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Graphical Abstract

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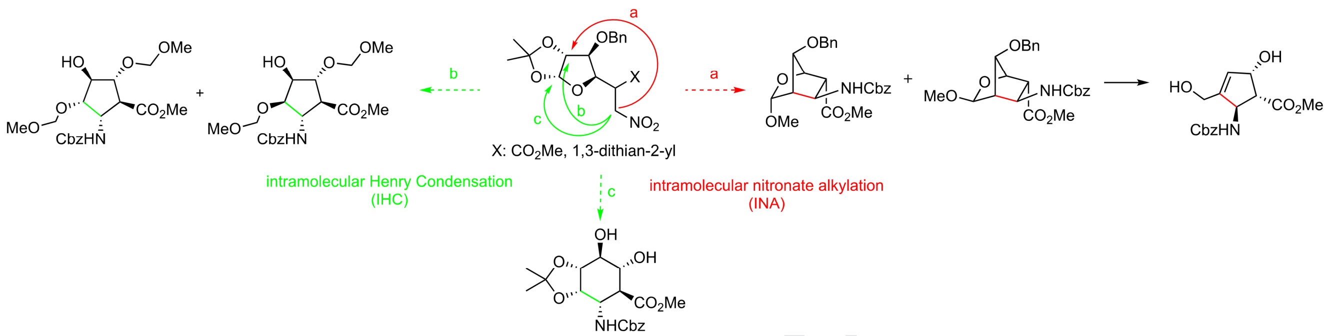

Highly functionalized cyclic and bicyclic β–amino acids from sugar β–nitroesters

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This paper is in recognition of the many great scientific achievements by Stephen Davies combined with enormous drive and tenacity for setting up new companies

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ABSTRACT

The synthesis of 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 via the 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.

1. Introduction

Research in proteins in an area of growing interest, but their potential applications is conditioned by their limited structural diversity both in terms of their primary and secondary structures, their conformational flexibility and their metabolic instability.[1–4] This is one reason why for the two last decades a great deal of attention has been devoted to the synthesis of non-natural amino acids. It constitutes the first step for the access to peptidomimetics that may improve the catalytic and recognition properties of natural peptides and provide drugs more resistant to enzymatic degradation.[5–8]

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 helixes, turns and sheets – are the ideal candidates for this purpose.[9–11] 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.[12–16] Specific representatives 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*, has been used to replace the central proline subunit in the tetrapeptide morphiceptin[18] to provide a pharmacologically more active peptidomimetic.[19] β–Oligopeptides consisting of *trans*-2-aminocyclopentanecarboxylic acids have a high propensity to fold as 12-helixes which are topologically similar to α-helixes,[20,21] while *cis*-2-aminocyclopentanecarboxylic acid oligomers were later shown to adopt sheet-like structures.[22] Short oligomers of enantiomerically pure *trans*-2-aminocyclohexanecarboxylic acid[3] adopt a 14-helix.[23,20] β-Amino acids containing bicyclic scaffolds are also considered as synthetic intermediates, building blocks for medicinal chemistry and 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 access to these targets continue to be a challenge for organic chemists.[31–33]

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. Previously, an intramolecular nitronate alkylation (INA) gave the first two reported trihydroxylated 2-aminocyclopentanecarboxylic acids (**1**[34–38] and **2**[39], Fig. 1); additionally the first reported tetrahydroxylated 2-aminocyclohexanecarboxylic acid **3**[40] was formed by an intramolecular Henry condensation (IHC).[41]

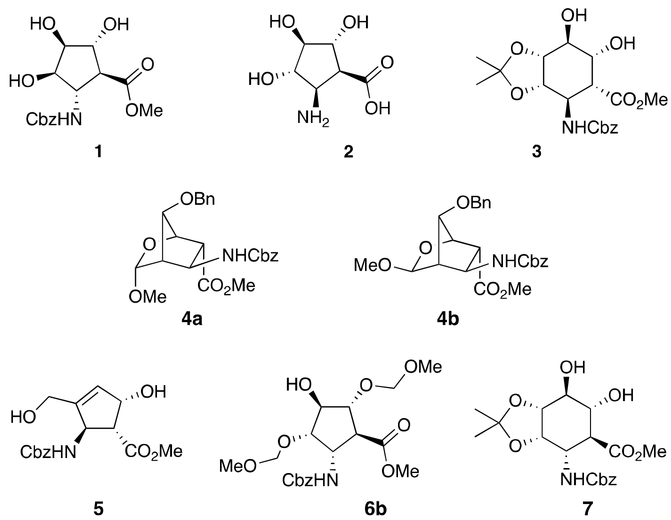


Figure 1. Known polyhydroxylated cyclopentane and cyclohexane β-amino acids (**1**, **2**, **3**), and new polysubstituted cyclic and bicyclic β-amino acids (**4a**, **4b**, **5**, **6b** and **7**).

