$ = 11.6 Hz, CH_2Ph); 4.60 (d, 1H, $J_{2,1}$ = 3.6 Hz, H-2); 4.68 (d, 1H, $J_{H,H'}$ = 11.6 Hz, CH_2Ph); 5.89 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1); 7.30–7.39 (m, 5H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 9.75, 26.52, 26.94, 56.67, 72.17, 74.30, 81.11, 81.26, 82.16, 104.87, 112.11, 127.67, 127.89, 128.40, 137.33. IR (NaCl, ν_{max}, cm^{-1}): nothing remarkable. MS (CI, *m*/*z*, %): 435 (16, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{17}H_{23}IO_5$: C, 47.02; H, 5.34. Found: C, 47.24; H, 5.45.

4.4. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methyl-6-nitro-α-D-glucofuranose 5

To a solution of compound **4** (3.72 g, 8.57 mmol) in dry DMSO (100 mL) were added phloroglucinol (4.17 g, 25.70 mmol) and $NaNO_2$ (2.36 g, 34.26 mmol). The mixture was stirred at room temperature for 72 h. TLC (EtOAc/hexane 1:3) showed that starting material had been consumed and the reaction mixture was partitioned between EtOAc (50 mL) and brine (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL) and the resulting organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:4) to afford compound **5** (2.28 g, 6.45 mmol, 75% yield) as a yellow oil. $[\alpha]_D^{25} = -46.4$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 1.33 (s, 3H, CH_3); 1.49 (s, 3H, CH_3); 3.36 (s, 3H, OCH_3); 4.07 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 4.19 (dd, 1H, $J_{4,5}$ = 7.3 Hz, $J_{4,3}$ = 3.0 Hz, H-4); 4.34 (ddd, 1H, $J_{5,6}$ = 7.9 Hz, $J_{5,4}$ = 7.3 Hz, $J_{5,6'}$ = 2.7 Hz, H-5); 4.55 (d, 1H, $J_{H,H'}$ = 11.6 Hz, CH_2Ph); 4.57 (dd, 1H, $J_{6,6'}$ = 13.1 Hz, $J_{6,5}$ = 7.9 Hz, H-6); 4.64 (d, 1H, $J_{2,1}$ = 3.6 Hz, H-2); 4.71 (d, 1H, $J_{H,H'}$ = 11.6 Hz, CH_2Ph); 4.79 (dd, 1H, $J_{6',6}$ = 13.1 Hz, $J_{6',5}$ = 2.7 Hz, H-6′); 5.89 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 7.32–7.39 (m, 5H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 26.17, 26.69, 58.57, 71.86, 75.15, 76.89, 79.02, 81.35, 81.56, 104.84, 112.04, 127.75, 128.12, 128.55, 136.79. IR (NaCl, ν_{max}, cm^{-1}): 1554, 1382 (st, NO_2). MS (CI, *m*/*z*, %): 354 (10, $[M+H]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.65; H, 6.79; N, 4.16.

4.5. 3-*O*-Benzyl-6-deoxy-5-*O*-methyl-6-nitro-D-glucono-1,4-lactone 7b

Compound **5** (2.53 g, 7.15 mmol) was treated with a mixture of TFA/H_2O (1:1, 110 mL) and was stirred at room temperature for 15 h. TLC (EtOAc/hexane 1:2) showed that the starting material had been consumed. The solvent was evaporated in vacuo and the residue was coevaporated with toluene (3 × 50 mL) to give the compound **6** as a clear gum, which was used in the next step without further purification.

The crude product (2.51 g, 8.02 mmol) was dissolved in dioxane/H_2O (2:1, 120 mL). Next $BaCO_3$ (1.74 g, 8.82 mmol) and then Br_2 (1 mL, 20.04 mmol) were added and the reaction mixture was stirred for 29 h at room temperature with the exclusion of light. TLC (EtOAc/hexane 1:1) showed that the starting material had been consumed. The reaction was quenched with saturated aq $Na_2S_2O_3$ (until the mixture was colourless) and the mixture was then extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:1) to afford compound **7b** (1.95 g, 6.28 mmol, 88% yield) as a yellowish oil. $[\alpha]_D^{25} = +25.3$ (*c* 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 2.81 (br, 1H, OH); 3.45 (s, 3H, OCH_3); 4.36–4.42 (m, 2H); 4.57–4.85 (m, 6H); 7.31–7.42 (m, 5H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 59.98, 71.79, 72.73, 75.61, 77.36, 77.88, 79.99, 127.94, 128.34, 128.66, 136.47, 174.46. IR (NaCl, ν_{max}, cm^{-1}): 3440 (br, OH); 1792 (st, C=O) 1555, 1381 (st, NO_2). MS (CI, *m*/*z*, %): 312 (29, $[M-H]^+$); 107 (100, $[OBn]^+$). Anal. Calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.30; H, 5.57; N, 4.52.

