

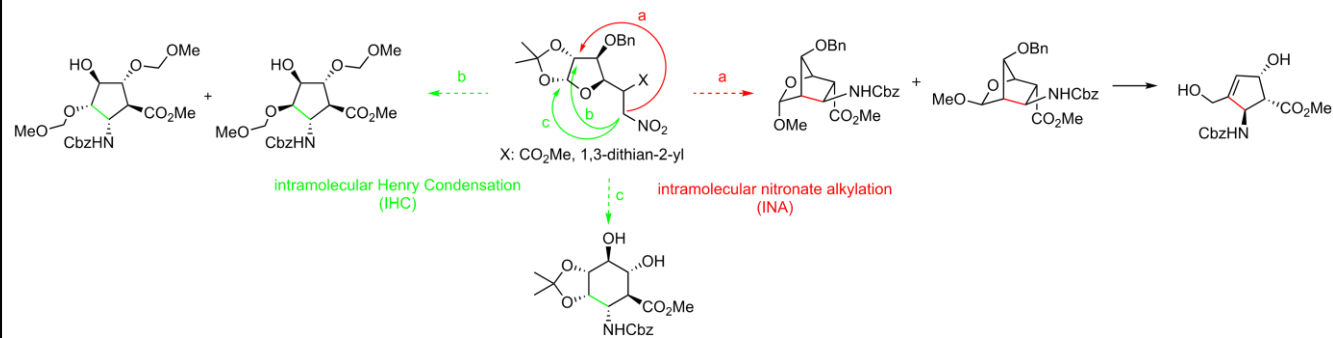
Graphical Abstract

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Highly functionalized cyclic and bicyclic β -amino acids from sugar β -nitroesters

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José M. Otero,^a Amalia M. Estévez,^a Juan C. Estévez,^a George W. J. Fleet^b and Ramón J. Estévez^{a,*}



Highly functionalized cyclic and bicyclic β -amino acids from sugar β -nitroesters

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Nitro sugars

Carbasugars

β -Amino acids

3-Nitropropionic acids

Molecular diversity

ABSTRACT

The synthesis of some highly functionalized bicyclic and cyclic β -amino acids from β -nitrosugars is reported. Specifically, our strategy for the synthesis of polyhydroxylated cyclopentane β -amino acids by an intramolecular C-alkylation of 6-nitro-2-O-triflates of furanosides has been applied to the preparation of the first two examples of a novel class of bicyclic β -amino acids and a novel cyclopentene β -amino acid. Also, our Henry reaction mediated strategy for the synthesis of polyhydroxylated cyclohexane β -amino acids has been extended to a divergent, stereoselective synthesis of new polysubstituted cyclohexane and cyclopentane β -amino acids.

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1. Introduction

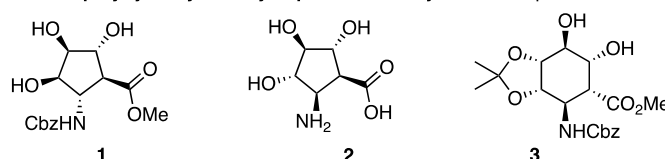
Peptidomimetics containing non-proteinogenic amino acids are an area of growing interest because the range of potential applications of proteins is limited by their reduced diversity both in terms of both primary and secondary structures, and their use as drugs is conditioned by their conformational flexibility and their metabolic instability.^{1,2,3,4} This is one reason why for the two last decades a great attention has been devoted to the synthesis of non-natural amino acids, as a first stage for the access to peptidomimetics that may improve the catalytic and recognition properties relative to natural peptides and can provide drugs more resistant to enzymatic degradation.^{5,6,7,8}

β -Amino acids with their structural similarity to α -amino acids and the increased propensity of their oligomers to fold in a range of structural motifs - including helices, turns and sheets - are the ideal candidates for this purpose.^{9,10,11} Particularly interesting are cyclic β -amino acids, because the rigidity provided by the ring promotes their folding as more stable secondary structures in short peptide sequences.^{12,13,14,15,16} Specifically representative are the four 2-aminocyclopentanecarboxylic acids. Thus, the natural (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin),¹⁷ a potent antifungal drug against *Candida albicans* that has been used to replace the central proline subunit in the tetrapeptide morphiceptin¹⁸ to provide a pharmacologically more active peptidomimetic.¹⁹ β -Oligopeptides consisting of *trans*-2-aminocyclopentanecarboxylic acids have a high propensity to fold as 12-helices topologically similar to α -helices,^{20,21} while *cis*-2-aminocyclopentanecarboxylic acid oligomers were later shown to adopt sheet-like structures.²² Short oligomers of optically pure *trans*-2-aminocyclohexanecarboxylic acid³ adopt a 14-helix.^{23,20} β -Amino acids containing bicyclic scaffolds were also considered as synthetic intermediates,

building blocks for medicinal chemistry, structural units of peptides.^{24,25} Specifically, several 3-aminobicyclo[2.2.1]heptane-2-carboxylic acids have been reported

In view of the promising pharmacological potential of highly functionalized carbocyclic β -amino acids bearing hydroxy, azido, amino or fluoro groups,^{26,16} some approaches for their preparation have been developed,^{27–30} but the access to these targets continue to be a challenge for organic chemists.^{31–33}

known polyhydroxylated cyclopentane and cyclohexane β -amino acids



new polysubstituted cyclic and bicyclic β -amino acids

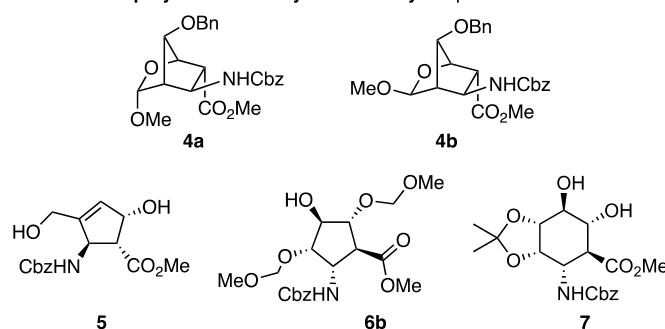


Figure 1

This paper describes the stereoselective syntheses of polyhydroxylated cycloalkane β -amino acids from nitro sugars that combine the diversity of sugars to generate nitrocycloalkanes as precursors of novel amino acids.

Specifically, an intramolecular nitronate alkylation (INA) gives two trihydroxylated 2-aminocyclopentanecarboxylic acids (**1**^{34–38} and **2**³⁹, Figure 1); the first reported tetrahydroxylated 2-aminocyclohexanecarboxylic acid **3**⁴¹ is formed by an intramolecular Henry condensation (IHC)⁴⁰. This work provides access to liposoluble (protected hydroxy substituents) or hydrosoluble (deprotected hydroxy groups) β -peptides of interest for biological and material chemistry applications.

Additional possibilities offered by these two synthetic approaches are exemplified by: (i) the novel bicyclic β -amino acids **4a** and **4b** and the novel monocyclic β -amino acid **5** were prepared using the INA approach and (ii) IHC based divergent syntheses of the polysubstituted cyclopentane β -amino acid **6b** and the polysubstituted cyclohexane β -amino acid **7**.

2. Results and discussion

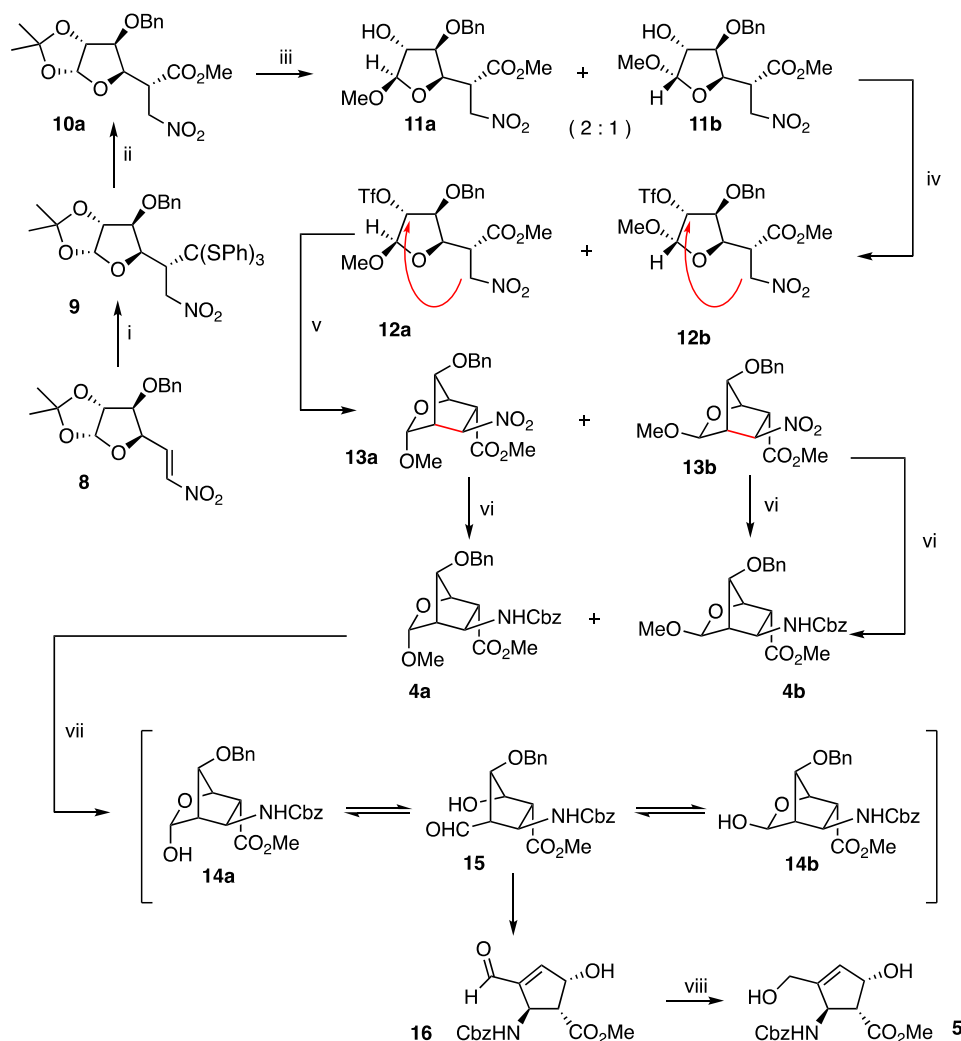
2.1. Synthesis of polysubstituted cyclopentene β -amino acid **5** and bicyclic β -amino acids **4a** and **4b**.