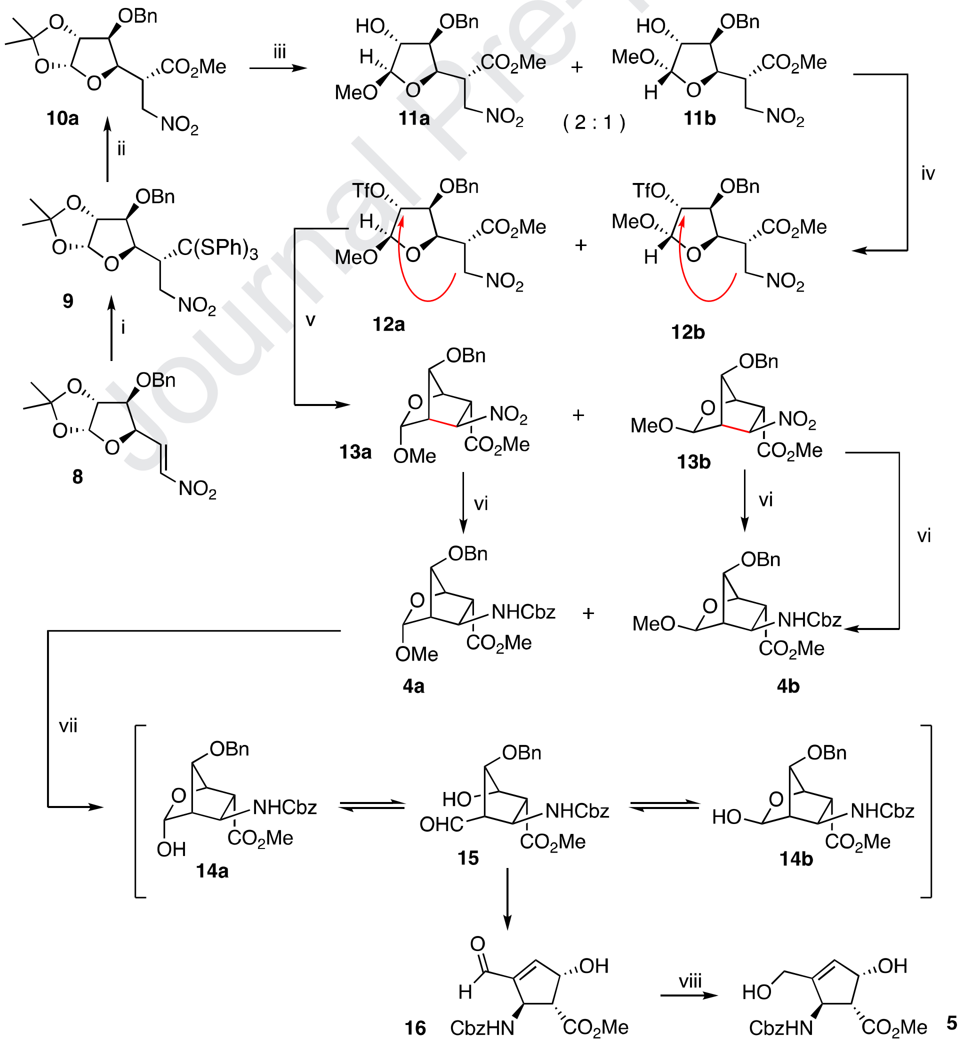
This work opened access to liposoluble (protected hydroxy substituents) or hydrosoluble (deprotected hydroxy groups) β–peptides of interest for biological and material chemistry applications.