4.6. (1*S*,4*S*,5*S*,6*R*,7*R*)-7-Benzyloxy-6-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptan-3-one 9b

Compound **7b** (1.84 g, 5.91 mmol) was dissolved in dry CH_2Cl_2 (41 mL) and the solution was cooled to −30 °C under argon. Pyridine (1.6 mL) and Tf_2O (1.4 mL, 8.87 mmol) were added and the mixture was stirred at −30 °C for 1 h. TLC (EtOAc/hexane 1:1) showed that the starting material had been consumed. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and was washed with 10% aq HCl (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness, affording the triflate derivative **8b** as a clear gum, which was used in the next step without further purification after storage in vacuo overnight.

TBAF (5.9 mL, 1 M solution in THF) was added to a solution of the crude product described above (2.62 g, 5.91 mmol) in THF (53 mL) and the resulting mixture was stirred under argon for 4 h. TLC (EtOAc/hexane 1:2) showed that the starting material had been consumed. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (50 mL). The solution was washed with H_2O (3 × 50 mL) and the organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:4) to afford compound **9b** (0.94 g, 3.21 mmol, 54% from **7b**) as a yellow oil. $[\alpha]_D^{27} = -63.7$ (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 3.57 (s, 3H, OCH_3); 4.05 (s, 1H, H-4); 4.30–4.32 (m, 1H, H-6); 4.33 (d, 1 H, $J_{H,H'}$ = 11.4 Hz, CH_2Ph); 4.44–4.46 (m, 1H, H-7); 4.55 (d, 1 H, $J_{H,H'}$ = 11.4 Hz, CH_2Ph); 4.81 (dd, 1 H, $J_{1,6}$ = 3.7 Hz, $J_{1,7}$ = 2.5 Hz, H-1); 4.88 (d, 1 H, $J_{5,6}$ = 2.3 Hz, H-5); 7.19–7.41 (m, 10H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 49.98, 58.05, 72.22, 79.51, 81.24, 83.97, 127.87, 128.33, 128.49, 135.46, 169.26. IR (NaCl, ν_{max}, cm^{-1}): 1806 (st, C=O); 1555, 1380 (st, NO_2). MS (CI, *m*/*z*, %): 294 (3, $[M+H]^+$); 107 (100, $[OBn]^+$). Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.62; H, 5.46; N, 4.55.

4.7. Methyl (1*S*,2*R*,3*S*,4*R*,5*S*)-2-benzyloxy-5-benzyloxycarbonylamino-3-hydroxy-4-methoxycyclopentanecarboxylate 11b

Raney-Ni suspension (0.8 mL, 1 g/mL) and citric acid (0.29 g, 1.50 mmol) were added to a deoxygenated solution of compound **9b** (0.40 g, 1.36 mmol) in MeOH (14 mL) and the mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 24 h. TLC (EtOAc/hexane 1:4) showed that the starting material had been consumed. The reaction mixture was filtered through Celite, eluted with MeOH, and the filtrate was evaporated in vacuo to give the corresponding amino acid derivative **10b**, which was used in the next step without further purification.