First, we studied the extension of the INA approach to nitro sugar **10a** (Scheme 1), previously obtained from sugar

nitroolefin **8**, via trithiane **9**, and applied to the preparation of polysubstituted cyclohexane β -amino acid **3** by means of the IHC approach.⁴¹

Reaction of the nitropropanoic acid ester **10a** with acetyl chloride in methanol provided a 2:1 mixture of anomers **11a** (65%) and **11b** (30%) (Scheme 1). The configuration of their respective anomeric carbons was clear deduced from the signals of the anomeric protons in their ¹H NMR spectra. The major anomer **11a** shows at 4.70 ppm a doublet ($J_{1,2}=10.0$ Hz), resulting from the *trans* coupling of protons H-1 and H-2; the spectrum of the minor anomer **11b** includes a doublet ($J_{1,2}=4.4$ Hz) at 4.97 ppm, showing H-1 and H-2 are *cis*.

As both anomers **11a** and **11b** produce the same final product **5**, the anomeric mixture **11a+11b** was directly reacted with triflic anhydride and pyridine, to give quantitatively the anomeric mixture of triflates **12a+12b**, which with TBAF in THF gave a base-induced INA to afford the bicyclic epimers **13a** (58%) and **13b** (21%).⁴²



Scheme 1. Conditions: i,ii) see reference 26. iii) AcCl, MeOH, 0 °C, 14 h (**11a**: 65%; **11b**: 30%). iv) TFAA, pyridine, Cl₂CH₂, -30 °C, 30 min. v) TBAF, THF, rt, 2 h (**13a**: 58%; **13b**: 21%). vi) a. H₂, 10% Raney-Ni, MeOH, rt, 3 h. b. saturated aq. NaHCO₃, CbzCl, MeOH, rt, 3 h (**4a**: 50% and **4b**: 52%, 2 steps). vii) 3:1 TFA/water, rt, 12 h (63%). viii) NaBH₄, 56:44 EtOH/water, rt, 10 min (99%).

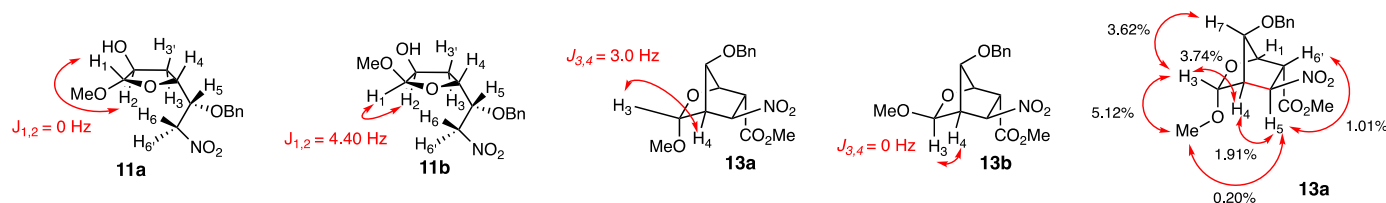


Figure 2

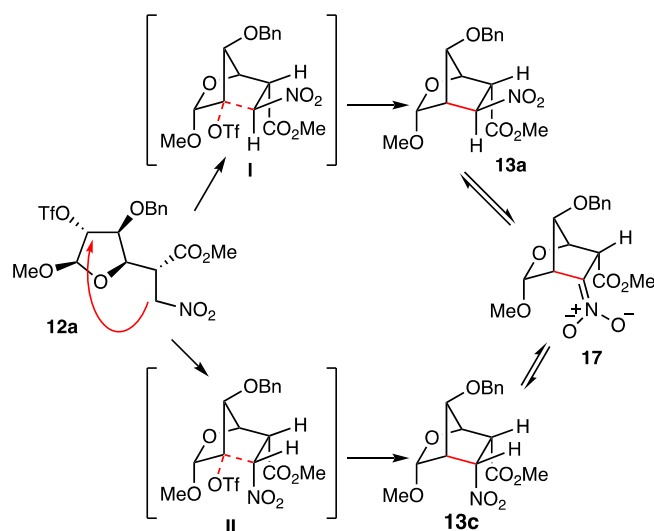
The *endo* configuration of the anomeric OMe group of the major compound **13a** (from **12a**) was indicated by the presence in its ^1H NMR spectrum of a doublet at 5.06 ppm ($J_{3,4}=3.0$ Hz), due to the coupling of protons H-3 and H-4. Moreover, the ^1H NMR spectrum of the minor compound **13b** (arising from **12b**) includes at 4.64 ppm a singlet, indicated the *exo* epimeric OMe group. These structural assignments were additionally supported by a NOE experiment of the major anomer **13a**, which showed a 3.62% NOE effect between H-3 and H-7 and the OMe group with a 0.20% NOE effect with H-5. Both effects confirm the *endo* disposition of its OMe group.

up to next bracket you cannot say a TS is thermodynamically more stable can you?, because the transition state **I** is thermodynamically more stable than the alternative transition state **II**, where stereoelectronic interactions among the CO_2Me , the NO_2 and the OMe groups are present [delete to here]. Alternatively, the INC reaction could be kinetically controlled directly leading to **13a**.

The bicyclic 3-nitropropanoic acid esters **13a** and **13b** were separated and independently converted into their respective protected β -carbamate esters **4a** and **4b**. Thus, catalytic hydrogenation of **13a**, with Raney-Ni as the catalyst, produced quantitatively the corresponding amine, which was immediately treated with CbzCl , to afford the bicyclic 3-carbamate **4a** (50% yield, 2 steps). A similar sequence was used for the transformation of the minor bicyclic 3-nitropropanoic acid ester **13b** into the corresponding 3-aminopropanoic acid derivative **4b** (52% yield, 2 steps). In a separate experiment the above mixture of epimeric 3-nitropropanoic acid esters **13a+13b** was subjected to this two steps sequence to give a mixture of carbamates **4a+4b** in 51% yield.

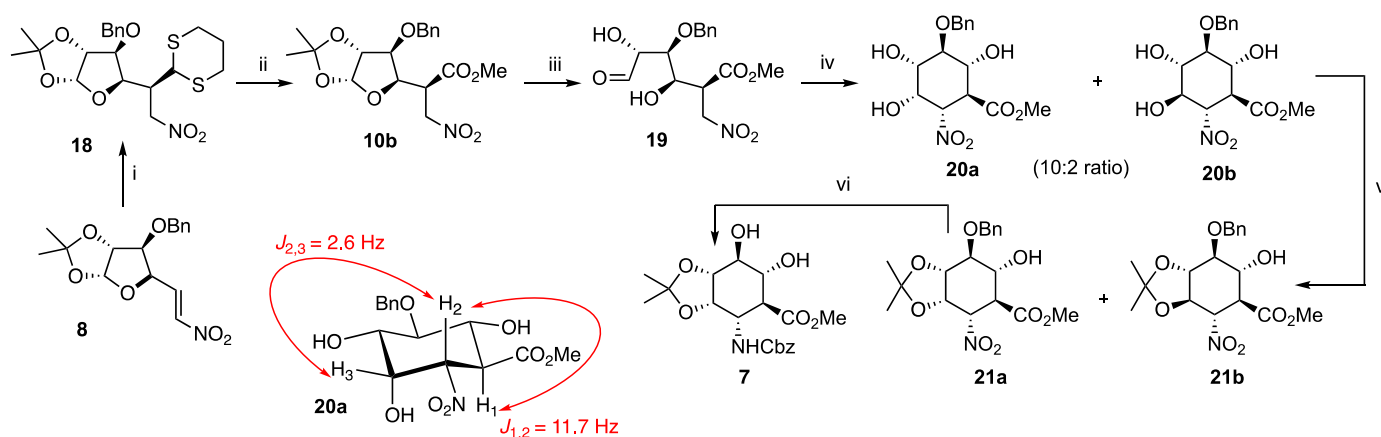
Hydrolysis of the anomeric carbamate mixture **4a+4b** with a TFA/water to the corresponding lactols **14a** and **14b** resulted in the subsequent elimination of benzyl alcohol to give aldehyde **16** (63%) as the sole product. The structure of **16** is clearly indicated by the ^1H NMR which has an olefinic proton at 6.80 ppm and the aldehyde proton at 9.77 ppm. Moreover, its ^{13}C NMR showed at 149.4 ppm for the olefinic CH and at 189.1 ppm for the aldehyde.

Treatment of **16** with sodium borohydride resulted in the selective reduction of the aldehyde to afford the polysubstituted cyclopentene β -amino acid **5** (99% yield) as the first example of a new family of alicyclic β -amino acids. The overall yield of **5** from the acetone **10a** was 24% and would likely increase with further optimization.



Scheme 2

The selective transformation of **12a** into **13a** was tentatively explained assuming that the triflate **12a** could produce both bicyclic compounds **13a** and **13c**, which, under the basic reaction conditions, are in equilibrium *via* nitronate **17**. Formation of the thermodynamically more stable compound **13a** is favored over compound **13c** (Scheme 2). [I would delete



Scheme 3. Conditions: i) reference 28. ii) a. $\text{BF}_3 \cdot \text{OEt}_2$, HgO , TFH, water, rt, 1.5 h. b. 2-Methyl-2-butene, NaClO_2 , NaH_2PO_4 , 3:1 MeOH/water, rt, 1 h. c. Trimethylsilyldiazomethane, 7:2 Et₂O/MeOH, rt, 15 min. (84% yield, 3 steps). iii) 2:1 TFA/water, rt, 5 h. iv) 2% aq. NaHCO_3 , MeOH, rt, 12 h (**20a**+**20b**: 73% yield, 2 steps). v) CuSO_4 , *p*-TsOH, 2,2-dimethoxypropane, acetone, rt, 24 h (isolated **21a**: 59%) vi) a. H_2 , 10% Pd/C, citric acid, MeOH, rt, 2 days. b. saturated aq. NaHCO_3 , CbzCl, MeOH, 0 °C to rt, 2 h (87%, 2 steps).