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** prepared using the INA approach and (ii) the 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), which was 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.[40]



Scheme 1. *Reagents and conditions:* i,ii) see reference 26. iii) AcCl, MeOH, 0 ºC, 14 h (**11a**: 65%; **11b**: 30%). iv) Tf_2O, pyridine, Cl_2CH_2, -30 ºC, 30 min. v) TBAF, THF, rt, 2 h (**13a**: 58%; **13b**: 21%). vi) a. H_2, 10% Raney-Ni, MeOH, rt, 3 h. b. saturated aq. $NaHCO_3$, CbzCl, MeOH, rt, 3 h (**4a**: 50% and **4b**: 52%, 2 steps). vii) 3:1 TFA/water, rt, 12 h (63%). viii) $NaBH_4$, 56:44 EtOH/water, rt, 10 min (99%).

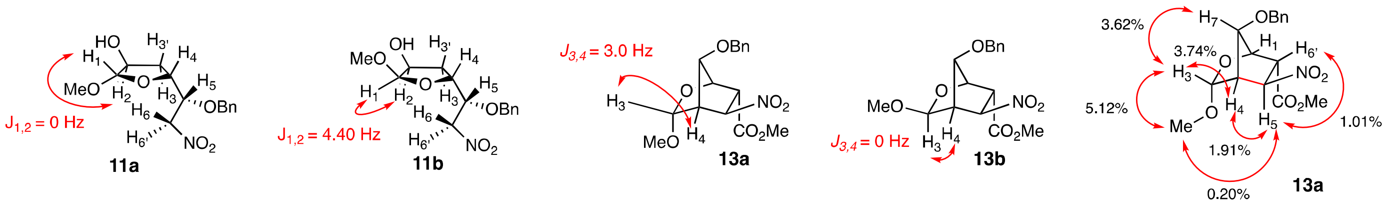
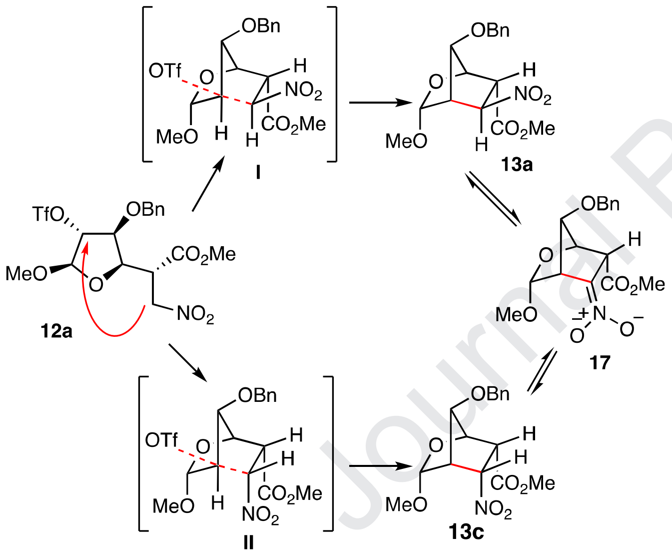


Figure 2. Representative H-H couplings and NOE enhancements.

The reaction of 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 clearly deduced from the signals of the anomeric protons in their ^{1}H 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*.



Scheme 2. Mechanistic proposal for the selective transformation of compound **12a** into compound **13a.**