The crude product obtained above (0.40 g, 1.36 mmol) was dissolved in MeOH (14 mL) and was treated with saturated aq $NaHCO_3$ (6.8 ml) and CbzCl (0.23 mL, 1.63 mmol). The resulting mixture was stirred at room temperature for 6 h. TLC (CH_2Cl_2/MeOH 9:1) showed that the starting material had been consumed and the reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc (20 mL) and was washed with H_2O (3 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:2) to afford compound **11b** (0.35 g, 0.82 mmol, 60% from **9b**) as a colourless oil. $[\alpha]_D^{26} = -33.5$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$, ppm): 2.65 (d, 1H, $J_{OH,3}$ = 5.2 Hz,

OH); 2.75 (dd, 1H, $J_{1,2}$ = 7.3 Hz, $J_{1,5}$ = 5.7 Hz, H-1); 3.48 (s, 3H, OCH_3); 3.71 (s, 4H, OCH_3 + H-2); 4.08–4.24 (m, 3H, H-3 + H-4 + H-5); 4.61 (d, 1H, $J_{H,H'}$ = 11.9 Hz, CH_2Ph); 4.69 (d, 1H, $J_{H,H'}$ = 11.9 Hz, CH_2Ph); 4.74 (br, 1H, NH); 5.00 (d, 1H, $J_{H,H'}$ = 12.1 Hz, CH_2Ph); 5.10 (d, 1H, $J_{H,H'}$ = 12.1 Hz, CH_2Ph); 7.27–7.35 (m, 10H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 52.29, 52.60, 55.82, 58.10, 65.23, 72.01, 74.12, 84.00, 84.48, 127.73, 127.76, 128.40, 129.64, 130.25, 136.21, 137.31, 154.88, 172.54. IR (NaCl, ν_{max}, cm^{-1}): 3377 (br, NH + OH); 1747 (st, C=O); 1665 (st, N–C=O). MS (CI, *m*/*z*, %): 430 (67, $[M+H]^+$); 398 (22, $[M-OCH_3]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.45; H, 6.19; N, 3.10.

4.8. Methyl (1*S*,2*R*,3*R*,4*R*,5*S*)-2-benzyloxy-5-benzyloxycarbonylamino-3-hydroxy-4-methoxycyclopentanecarboxylate 13b

A solution of compound **11b** (0.30 g, 0,70 mmol) in dry CH_2Cl_2 (5 mL) was cooled to −30 °C. Pyridine (0.2 mL) and Tf_2O (0.17 mL, 1.04 mmol) were added and the mixture was stirred at −30 °C for 1 h. TLC (EtOAc/hexane 1:2) revealed that the starting material had been consumed. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and was washed with 10% aq HCl (30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness to give the corresponding triflate **12**, which was used in the next step without further purification.

This crude product (0.39 g, 0.70 mmol) was dissolved in dry DMF (16 mL) and CF_3CO_2Na (0.57 g, 4.24 mmol) was added. The reaction mixture was stirred at 50 °C for 48 h. TLC (EtOAc/hexane 1:2) revealed that the starting material had been consumed. After the solvent was removed in vacuo, solid residue containing **13a** was directly dissolved in a 1 M solution of MeONa in MeOH (10 mL) and the solution was stirred for 24 h, when TLC (EtOAc/hexane 1:2) revealed that the starting material had been consumed. The solvent was removed in vacuo and the residue was diluted with CH_2Cl_2 (20 mL) and was washed with H_2O (3 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:2) to afford compound **13b** (0.14 g, 0.33 mmol, 45% from **11b**) as a colourless oil. $[\alpha]_D^{22} = -44.9$ (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 2.83 (br, 1H, OH); 2.90 (dd, 1H, $J_{1,2}$ = 7.8 Hz, $J_{1,5}$ = 7.3 Hz, H-1); 3.41 (s, 3H, OCH_3); 3.50 (dd, 1H, $J_{4,5}$ = 4.7 Hz, $J_{4,3}$ = 2.6 Hz, H-4); 3.72 (s, 3H, OCH_3); 4.00 (dd, 1H, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 5.7 Hz, H-2); 4.10 (dd, 1H, $J_{3,2}$ = 5.7 Hz, $J_{3,4}$ = 2.6 Hz, H-3); 4.23 (dd, 1H, $J_{5,1}$ = 7.3 Hz, $J_{5,4}$ = 4.7 Hz, H-5); 4.57 (d, 1H, $J_{H,H'}$ = 11.4 Hz, CH_2Ph); 4.65 (d, 1H, $J_{H,H'}$ = 11.4 Hz, CH_2Ph); 5.01 (d, 1H, $J_{H,H'}$ = 12.2 Hz, CH_2Ph); 5.04 (d, 1H, $J_{NH,5}$ = 7.3 Hz, NH); 5.13 (d, 1H, $J_{H,H'}$ = 12.2 Hz, CH_2Ph); 7.28–7.40 (m, 10H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 52.35, 53.57, 56.36, 57.67, 66.78, 72.66, 73.75, 81.09, 89.10, 127.97, 128.18, 128.46, 128.59, 130.25, 137.41, 138.10, 154.89, 173.17. IR (NaCl, ν_{max}, cm^{-1}): 3365 (br, NH + OH); 1740 (st, C=O); 1666 (st, N–C=O). MS (CI, *m*/*z*, %): 430 (54, $[M+H]^+$); 398 (20, $[M-OCH_3]^+$); 91 (100, $[CH_2Ph]^+$). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.21; H, 6.10; N, 3.35.