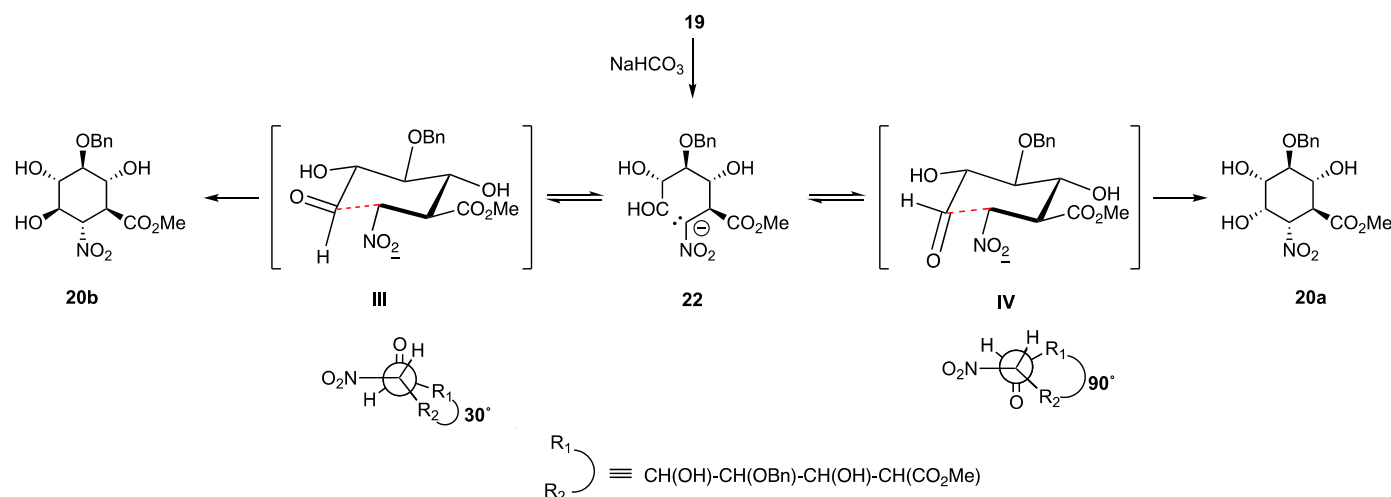
2.2. Synthesis of the polysubstituted cyclohexane β -amino acid 7.

The second approach to polysubstituted cycloalkane β -amino acids (Schemes 3 and 4) allowed the development of a general divergent synthesis of polyhydroxylated cyclopentane and cyclohexane β -amino acids. The key compound **18** (Scheme 3) was easily and efficiently obtained⁴³ as the major component (58% yield) of the Michael addition of the lithium salt of 1,3-dithiane to the corresponding nitroolefin **8**.

Transformation of the dithianyl unit in **18** into the methoxycarbonyl derivative **10b** was achieved in a 84% overall yield in three steps: transformation of the dithiane group in an aldehyde by HgO , oxidation of the aldehyde to a carboxyl group by NaClO_2 and generation of the methoxycarbonyl group of **10b** by esterification with trimethylsilyldiazomethane.^{41,43} Hydrolysis of the acetonide in **10b** by trifluoroacetic acid/water gave the 6-nitrohexanaldehyde **19**; which with NaHCO_3 as a base,⁴¹ induced ICH to give of an inseparable 10:2 mixture of the cyclohexane β -nitro esters **20a** and **20b** (73% yield, two steps) as indicated by the intensities

of the respective ^{13}C NMR signals by the carbons at C-2 bearing the nitro groups. The complex ^1H NMR spectrum of this mixture **20a**+**20b** showed a double doublet at $\delta=4.88$ ppm, due to the proton at C-2 carbon bearing the nitro group of the major component **20a**. The coupling constant $J_{1,2}=11.7$ Hz justify assignment of *trans* di-axial arrangement of the protons at positions C-1 and C-2 in **20a** and the coupling constant $J_{2,3}=2.6$ Hz due to the axial and equatorial arrangement of protons at positions C-2 and C-3, respectively. In this compound the nitro, the carboxyl and γ -hydroxyl groups are all equatorial. [I think you should use disposition very sparingly] Accordingly, structure **20b** was assigned to the minor component.

The diastereomeric ratio indicated that the cyclization leading to **20a** and **20b** is subjected to a kinetic control (Scheme 4). The Henry cyclization of nitronate **22** can occur *via* the chair-like transition states **III** or **IV**. Nucleophilic attack of the nitronate on the carbonyl is more favoured for **IV** than for **III** due to stereoelectronic factors, so the major component of the reaction mixture is **20a**. **20b** in which all groups are equatorial might be expected to be thermodynamically more stable.

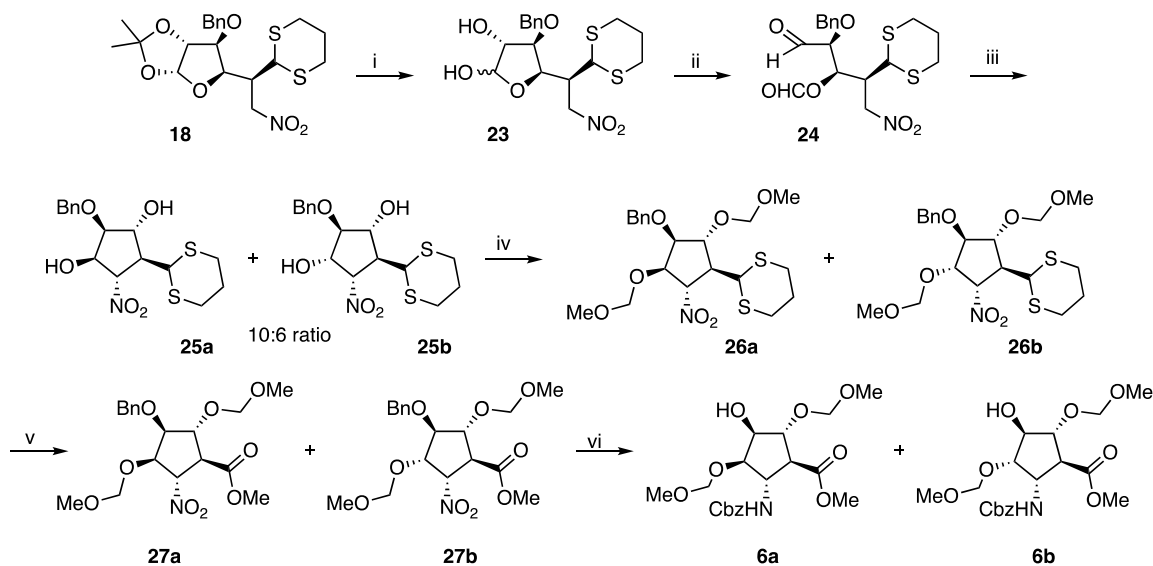


Scheme 4

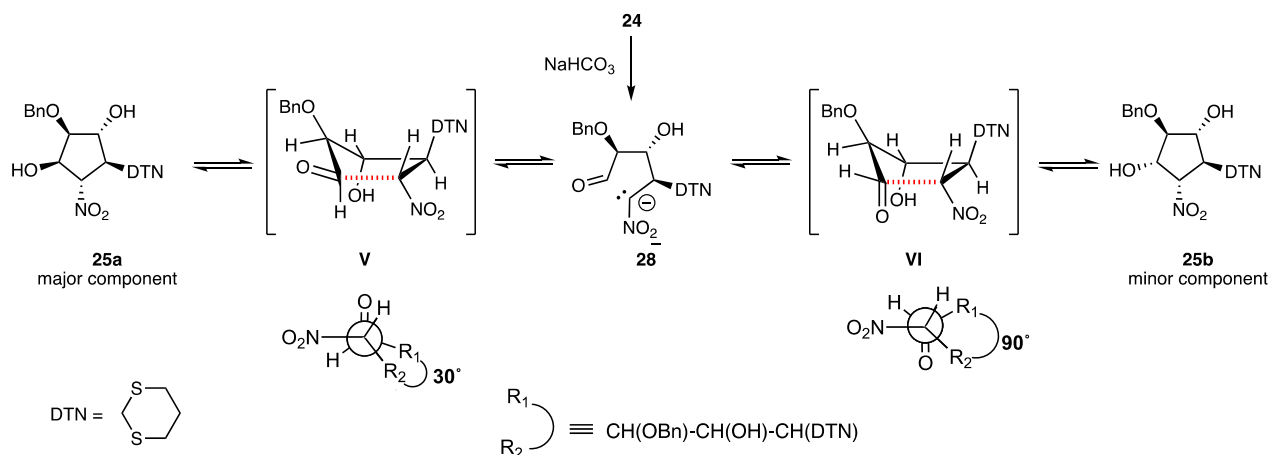
Reaction of the mixture **20a+20b** with 2,2-dimethoxypropane and *p*-TsOH, formed a separable mixture of the two acetonides **21a+21b** (10:2), from which the major component **21a** was partially isolated (59% yield) by column chromatography and unambiguously characterized by an X-ray crystallographic analysis (Figure 2).⁴⁴ Catalytic hydrogenation of **21a** in methanol, in the presence of citric acid and 10% Pd/C, resulted in reduction of the nitro group to the amine and simultaneous hydrogenolysis of the benzyl group; direct treatment of the amine with CbzCl gave the carbamate **7** (35%, 2 steps), as the third reported example of a polyhydroxylated cyclohexane β -amino acid

2.3. Synthesis of polysubstituted cyclopentane β -amino acids **6a** and **6b**.

Compound **18** can also be used to prepare polyhydroxylated cyclopentane β -amino acids by the intramolecular Henry reaction. Hydrolysis of the isopropylidene group in **18**, with a 3:1 AcOH/water mixture afforded the lactols **23**, which on oxidation with lead tetraacetate gave the nitroaldehyde **24** (Scheme 5).



Scheme 5. Conditions: i) 3:1 AcOH/water, reflux, 2.5 h. ii) Pb(AcO)₄, benzene, rt, 2 h. iii) 2% aq. NaHCO₃, rt, 24 h. (**25a+25b**: 82%, 3 steps). iv) CH₂(OCH₃)₂, P₂O₅, CH₂Cl₂, reflux, 12 h (**26a+26b**: 89%, 3 steps). v) a. BF₃·OEt₂, HgO, TFH, water, rt, 1.5 h. b. 2-methyl-2-butene, NaClO₂, NaH₂PO₄, 3:1 MeOH/water, rt, 1 h. c. Trimethylsilyldiazomethane, 7:2 Et₂O/MeOH, rt, 15 min. (**27a+27b**: 67%, 3 steps) vi) a. H₂, 10% Pd/C, citric acid, MeOH, rt, 2 days. b. saturated aq. NaHCO₃, CbzCl, MeOH, rt, 3 h. (**6a**: 47%, **6b**: 24%).