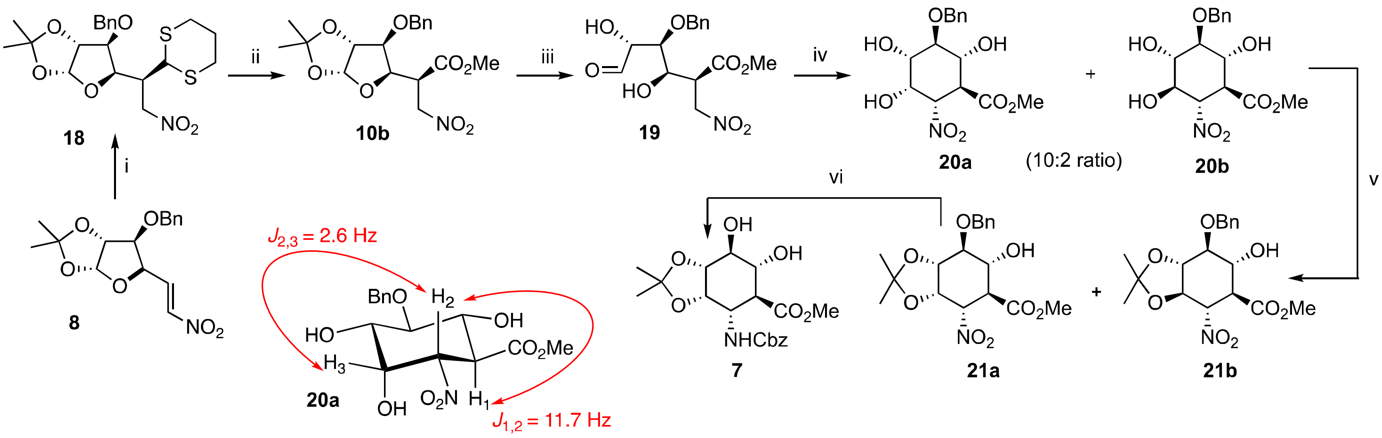
As both anomers **11a** and **11b** produce the same final product **5**, the anomeric mixture **11a**+**11b** was directly reacted with triflic anhydride and pyridine, to quantitatively give the anomeric mixture of triflates **12a**+**12b**, which upon treatment with TBAF in THF gave a base-induced INA to afford the bicyclic epimers **13a** (58%) and **13b** (21%).[42] The *endo* configuration of the anomeric OMe group of the major compound **13a** (from **12a**) was indicated by the presence in its ^{1}H 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 (Fig. 2). Moreover, the ^{1}H NMR spectrum of the minor compound **13b** (from **12b**) includes at 4.64 ppm a singlet, indicating 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 (Fig. 2). Both effects confirm the *endo* disposition of its OMe group.

The selective transformation of **12a** into **13a** was tentatively explained by assuming that 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). 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, quantitatively produced 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 TFA/water to give the corresponding lactols **14a** and **14b** resulted in subsequent elimination of benzyl alcohol to give aldehyde **16** (63%) as the sole product. The structure of **16** is clearly indicated by the ^{1}H NMR spectrum, which has an olefinic proton at 6.80 ppm and the aldehyde proton at 9.77 ppm. Moreover, its ^{13}C NMR spectrum showed peaks at 149.4 ppm for the olefinic CH and at 189.1 ppm for the aldehyde.

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



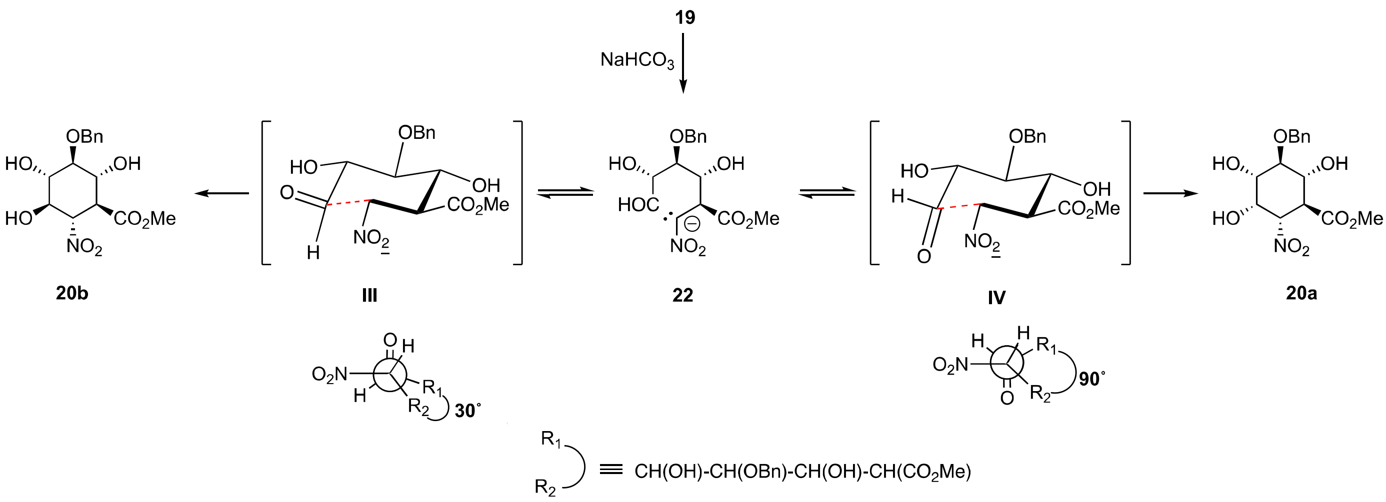
Scheme 3. *Reagents and conditions:* i) reference 28. ii) a. $BF_3 \cdot OEt_2$, HgO, TFH, water, rt, 1.5 h. b. 2-Methyl-2-butene, $NaClO_2$, NaH_2PO_4, 3:1 MeOH/water, rt, 1 h. c. Trimethylsilyldiazomethane, 7:2 Et_2O/MeOH, rt, 15 min. (84%, 3 steps). iii) 2:1 TFA/water, rt, 5 h. iv) 2% aq. $NaHCO_3$, MeOH, rt, 12 h (**20a**+**20b**: 73%, 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 (Scheme 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 obtained[43] 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 84% overall yield over three steps: transformation of the dithiane group to 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.[40,43] Hydrolysis of the acetonide in **10b** with trifluoroacetic/water gave the 6-nitrohexanaldehyde **19**; which with $NaHCO_3$ as a base[40] induced IHC to give an inseparable 10:2 mixture of the cyclohexane β–nitro esters **20a** and **20b** (73% yield, two steps) as shown from the signals of the carbon bearing the nitro groups in the ^{13}C NMR spectrum. The complex ^{1}H NMR spectrum of this mixture **20a**+**20b** showed a doublet of doublets at δ=4.88 ppm, due to the proton at the C-2 carbon bearing the nitro group of the major component **20a**. The coupling constant $J_{1,2}$=11.7 Hz justifies the assignment of the *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 is due to the axial and equatorial arrangement of the protons at positions C-2 and C-3, respectively. In this compound the nitro, carboxyl and γ-hydroxyl groups are all equatorial. Accordingly, structure **20b** was assigned to the minor component.