4.9. Methyl (1*S*,2*R*,3*R*,4*R*,5*S*)-5-benzyloxycarbonylamino-2,3-isopropylidenedioxy-4-methoxycyclopentanecarboxylate (16)

Compound **13b** (0.14 g, 0.33 mmol) was dissolved in MeOH (5 mL) and the solution was deoxygenated. Pd–C (0.14 g, 10% w/w) and citric acid (0.07 g, 0.36 mmol) were added and the suspension was stirred at room temperature under a hydrogen atmosphere (1 atm) for 5 h. TLC (EtOAc/hexane 1:2) showed that the starting material had been consumed. The reaction mixture was filtered through Celite, eluted with MeOH, and the filtrate was evaporated in vacuo to give the amino acid ester **14**, which was used in the next step without further purification.

The crude product (0.06 g, 0.29 mmol) was directly dissolved in MeOH (5 mL). Saturated aq $NaHCO_3$ (1.5 ml) and CbzCl (0.05 mL, 0.35 mmol) were added and the resulting mixture was stirred at room temperature. After 4 h TLC (CH_2Cl_2/MeOH 9:1) showed that the starting material had been consumed. The reaction mixture was concentrated to dryness and the residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to provide amino acid derivative **15**.

$CuSO_4$ (0.10 g), 2,2-dimethoxypropane (4.6 mL) and PTSA (catalytic amount) were added to a solution of the residue obtained above (0.10 g, 0.29 mmol) in dry acetone (3 mL). The mixture was stirred at room temperature under argon for 12 h, after which TLC (EtOAc/hexane 2:1) showed that the starting material had been consumed. The reaction mixture was concentrated to dryness and the residue was dissolved in EtOAc (10 mL) and was washed with H_2O (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane 1:3) to afford compound **16** (0.10 g, 0.25 mmol, 80% from **13b**) as a colourless oil. $[\alpha]_D^{17} = -74.6$ (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 1.31 (s, 3H, CH_3); 1.50 (s, 3H, CH_3); 3.02–3.04 (m, 1H, H-1); 3.37 (s, 3H, CH_3); 3.69 (br, 4H, CH_3 + H-4); 4.45–4.50 (m, 2H, H-3 + H-2); 5.08 (d, 1H, $J_{H,H'}$ = 11.8 Hz, CH_2Ph); 5.10 (m, 1H, H-5); 5.15 (d, 1H, $J_{H,H'}$ = 11.8 Hz, CH_2Ph); 5.35 (br, 1H, NH); 7.30–7.38 (m, 5H, H-ar). ^{13}C NMR ($CDCl_3$, ppm): 23.7, 26.1, 51.9, 53.2, 57.1, 57.6, 66.2, 79.5, 82.5, 87.3, 111.5, 127.6, 127.7, 128.1, 136.2, 155.1, 170.9. IR (NaCl, ν_{max}, cm^{-1}): 3327 (br, NH); 1759 (st, C=O); 1659 (st, N–C=O). MS (CI, *m*/*z*, %): 380 (47, $[M+H]^+$); 348 (25, $[M-OCH_3]^+$); 244 (45 $[M-CO_2Bn]^+$). Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 59.91; H, 6.43; N, 3.87.

Acknowledgement

We thank the Spanish Ministry of Science and Innovation for financial support (CTQ2005-00555 and CTQ2008-03105) and for F.P.U. grants to Fernando Fernández Nieto and Amalia M. Estévez.

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