Scheme 6

Compound **24** upon treatment with 2% aqueous sodium bicarbonate cyclized to an inseparable mixture of cyclopentanes **25a** and **25b** (89% yield) in an approximate 10:6 ratio as indicated by the ¹³C NMR intensities of the signals at 93.6 ppm and 89.4 ppm, due to carbons bearing the nitro groups. Crystallization of the crude mixture from dichloromethane provided crystals constituted by the same mixture of both compounds **25a** and **25b**, whose structures were unequivocally established by an X-ray crystallographic analysis (Figure 3).⁴¹ The intramolecular Henry reaction of

nitronate **28** can occur *via* transition states **V** and **VI** (Scheme 6). The reaction is subject to thermodynamic control. Formation of the major component of the reaction mixture (**25a**, the thermodynamic more stable epimer) occur *via* **V** (the thermodynamically less stable transition state, due to stereoelectronic reasons).

Protection of the hydroxy groups of the epimeric mixture **25a+25b** by formaldehyde dimethyl acetal and phosphorous pentoxide gave an inseparable mixture of cyclopentanes

26a+26b (89% yield), which was subjected to the same three steps sequence as for the transformation of the dithianyl group of compound **18** into the methoxycarbonyl group compound **10b**. This provided an inseparable mixture of cyclopentane β -nitroesters **27a** and **27b** (67% yield, 3 steps). Finally, this mixture, under the conditions used for the transformation of

compound **21a** into compound **8**, gave compound **6a** (47% yield, derivative of the known polyhydroxylated cyclopentane β -amino acid **1**) and **6b** (24% yield, derivative of a new polyhydroxylated cyclopentane β -amino acid), separable by column chromatography.

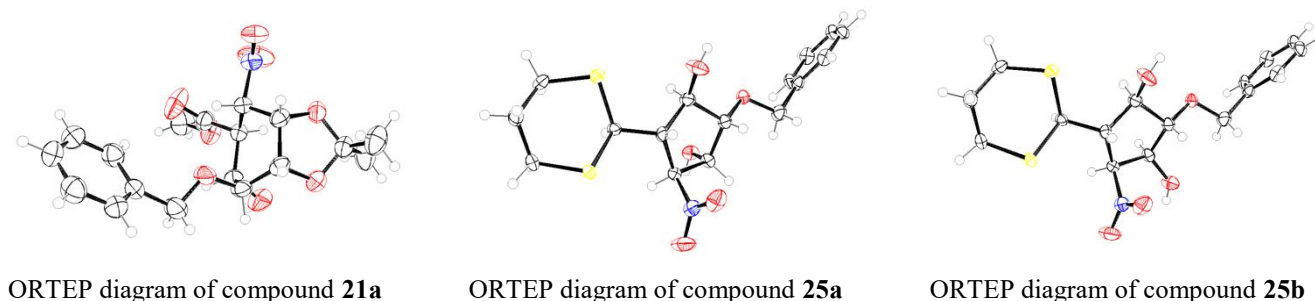


Figure 3

3. Conclusions

In summary, we have synthesized some novel polysubstituted bicyclic and cyclopentene β -amino acids and increased the limited number of reported polyhydroxylated cyclopentane and cyclohexane β -amino acids.

Our previous strategy for the synthesis of polyhydroxylated cyclopentane β -amino acids by an intramolecular C-alkylation of 6-nitro-2-O-triflates of furanosides has been extended to the corresponding 5-carbomethoxy-6-nitro-2-O-triflates to give the first two examples of a novel class of bicyclic β -amino acids (compounds **4a** and **4b**), from which the novel disubstituted cyclopentene β -amino acid **5** was easily derived.

5-Dithianyl-6-nitroglucofuranosides allows the synthesis of the polysubstituted cyclohexane β -amino acid **7** and two polysubstituted cyclopentane β -amino acids **6a** and **6b**.

4. Experimental section.

4.1. General.

All non-aqueous reactions were carried out under a positive atmosphere of argon in flame-dried glassware unless otherwise stated. Air- and moisture-sensitive liquid reagents were added by dry syringe or cannula. Anhydrous tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon and all other solvents and reagents were used as obtained from commercial sources without further purification unless stated. Flash chromatography was performed using 60 Merck 230–400 mesh (flash, 0.04–0.063) silica. Thin layer chromatography (t.l.c.) was carried out on aluminium backed sheets coated with 60 GF254 silica. Plates were developed using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid, or in 5% w/v ninhydrin in methanol. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX 250 (250 MHz for ^1H and 62.5 MHz for ^{13}C) and Varian Inova 400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometers at room temperature unless otherwise stated. All chemical shifts are quoted on the δ scale using residual solvent as internal standard; s, d, t, q, m, and br designate singlet, doublet, triplet, quadruplet, multiplet, and broad, respectively. Coupling constants (J) are measured in Hz. Low resolution mass spectra were recorded on a Micromass Autospec spectrometer [by chemical ionisation (NH_3 , Cl) as stated]. Infrared spectra were recorded on a FT-IR Mattson Cygnus-100 spectrometer. Only the characteristic peaks are quoted (in units of cm^{-1}). All the spectra were

measured in KBr. Optical rotations were measured on a Jasco DIP-370 polarimeter with a path length of 0.5 dm and Na (589 nm) lamp. Concentrations are given in g/100 mL. Elemental analyses were carried out on a Carlo Erba EA 1108 analyser. Compounds **8**⁴⁵, **10a**⁴¹ and **18**⁴³ were prepared according to known procedures.

4.2. Methyl 3-O-benzyl-5-deoxy-1-O-methyl-5-nitromethyl- β -D-glucosylfuranosiduronate (11a**) and methyl 3-O-benzyl-5-deoxy-1-O-methyl-5-nitromethyl- α -D-glucosylfuranosiduronate (**11b**).**

Acetyl chloride (0.81 mL, 6.4 mmol) was added to a cooled (0 °C) solution of compound **10a** (0.72 g, 1.89 mmol) in dry methanol (12 mL) and the solution was stirred at 0 °C for 14 hours. The reaction mixture was then basified (Na_2CO_3), filtered and concentrated to dryness in a rotary evaporator. Flash column chromatography of the crude (1:2 ethyl acetate/hexane) provided compound **11a** (0.40 g, 65% yield) and compound **11b** (0.20 g, 30% yield), both as yellow oils. **Compound 11a**: $[\alpha]_{\text{D}}^{20}$: -70 (c 0.7, CHCl_3). ^1H NMR (CDCl_3 , 250 MHz, ppm): 2.59 (bs, 1 H, -OH); 3.30 (s, 3 H, CH_3O); 3.49–3.53 (m, 1 H, H-5); 3.54 (s, 3 H, CH_3O); 3.97 (dd, 1 H, $J_{3,4}=5.5$ Hz, $J_{3,2}=1.1$ Hz, H-3); 4.12 (s, 1 H, H-2); 4.37 (d, 1 H, $J=6.8$ Hz, -CHHPh); 4.56 (d, 1 H, $J=6.8$ Hz, -CHHPh); 4.61–4.64 (m, 1 H, H-4); 4.70 (s, 1 H, H-1); 4.73 (dd, 1 H, $J=3.6$ Hz, $J=14.3$ Hz, -CHHNO₂); 4.87 (dd, 1 H, $J=7.1$ Hz, $J=14.3$ Hz, -CHHNO₂); 7.20–7.35 (m, 5 H, 5xAr-H). ^{13}C NMR (CDCl_3 , 62.5 MHz, ppm): 43.5 (CH); 52.4 (CH_3); 56.0 (CH_3); 72.5 (CH_2); 73.7 (CH_2); 78.2 (CH); 78.5 (CH); 83.4 (CH); 109.9 (CH); 127.8 (3xCH); 128.4 (2xCH); 137.1 (C); 170.9 (C). IR (ν , cm^{-1}): 3528 (OH); 1741 (CO); 1557 (NO₂); 1377 (NO₂). MS-Cl (m/z , %): 324 (3, $[\text{M}-\text{CH}_3\text{O}]^+$); 169 (75, $[\text{M}-\text{C}_7\text{H}_5\text{NO}_5]^+$); 91 (100, $[\text{PhCH}_2]^+$). Elemental analysis: calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_8$: C: 54.08; H: 5.96; N: 3.94; found: C: 54.32; H: 6.08; N: 4.07. **Compound 11b**: $[\alpha]_{\text{D}}^{20}$: +51.6° (c 1.2, CHCl_3). ^1H NMR (CDCl_3 , 250 MHz, ppm): 2.81 (bs, 1 H, -OH); 3.44 (s, 3 H, CH_3O); 3.56–3.63 (m, 1 H, H-5); 3.67 (s, 3 H, CH_3O); 4.09 (dd, 1 H, $J_{3,4}=5.5$ Hz, $J_{3,2}=2.8$ Hz, H-3); 4.20–4.23 (m, 1 H, H-2); 4.51 (d, 1 H, $J=6.5$ Hz, -CHHPh); 4.55 (dd, 1 H, $J_{4,3}=5.5$ Hz, $J_{4,5}=8.0$ Hz, H-4); 4.73 (d, 1 H, $J=6.5$ Hz, -CHHPh); 4.80–4.87 (m, 2 H, - CH_2NO_2); 4.97 (d, 1 H, $J_{1,2}=4.4$ Hz, H-1); 7.26–7.39 (m, 5 H, 5xAr-H). ^{13}C NMR (CDCl_3 , 62.5 MHz, ppm): 43.4 (CH); 52.3 (CH_3); 55.9 (CH_3); 72.4 (CH); 73.6 (CH_2); 78.1 (CH); 78.5 (CH); 83.3 (CH); 109.8 (CH); 127.7 (2xCH); 127.8 (CH); 128.3 (2xCH); 136.9 (C); 170.8

(C). IR (ν , cm^{-1}): 3528 (OH); 1752 (CO); 1565 (NO_2); 1380 (NO_2). MS-Cl (m/z , %): 324 (5, $[\text{M}-\text{CH}_3\text{O}]^+$); 169 (40, $[\text{M}-\text{C}_7\text{H}_9\text{NO}_5]^+$); 91 (100, $[\text{PhCH}_2]^+$). Elemental analysis: calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_8$: C, 54.08; H, 5.96; N, 3.94; found C, 54.27; H, 6.10; N, 4.04.

4.3. Methyl (1*R*,3*R*,4*S*,5*S*,6*R*,7*R*)-7-(benzyloxy)-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptan-6-carboxylate (**13a**) and methyl (1*R*,3*S*,4*S*,5*S*,6*R*,7*R*)-7-(benzyloxy)-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptan-6-carboxylate (**13b**).

Dry pyridine (1.47 mL, 5.52 mmol) and triflic anhydride (1.32 mL, 2.58 mmol) were added, under argon, to a cooled (-30°C) solution of a recently obtained anomeric mixture **11a+11b** in dry dichloromethane (13.8 mL). The new solution was stirred at -30°C for 30 min, and then was diluted with dichloromethane (30 mL) and washed with 2 M aq. HCl (3 mL). The water layer was extracted with dichloromethane (2x30 mL) and the pooled organic fractions were dried (anhydrous Na_2SO_4) and concentrated to dryness under vacuum.

Then, a 1 M solution of TBAF in dry THF (3.6 mL) was added, under argon, to a solution of the resulting crude in dry THF (15 mL) and the new solution was stirred at rt for 2 hours. The solvent was removed under vacuum, the residue was solved in dichloromethane (30 mL) and the solution was washed with water (3x30 mL), dried (anhydrous Na_2SO_4) and concentrated to dryness in a rotary evaporator. Flash column chromatography of the residue (eluent: 1:4 ethyl acetate/hexane) allowed to isolate compound **13a** (0.26 g, 58% yield, 2 steps) and compound **13b** (0.05 g, 21% yield, 2 steps), as yellow oils. **Compound 13a**: $[\alpha]_{\text{D}}^{20}$: -49 (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 250 MHz, ppm): 3.33 (s, 3 H, $-\text{CH}_3$); 3.68-3.73 (m, 1 H, H-6); 3.79 (s, 3 H, $-\text{CH}_3$); 4.00-4.05 (m, 1 H, H-4); 4.13-4.18 (m, 1 H, H-7); 4.35 (d, 1 H, $J=6.5$ Hz, $-\text{CHHPh}$); 4.50 (d, 1 H, $J=6.5$ Hz, $-\text{CHHPh}$); 4.53-4.57 (m, 1 H, H-1); 5.06 (d, 1 H, $J_{3,4}=3.0$ Hz, H-3); 5.52 (d, 1 H, $J_{5,4}=3.8$ Hz, H-5); 7.17-7.37 (m, 5 H, 5xAr-H). ^{13}C NMR (CDCl_3 , 62.5 MHz, ppm): 48.3 (CH); 52.3 (CH_3); 52.4 (CH); 55.8 (CH_3); 71.9 (CH_2); 79.6 (CH); 79.7 (CH); 81.7 (CH); 101.3 (CH); 127.7 (2xCH); 128.1 (CH); 128.4 (CH); 128.5 (CH); 136.3 (C); 169.4 (C). IR (ν , cm^{-1}): 1750 (s, CO); 1565 (NO_2); 1383 (NO_2). MS-Cl (m/z , %): 338 (42, $[\text{M}+\text{H}]^+$); 121 (100, $[\text{MH}-\text{C}_{12}\text{H}_{13}\text{NO}_3]^+$); 91 (95, $[\text{PhCH}_2]^+$). Analysis: calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_7$: C, 56.97; H, 5.68; N, 4.15; found C, 57.13; H, 5.83; N, 4.20. **Compound 13b**: $[\alpha]_{\text{D}}^{20}$: +23 (c 1.3, CHCl_3). ^1H NMR (CDCl_3 , 250 MHz, ppm): 3.36 (s, 3 H, $-\text{CH}_3$); 3.56-3.59 (m, 1 H, H-4); 3.80 (s, 3 H, $-\text{CH}_3$); 3.97-4.02 (m, 1 H, H-6); 4.34 (d, 1 H, $J=6.5$ Hz, $-\text{CHHPh}$); 4.43-4.53 (m, 3 H, $-\text{CHHPh}$, H-1, H-7); 4.64 (s, 1 H, H-3); 4.95 (d, 1 H, $J_{5,4}=3.8$ Hz, H-5); 7.18-7.38 (m, 5 H, 5xAr-H). ^{13}C NMR (CDCl_3 , 62.5 MHz, ppm): 48.6 (CH); 52.4 (CH_3); 52.8 (CH); 55.4 (CH_3); 72.2 (CH_2); 78.1 (CH); 81.8 (CH); 82.2 (CH); 103.2 (CH); 127.7 (2xCH); 128.1 (CH); 128.5 (2xCH); 136.5 (C); 170.3 (C). IR (ν , cm^{-1}): 1745 (CO); 1548 (NO_2); 1376 (NO_2). MS-Cl (m/z , %): 338 (30, $[\text{M}+\text{H}]^+$); 121 (100, $[\text{MH}-\text{C}_{12}\text{H}_{13}\text{NO}_3]^+$); 91 (90, $[\text{PhCH}_2]^+$). Analysis: calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_7$: C, 56.97; H, 5.68; N, 4.15; found C, 57.03; H, 5.75; N, 4.19.

4.4. Methyl (1*R*,3*R*,4*S*,5*S*,6*R*,7*R*)-7-(benzyloxy)-5-(((benzyloxy)carbonyl)amino)-3-methoxy-2-oxabicyclo[2.2.1]heptan-6-carboxylate (**4a**).

10% Raney-Ni (3.2 mL) was added to a deoxygenated solution of compound **13a** (0.19 g, 0.56 mmol) in methanol (8.4

mL) and the suspension was stirred at rt for 3 hours, under a hydrogen atmosphere. The suspension was filtered through a celite pad and the solvent was removed off in a rotary evaporator. Then, saturated aq. NaHCO_3 (2.8 mL) was added to a solution of the resulting crude amine in methanol (4.5 mL), the mixture was cooled (0°C), benzyl chloroformate (0.1 mL, 0.68 mmol) was added drop by drop, under stirring, and the reaction was continued at rt for 3 hours. Once the two layers were separated, the aqueous layer was extracted with ethyl acetate (3x10 mL) and the combined organic layers were dried (anhydrous Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. Flash column chromatography of the oil residue (eluent: 1:3 ethyl acetate/ hexane) provided pure compound **4a** (0.2 g, 50% yield, 2 steps), as a yellow oil. $[\alpha]_{\text{D}}^{20}$: +32.2° (c 0.8, CHCl_3). ^1H NMR (CDCl_3 , 250 MHz, ppm): 2.53 (bs, 1 H, H-4); 2.89-2.94 (m, 1 H, H-6); 3.32 (s, 3 H, $-\text{CH}_3$); 3.74 (s, 3 H, $-\text{CH}_3$); 4.11-4.15 (m, 1 H, H-7); 4.45-4.60 (m, 3 H, $-\text{CH}_2\text{Ph}$, H-1); 4.92 (d, 1 H, $J_{3,4}=2.5$ Hz, H-3); 5.03-5.22 (m, 3 H, $-\text{CH}_2\text{Ph}$, H-5); 5.48 (d, 1 H, $J=9.9$ Hz, $-\text{NH}-$); 7.27-7.43 (m, 10 H, 10xAr-H). ^{13}C NMR (CDCl_3 , 62.5 MHz, ppm): 47.3 (CH); 49.0 (CH); 51.9 (CH_3); 55.4 (CH_3); 56.0 (CH); 66.4 (CH_2); 72.2 (CH_2); 79.3 (CH); 82.8 (CH); 101.8 (CH); 127.8 (3xCH); 128.1 (CH); 128.2 (2xCH); 128.3 (CH); 128.6 (3xCH); 136.5 (2xC); 155.1 (C); 170.4 (C). IR (ν , cm^{-1}): 3433 (NH); 1747 (CO); 1726 (CO). MS-Cl (m/z , %): 442 (65, $[\text{M}+\text{H}]^+$); 334 (100, $[\text{M}-\text{C}_7\text{H}_7\text{O}]^+$); 291 (25, $[\text{M}-\text{C}_8\text{H}_8\text{NO}_2]^+$). Analysis: calculated for $\text{C}_{24}\text{H}_{27}\text{NO}_7$: C, 65.29; H, 6.16; N, 3.17; found C, 65.51; H, 5.87; N, 2.99.

4.5. Methyl (1*R*,3*R*,4*S*,5*S*,6*R*,7*R*)-7-(Benzyloxy)-5-(((benzyloxy)carbonyl)amino)-3-methoxy-2-oxabicyclo[2.2.1]heptan-6-carboxylate (**4b**).

When compound **13b** (0.027 g, 0.08 mmol) was subjected to the procedure for the preparation of compound **4a**, compound **4b** was obtained (0.019 g, 52% yield, 2 steps), as a yellow oil. $[\alpha]_{\text{D}}^{20}$: +129° (c 1.2, CHCl_3). ^1H NMR (CDCl_3 , 250 MHz, ppm): 2.43 (bs, 1 H, H-4); 2.87-2.93 (m, 1 H, H-6); 3.32 (s, 3 H, $-\text{CH}_3$); 3.74 (s, 3 H, $-\text{CH}_3$); 4.37-4.56 (m, 5 H, H-1, H-5, H-7, $-\text{CH}_2\text{Ph}$); 4.62 (bs, 1 H, H-3); 5.09 (ABq, 2 H, $J=12.35$ Hz, $-\text{CH}_2\text{Ph}$); 5.38 (d, 1 H, $J=9.6$ Hz, $-\text{NH}-$); 7.28-7.40 (m, 10 H, 10xAr-H). ^{13}C NMR (CDCl_3 , 62.5 MHz, ppm): 50.0 (CH); 51.4 (CH); 52.2 (CH_3); 55.3 (CH_3); 55.6 (CH); 66.7 (CH_2); 72.8 (CH_2); 77.7 (CH); 83.2 (CH); 104.2 (CH); 127.9 (3xCH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 128.5 (2xCH); 128.7 (2xCH); 136.4 (C); 136.8 (C); 155.4 (C); 171.5 (C). IR (ν , cm^{-1}): 3425 (NH); 1743 (CO); 1728 (CO). MS-Cl (m/z , %): 442 (47, $[\text{M}+\text{H}]^+$); 334 (100, $[\text{M}-\text{C}_7\text{H}_7\text{O}]^+$); 291 (5, $[\text{M}-\text{C}_8\text{H}_8\text{NO}_2]^+$). Analysis: calculated for $\text{C}_{24}\text{H}_{27}\text{NO}_7$: C, 65.29; H, 6.16; N, 3.17; found C, 65.40; H, 6.05; N, 2.95.

4.6. Methyl (1*R*,2*R*,5*S*)-2-(((benzyloxy)carbonyl)amino)-3-formyl-5-hydroxycyclopent-3-enecarboxylate (**16**).

When a mixture of **13a+13b** (0.35 g, 0.78 mmol) was subjected to the method for the preparation of carbamate **4a**, a mixture of carbamates **4a+4b** was obtained (0.13 g, 51%, 2 steps), as an oil, after flash column chromatography (1:3 ethyl acetate/ hexane).

This mixture of anomers **4a** and **4b** (0.11 g) was added to a 3:1 TFA/water mixture (2 mL) and the solution was stirred at rt for 12 hours. The solvents were removed under vacuum and the residue was co-evaporated with toluene (3x5 mL). Flash

column chromatography of the residue (eluent: 1:1 ethyl acetate/hexane) allowed to isolate compound **16** (0.50 g, 0.16 mmol, 63% yield), as a yellow oil. $[\alpha]_D^{20}$: +129° (c 0.8, CHCl₃). ¹H NMR (CDCl₃, 250 MHz, ppm): 3.40 (d, 1 H, $J_{OH,5}$ =6.8 Hz, -OH); 3.54 (m, 1 H, H-1); 3.73 (s, 3 H, CH₃O-); 4.95-5.30 (m, 4 H, H-2, H-5, -CH₂Ph); 5.55 (d, 1 H, $J_{NH,2}$ =6.6 Hz, -NH-); 6.80 (bs, 1 H, H-4); 7.29-7.37 (m, 5 H, 5xAr-H); 9.77 (s, 1 H, -CHO). ¹³C NMR (CDCl₃, 62.5 MHz, ppm): 52.2 (CH₃); 54.5 (CH); 56.2 (CH); 66.7 (CH₂); 74.2 (CH); 127.9 (2xCH); 128.1 (CH); 128.4 (2xCH); 136.0 (C); 145.0 (C); 149.4 (CH); 155.5 (C); 171.4 (C); 189.1 (CH). IR (ν, cm⁻¹): 3352 (OH + NH); 1694 (CO). MS-Cl (m/z, %): 320 (85, [M+H]⁺); 276 (99, [MH-CO₂]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₆H₁₇NO₆: C, 60.18; H, 5.37; N, 4.39; found C, 60.36; H, 5.57; N, 4.54.

4.7. Methyl (1*R*,2*R*,5*S*)-2-(((Benzyloxy)carbonyl)amino)-5-hydroxy-3-(hydroxymethyl)cyclopent-3-ene carboxylate (**5**).

A solution of NaBH₄ (0.02 g, 0.05 mmol) in water (0.04 mL) was added to a stirred solution of compound **5** (0.017 g, 0.04 mmol) in a 56:44 ethanol/water mixture (0.04 mL) and the stirring was continued at rt for 10 min. The reaction mixture was extracted with ethyl acetate (5 mL) and the aqueous layer was extracted with ethyl acetate (2x5 mL). The pooled organic layers were dried (anhydrous Na₂SO₄), filtered and concentrated to dryness in a rotary evaporator. The residue was subjected to flash column chromatography (eluent: 1:1 ethyl acetate/hexane) and compound **8** was isolated (0.017 g, 99% yield), as a yellow oil. $[\alpha]_D^{20}$: +94° (c 0.7, MeOH). ¹H NMR (CDCl₃, 250 MHz, ppm): 3.15-3.30 (2 H, m, H-1, -OH); 3.74 (s, 3 H, CH₃O-); 4.05-4.17 (m, 2 H, -CH₂OH); 4.22 (dd, 1 H, J =2.7 Hz, J =6.0 Hz, -OH); 4.90-5.22 (m, 5 H, H-2, -NH-, H-5, -CH₂Ph); 5.81-5.86 (m, 1 H, H-4); 7.30-7.38 (m, 5 H, 5xAr-H). ¹³C NMR (CDCl₃, 62.5 MHz, ppm): 52.2 (CH₃); 55.7 (CH); 57.5 (CH); 58.8 (CH₂); 67.1 (CH₂); 74.0 (CH); 128.1 (3xCH); 128.2 (CH); 128.5 (2xCH); 136.0 (C); 148.4 (C); 156.3 (C); 171.5 (C). IR (ν, cm⁻¹): 3315 (OH + NH); 1735 (CO); 1694 (CO). MS-Cl (m/z, %): 340 (1, [M+H]⁺); 322 (22, [M-OH]⁺); 280 (15, [M-C₂H₃O₂]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₆H₁₉NO₆: C, 59.81; H, 5.96; N, 4.36; found C, 60.00; H, 6.02; N, 4.47.

4.8. 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-*C*-methoxycarbonyl-6-nitro-β-*L*-idofuranose (**10b**).

Boron trifluoride etherate (0.63 mL, 4.95 mmol) was added to a suspension of HgO (1.07 g, 4.95 mmol) in TFH (5 mL) and water (1 mL). Then a solution of compound **18** (0.44 g, 0.99 mmol) in THF (1 mL) was added, under argon, to this suspension and the resulting mixture was stirred at rt for 1.5 hours. Then, dichloromethane (20 mL) was added, the suspension was filtered and the filtrate was washed with saturated aq. NH₄Cl (4x20 mL), dried (anhydrous Na₂SO₄) and concentrated to dryness in a rotary evaporator. After, 2-methyl-2-butene (0.8 mL, 6.93 mmol), NaClO₂ (0.14 g, 1.29 mmol) and NaH₂PO₄·2H₂O (0.18 g, 1.19 mmol) were added to a solution of the resulting chromatographically pure residue in 3:1 MeOH/water (5 mL) and the mixture was stirred at rt for 1 h. This mixture was next diluted with water (15 mL), acidified with 10% aq. HCl and extracted with ethyl acetate (4x20 mL). The combined organic layers were dried (anhydrous Na₂SO₄), filtered and the liquids were removed under vacuum in a rotary evaporator. Finally, a 2 M solution of

trimethylsilyldiazomethane in ethylic ether (0.59 mL, 1.19 mmol) was added to a solution of the resulting oil residue in a 7:2 ethylic ether/methanol mixture (11 mL), and the new mixture was stirred at rt for 15 min and then concentrated to dryness under vacuum in a rotary evaporator. Flash column chromatography of the residue (1:4 ethyl acetate/hexane) provided compound **10b** (0.32 g, 84% yield, 3 steps), as white amorphous solid. m.p. 76-77 °C (Et₂O/hexane). $[\alpha]_D^{20}$: -43.0 (c 1.40, CHCl₃). ¹H NMR (CDCl₃, 250 MHz, ppm): 1.33 (s, 3 H, CH₃); 1.50 (s, 3 H, CH₃); 3.66 (s, 3 H, OCH₃); 3.88-3.96 (m, 2 H, H-3 + H-5); 4.38 (d, 1H, J =11.4 Hz, CH₂Ph); 4.44 (dd, 1 H, $J_{5,6}$ =3.6 Hz, $J_{6,6}$ =15.1 Hz, H-6); 4.58 (dd, 1 H, $J_{3,4}$ =3.6 Hz, $J_{4,5}$ =8.3 Hz, H-4); 4.61 (d, 1 H, $J_{1,2}$ =3.6 Hz, H-2); 4.64 (d, 1 H, J =11.4 Hz, CH₂Ph); 4.83 (dd, 1 H, $J_{5,6}$ =8.8 Hz, $J_{6,6}$ =15.1 Hz, H-6); 5.93 (d, 1 H, $J_{1,2}$ =3.6 Hz, H-1); 7.27-7.38 (m, 5 H, 5 x H-Ph). ¹³C NMR (CDCl₃, 62.5 MHz, ppm): 26.1 (CH₃); 26.7 (CH₃); 42.5 (CH); 52.6 (OCH₃); 71.8 (CH₂); 71.9 (CH₂); 77.5 (CH); 81.3 (2 x CH); 104.8 (CH); 112.0 (C); 128.3 (2 x CH); 128.4 (CH); 128.7 (2 x CH); 136.1 (C); 170.3 (CO). IR (ν, cm⁻¹): 1740 (CO); 1554 (NO₂); 1380 (NO₂). MS-Cl (m/z, %): 382 (6, MH⁺); 335 (8, [M-NO₂]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₈H₂₃NO₈: C 56.69, H 6.08, N 3.67; found C 56.61, H 6.18, N 3.68.

4.9. Methyl (1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-5-benzyloxy-6-hydroxy-3,4-isopropylidenedioxy-2-nitrocyclohexanecarboxylate (**21a**).

A solution of compound **10b** (0.23 g, 0.60 mmol) in a 2:1 TFA/water mixture (12 mL) was stirred at rt for 5 h. The solvent was removed in a rotary evaporator and the residue was co-evaporated with toluene (3 x 6 mL). The resulting chromatographically pure colorless oil (compound **19**) was dissolved in methanol (11 mL), 2% aq. NaHCO₃ (3.8 mL, 0.90 mmol) was added and the mixture was stirred at rt for 12 hours, neutralized with a DOWEX 50 WX4-50 acidic resin, filtered and concentrated to dryness in a rotary evaporator. Flash column chromatography of the solid residue (20:1 dichloromethane/methanol) provided a 10:2 inseparable mixture of compounds **20a** and **20b** (0.15 g, 73%, 2 steps), as an amorphous white solid.

Anhydrous CuSO₄ (0.21 g, 1.32 mmol) and *p*-TsOH·H₂O (0.02 g, 0.12 mmol) were added to a solution of this mixture in acetone (6 mL) and 2,2-dimethoxypropane (9 mL), and the new mixture was stirred at rt for 24 hours and then it was neutralized with saturated aq. NaHCO₃, filtered and concentrated to dryness in a rotary evaporator. A solution of the residue in ethyl acetate (10 mL) was washed with saturated aq. NaCl (2x10 mL), dried (anhydrous Na₂SO₄), filtered and concentrated to dryness under reduced pressure. The crude residue was subjected to flash column chromatography (eluent: 1:2.5 ethyl acetate/hexane) and compound **21a** was isolated as a white amorphous solid (0.10 g, 59% yield), together with an inseparable mixture of **21a** and **21b** (10 mg) which was discarded. **Compound 21a**: m.p. 162-164 °C (dichloromethane/ethylic ether). $[\alpha]_D^{20}$: -22.2 (c 2.11, CHCl₃). ¹H NMR (CDCl₃, 400 MHz, ppm): 1.37 (s, 3 H, CH₃); 1.49 (s, 3 H, CH₃); 2.85 (d, 1 H, $J_{6,OH}$ =5.1 Hz, OH); 3.44 (dd, 1 H, $J_{1,6}$ =9.3 Hz, $J_{1,2}$ =11.8 Hz, H-1); 3.64 (dd, 1 H, $J_{4,5}$ =5.5 Hz, $J_{5,6}$ =7.0 Hz, H-5); 3.74 (ddd, 1 H, $J_{6,OH}$ =5.1 Hz, $J_{5,6}$ =7.0 Hz, $J_{1,6}$ =9.3 Hz, H-6); 3.80 (s, 3 H, OCH₃); 4.41 (dd, 1 H, $J_{4,5}$ =5.5 Hz, $J_{3,4}$ =5.9 Hz, H-4); 4.65 (d, 1 H, J =11.7 Hz, CH₂Ph); 4.81 (d, 1 H, J =11.7 Hz, CH₂Ph); 4.91 (dd, 1 H, $J_{2,3}$ =3.9 Hz, $J_{3,4}$ =5.9 Hz, H-5); 5.10 (dd, 1 H, $J_{2,3}$ =3.9 Hz, $J_{1,2}$ =11.8 Hz, H-2); 7.30-7.38 (m, 5 H, 5 x H-Ph). ¹³C NMR (CDCl₃, 62.5 MHz, ppm):

25.2 (CH₃); 27.1 (CH₃); 45.7 (CH); 52.8 (OCH₃); 70.4 (CH); 73.0 (CH₂); 73.6 (CH); 78.0 (CH); 80.2 (CH); 81.2 (CH); 111.1 (C); 128.0 (2 x CH); 128.2 (CH); 128.6 (2 x CH); 137.1 (C); 171.8 (CO). IR ($\bar{\nu}$, cm⁻¹): 3488 (OH); 1725 (CO); 1549 (s, NO₂); 1381 (m, NO₂). MS-Cl (m/z, %): 382 (4, MH⁺); 366 (3, [M-CH₃]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₈H₂₃NO₈: C 56.69, H 6.08, N 3.67; found C 56.89, H 6.05, N 3.72.

4.10. Methyl (1*S*,2*S*,3*S*,4*R*,5*S*,6*R*)-2-benzoyloxycarbonylamino-5,6-dihydroxy-3,4-isopropylidenedioxycyclohexanecarboxylate (7).

10% Pd/C (0.18 g) was added to a deoxygenated solution of compound **21a** (0.18 g, 0.48 mmol) and citric acid (0.09 g, 0.48 mmol) in methanol (7 mL), and the mixture was stirred at rt for 2 days, under a hydrogen atmosphere and then filtered through a celite pad. The filtrate was concentrated to dryness under reduced pressure. The chromatographically pure compound obtained was directly solved in methanol (5 mL), and saturated aq. NaHCO₃ (3 mL). Benzyl chloroformate (0.08 mL, 0.60 mmol) was added at 0°C and the mixture was stirred at rt for 2 hours. The methanol was removed off in a rotary evaporator, water (5 mL) was added, the suspension was extracted with ethyl acetate (3x10 mL), and the pooled organic layers were dried (anhydrous Na₂SO₄), filtered and concentrated to dryness under reduced pressure. Flash column chromatography of the crude (1:1 ethyl acetate/hexane) provided compound **7** (0.15 g, 87% yield, 2 steps), as a colorless oil. [α]_D²⁰: -8.8 (c, 2.36, acetone). ¹H NMR (CD₃COCD₃, 250 MHz, ppm): 1.29 (s, 3 H, CH₃); 1.46 (s, 3 H, CH₃); 3.50-3.70 (m, 2 H, H-1 + H-2); 3.58 (s, 3 H, OCH₃); 4.04-4.09 (m, 1 H, H-6); 4.30-4.42 (m, 3 H, H-3 + H-4 + H-5); 5.00-5.18 (m, 2 H, CH₂Ph); 7.31-7.41 (m, 5 H, 5 x H-Ph). ¹³C RMN (CD₃COCD₃, 62.5 MHz, ppm): 27.5 (CH₃); 29.5 (CH₃); 51.1 (CH); 52.1 (CH); 52.9 (CH₃); 67.6 (CH₂); 73.3 (CH); 77.5 (CH); 77.8 (CH); 81.2 (CH); 110.6 (C); 129.8 (2 x CH); 130.1 (2 x CH); 130.2 (CH); 139.0 (C); 157.3 (C); 173.7 (CO). IR ($\bar{\nu}$, cm⁻¹): 3442 (OH); 3358 (NH); 1735 (CO). MS-Cl (m/z, %): 396 (2%, MH⁺); 338 (24%, [MH-C₂H₃O₂]⁺); 91 (100%, [PhCH₂]⁺). Analysis: calculated for C₁₉H₂₅NO₈: C 57.71; H 6.37; N 3.54; found C 57.98, H 6.45, N 3.27.

4.11. (1*R*,2*S*,3*R*,4*S*,5*S*)-2-(benzyloxy)-4-(1,3-dithian-2-yl)-5-nitrocyclopentane-1,3-diol (**25a**) and (1*S*,2*S*,3*R*,4*S*,5*S*)-2-(benzyloxy)-4-(1,3-dithian-2-yl)-5-nitrocyclopentane-1,3-diol (**25b**)

A solution of compound **18** (1.02 g, 1.8 mmol) in a 3:1 acetic acid/water mixture (46 mL) was refluxed for 2.5 hours, the solvents were removed under vacuum and the residue was co-evaporated with toluene (3 x 10 mL) to give a chromatographically pure colorless oil.

Pb(AcO)₄ (1.02 g, 2.31 mmol) was added to a solution of this crude oil in benzene (23 mL) and the suspension was stirred at rt for 2 hours, filtered and diluted with chloroform (50 mL). The new solution was washed with water (50 mL), saturated aq. sodium bicarbonate (50 mL) and saturated aq. sodium chloride (50 mL), dried (anhydrous Na₂SO₄), filtered and concentrated to dryness under reduced pressure. This provided a chromatographically pure colorless oil that was solved in a mixture of methanol (60 mL) and 2% aq. sodium bicarbonate (20 mL, 4.62 mmol). The solution was stirred at rt for 24 hours, then was neutralized with DOWEX 50 WX4-50

acid resin, filtered and the solvents were removed off under reduced pressure. Flash column chromatography of the crude (1:2 ethyl acetate/hexane) provided a 10:6 inseparable mixture of compounds **25a** and **25b** (0.71 g, 82% yield, 3 steps), as a white amorphous solid that produced white crystals of **25a** + **25b**, also in a 10:6 ratio, upon crystallization from dichloromethane. ¹H NMR (CD₃OD, 250 MHz, ppm): 1.71-2.04 (m, 4 H, 2 x H-dithiane-**25a** + 2 x H-dithiane-**25b**); 2.61-2.91 (m, 8H, 4 x H-dithiane-**25a** + 4 x H dithiane-**25b**); 3.04-3.23 (m, 2 H, H-**25a** + H-**25b**); 3.71-3.81 (m, 2 H, H-**25a** + H-**25b**); 3.98-4.05 (m, 2 H, H-**25a** + H-**25b**); 4.15-5.15 (m, 10 H, 5 x H-**25a** + 5 x H-**25b**); 7.25-7.40 (m, 10 H, 5 x H-Ph-**25a** + 5 x H-Ph-**25b**). ¹³C NMR (CD₃OD, 62.5 MHz, ppm): 26.2 (CH₂-**25a**); 26.3 (CH₂-**25b**); 28.9 (2 x CH₂-**25a**); 29.9 (CH₂-**23a**); 30.1 (CH₂-**25b**); 48.3 (CH-**25b**); 48.7 (CH-**25a**); 52.2 (CH-**25b**); 53.5 (CH-**25a**); 72.7 (CH₂-**22a**); 73.2 (CH₂-**25b**); 74.1 (CH-**25b**); 74.9 (CH-**25a** + CH-**25b**); 77.1 (CH-**25a**); 85.0 (CH-**25a**); 87.6 (CH-**25b**); 89.4 (CH-**25b**); 93.6 (CH-**25a**); 128.5 (CH-**25a**); 128.6 (2 x CH-**25b**); 128.8 (2 x CH-**25a**); 128.9 (CH-**25b**); 129.1 (2 x CH-**25b**); 129.3 (2 x CH-**25a**); 138.8 (C-**25a**); 139.2 (C-**25b**). IR ($\bar{\nu}$, cm⁻¹): 3512 (OH); 3381 (OH); 1551 (NO₂); 1372 (NO₂). MS-Cl (m/z, %): 371 (4, M⁺); 174 (52); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₆H₂₁NO₅S₂: C 51.73, H 5.70, N 3.77, S 17.26; found C 51.56, H 6.00, N 3.57, S 17.61.

4.12. 2-((1*S*,2*R*,3*S*,4*R*,5*S*)-3-(benzyloxy)-2,4-bis(methoxymethoxy)-5-nitrocyclopentyl)-1,3-dithiane (**26a**) and 2-((1*S*,2*R*,3*S*,4*S*,5*S*)-3-(benzyloxy)-2,4-bis(methoxymethoxy)-5-nitrocyclopentyl)-1,3-dithiane (**26b**)

Formaldehyde dimethyl acetal (1.7 mL, 18.57 mmol) and phosphorous pentoxide (0.527 g, 3.71 mmol) were added to a stirred solution of a 10:6 mixture of **25a** and **25b** (0.23 g, 0.62 mmol) in dry dichloromethane. The suspension was refluxed under stirring for 12 hours, then filtered, and the solvent was removed off under vacuum in a rotary evaporator. Flash column chromatography of the crude (1:6 ethyl acetate/hexane) provided an inseparable mixture of compounds **26a** and **26b** in 10:6 ratio (0.25 g, 89% yield), as a yellow oil. ¹H NMR (CDCl₃, 250 MHz, ppm): 1.79-2.13 (m, 4 H, 2 x H-dithiane-**26a** + 2 x H-dithiane-**26b**); 2.61- 2.90 (m, 8H, 4 x H-dithiane-**26a** + 4 x H-dithiane-**26b**); 3.18-3.42 (m, 2 H, H-**26a** + H-**26b**); 3.29 (s, 3 H, OCH₃-**26b**); 3.31 (s, 3 H, OCH₃-**26a**); 3.37 (s, 3 H, OCH₃-**26a**); 3.39 (s, 3 H, OCH₃-**26b**); 3.70-3.96 (m, 4 H, H-**26a** + H-**26a** + H-**26b**); 4.08-4.38 (m, 4 H, 2 x H-**26a** + 2 x H-**26b**); 4.56-4.80 (m, 12 H, 2 x CH₂OMe-**26a** + CH₂Ph-**26a** + 2 x CH₂OMe-**26b** + CH₂Ph-**26b**); 5.13 (dd, 1 H, *J*=7.3 Hz, *J*=8.9 Hz, H-**26b**); 5.23 (t, 1 H, *J*=6.6 Hz, H-**26a**); 7.23-7.35 (m, 10 H, 5 x H-Ph-**26a** + 5 x H-Ph-**26b**). ¹³C NMR (CDCl₃, 62.5 MHz, ppm): 24.9 (CH₂-**26b**); 25.0 (CH₂-**26a**); 27.3 (CH₂-**26b**); 27.4 (CH₂-**26b**); 29.2 (CH₂-**26a**); 29.4 (CH₂-**26a**); 46.9 (CH-**26b**); 47.6 (CH-**26a**); 50.4 (CH-**26a**); 51.4 (CH-**26b**); 55.5 (OCH₃-**26b**); 55.6 (OCH₃-**26b**); 55.6 (OCH₃-**26a**); 55.7 (OCH₃-**26a**); 71.5 (CH₂-**26b**); 71.9 (CH₂-**26a**); 78.9 (CH-**26b**); 79.1 (CH-**26a**); 80.1 (CH-**26b**); 81.0 (CH-**26b**); 81.2 (CH-**26a**); 83.5 (CH-**26b**); 86.4 (CH-**26a**); 90.6 (CH-**26b**); 95.8 (CH₂-**26b**); 96.0 (CH₂-**26a** + CH₂-**26b**); 96.5 (CH₂-**26a**); 127.4 (2 x CH-**26b**); 127.6 (2 x CH-**26b**); 127.7 (CH-**26b**); 127.7 (CH-**26b**); 128.1 (2 x CH-**26b**); 128.2 (2 x CH-**26b**); 137.0 (C-**26b**); 137.3 (C-**26b**). IR ($\bar{\nu}$, cm⁻¹): 1554 (NO₂); 1368 (NO₂). MS-Cl (m/z, %): 459 (3, M⁺); 119 (57, [C₄H₇S₂]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₂₀H₂₉NO₇S₂: C 52.27, H 6.36, N 3.05, S 13.95; found C 52.45, H 6.22, N 2.89, S 14.05.

4.13. Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-4-benzyloxy-3,5-bis-methoxymethoxy-2-nitrocyclopentanecarboxylate (**27a**) and methyl (1*S*,2*S*,3*S*,4*S*,5*R*)-4-benzyloxy-3,5-bis-methoxymethoxy-2-nitrocyclopentanecarboxylate (**27b**).

When the above mixture of **26a**+**26b** (0.24 g, 0.66 mmol) was subjected to the method for the preparation of compound **10b**, an inseparable mixture of compounds **27a** and **27b** (0.18 g, 67%) was obtained as a colorless oil, after flash column chromatography (1:5 ethyl acetate/hexane). ¹H NMR (CDCl₃, 250 MHz, ppm): 3.29 (s, 3 H, OCH₃-**27b**); 3.30 (s, 3 H, OCH₃-**27a**); 3.33 (s, 3 H, OCH₃-**27b**); 3.36 (s, 3 H, OCH₃-**27a**); 3.55 (dd, 1 H, *J*_{1,5}=2.7 Hz, *J*_{1,2}=6.9 Hz, H-1-**27a**); 3.70 (s, 3 H, OCH₃-**27a**); 3.76 (s, 3 H, OCH₃-**27b**); 3.83 (dd, 1 H, *J*_{1,5}=6.7 Hz, *J*_{1,2}=9.6 Hz, H-1-**27b**); 3.95-3.98 (m, 2 H, H-5-**27a** + H-5-**27b**); 4.21-4.25 (m, 1 H, H-4-**27b**); 4.44-4.76 (m, 15 H, H-3-**27a** + H-4-**27a** + 2 x CH₂OMe-**27a** + CH₂Ph-**27a** + H-3-**27b** + 2 x CH₂OMe-**27b** + CH₂Ph-**27b**); 5.30 (dd, 1 H, *J*_{2,3}=5.5 Hz, *J*_{1,2}=9.6 Hz, H-2-**27b**); 5.45 (dd, 1 H, *J*_{1,2}=6.9 Hz, *J*_{2,3}=8.2 Hz, H-2-**27a**); 7.25-7.36 (m, 10 H, 5 x H-Ph-**27a** + 5 x H-Ph-**27b**). ¹³C NMR (CDCl₃, 62.5 MHz, ppm): 50.4 (CH-**27b**); 52.0 (CH-**27a**); 52.5 (OCH₃-**27b**); 52.7 (OCH₃-**27a**); 55.4 (OCH₃-**27b**); 55.5 (OCH₃-**27a**); 55.6 (OCH₃-**27a**); 55.7 (OCH₃-**27b**); 71.7 (CH₂-**27a**); 71.8 (CH₂-**27b**); 78.5 (CH-**27b**); 78.9 (CH-**27a**); 80.4 (CH-**27a**); 80.6 (CH-**27a**); 81.7 (CH-**27b**); 84.3 (CH-**27b**); 85.6 (CH-**27b**); 88.5 (CH-**27a**); 95.8 (CH₂-**27b**); 95.9 (CH₂-**27a**); 96.0 (CH₂-**27b**); 96.3 (CH₂-**27a**); 127.6 (2 x CH-**27a** + 2 x CH-**27b**); 127.8 (CH-**27a**); 127.9 (CH-**27b**); 128.3 (2 x CH-**27a**); 128.3 (2 x CH-**27b**); 137.1 (C-**27b**); 137.2 (C-**27a**); 169.8 (CO-**27a**); 171.3 (CO-**27b**). IR (ν̄, cm⁻¹): 1741 (CO); 1558 (NO₂); 1377 (NO₂). MS-Cl (m/z, %): 400 (7, MH⁺); 354 (4, [M-C₂H₅O]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₈H₂₅NO₉: C 54.13, H 6.31, N 3.51; found C 53.86, H 6.45, N 3.23.

4.14. Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-(((benzyloxy)carbonyl)amino)-4-hydroxy-3,5-bis(methoxymethoxy)cyclopentane-1-carboxylate (**6a**) and methyl (1*S*,2*S*,3*S*,4*S*,5*R*)-2-(((benzyloxy)carbonyl)amino)-4-hydroxy-3,5-bis(methoxymethoxy)cyclopentane-1-carboxylate (**6b**).

A mixture of compounds **27a** and **27b** was subjected to the conditions previously used for the transformation of **21a** into **7**. The resulting crude product, after flash column chromatography (1:1 ethyl acetate/hexane), allowed to isolate compound **6a** (0.16 g, 47% yield, yellow oil) and compound **6b** (0.28 g, 24% yield, yellow oil). **Compound 6a**: [α]_D²⁰: -4.9 (c 2.25, CHCl₃). ¹H NMR (CDCl₃, 250 MHz, ppm): 2.80-2.86 (m, 1 H, H-1); 3.20 (s, 1 H, OH); 3.32 (s, 3 H, OCH₃); 3.34 (s, 3 H, OCH₃); 3.68 (s, 3 H, OCH₃); 4.04-4.22 (m, 4 H, H-2 + H-3 + H-4 + H-5); 4.65-4.75 (m, 4 H, 2 x CH₂OMe); 5.08 (s, 2 H, CH₂Ph); 5.69 (d, 1 H, *J*=7.7 Hz, NH); 7.31-7.33 (m, 5 H, 5 x H-Ph). ¹³C NMR (CDCl₃, 62.5 MHz, ppm): 51.5 (CH); 52.1 (OCH₃); 55.3 (OCH₃); 55.5 (OCH₃); 56.5 (CH); 66.5 (CH₂); 73.9 (CH); 79.6 (CH); 82.4 (CH); 95.9 (CH₂); 96.0 (CH₂); 127.9 (3 x CH); 128.3 (2 x CH); 136.1 (C); 155.5 (CO); 172.5 (CO). IR (ν̄, cm⁻¹): 3346 (OH + NH), 1731 (CO). MS-Cl (m/z, %): 414 (13, MH⁺); 354 (24, [M-C₂H₃O₂]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₉H₂₇NO₉: C 55.20, H 6.58, N 3.39; found C 55.45, H 6.81, N 3.31. **Compound 6b**: [α]_D²⁰: -19.1 (c 2.05, CHCl₃). ¹H NMR (CDCl₃, 250 MHz, ppm): 2.86-2.93 (m, 1 H, H-1); 3.37 (s, 3 H, OCH₃); 3.38 (s, 3 H, OCH₃); 3.42-4.42 (m, 5 H, OH + H-2 + H-3 + H-4 + H-5);

3.68 (s, 3 H, OCH₃); 4.64-4.76 (m, 4 H, 2 x CH₂OMe); 5.08 (s, 2 H, CH₂Ph); 5.51 (d, 1 H, *J*=7.6 Hz, NH); 7.31-7.35 (m, 5 H, 5 x H-Ph). ¹³C NMR (CDCl₃, 62.5 MHz, ppm): 52.2 (OCH₃); 52.4 (OCH₃); 53.6 (CH); 55.6 (OCH₃); 55.8 (CH); 66.7 (CH₂); 79.9 (CH); 80.1 (CH); 84.4 (CH); 96.1 (CH₂); 97.0 (CH₂); 128.0 (2 x CH); 128.0 (CH); 128.4 (2 x CH); 136.2 (C); 155.7 (CO); 172.5 (CO). IR (ν̄, cm⁻¹): 3438 (OH + NH), 1729 (CO); 1704 (CO). MS-Cl (m/z, %): 414 (8, MH⁺); 354 (16, [M-C₂H₃O₂]⁺); 91 (100, [PhCH₂]⁺). Analysis: calculated for C₁₉H₂₇NO₉: C 55.20, H 6.58, N 3.39; found C 55.38, H 6.72, N 3.21.

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Acknowledgments

This work has received financial support from the Spanish Ministry of Science and Innovation (CTQ2009-08490), the Xunta de Galicia (Centro Singular de Investigación de Galicia, accreditation 2016–2019, ED431B 2018/13; Project CN2011/037 and Project GRC2014/040), and the European Union (European Regional Development Fund-ERDF).

Supplementary Material