The diastereomeric ratio indicated that the cyclization leading to **20a** and **20b** is subject to 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**. Compound **20b** in which all groups are equatorial might be expected to be thermodynamically more stable.

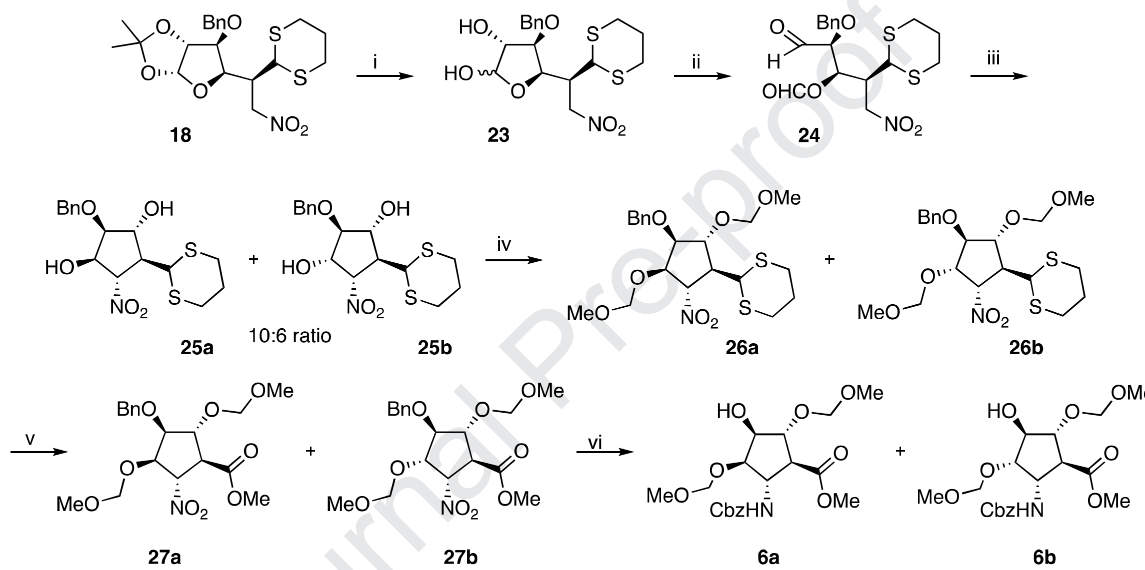


Scheme 4. Mechanistic proposal for the selective transformation of compound **19** into the mixture **20a**+**20b**

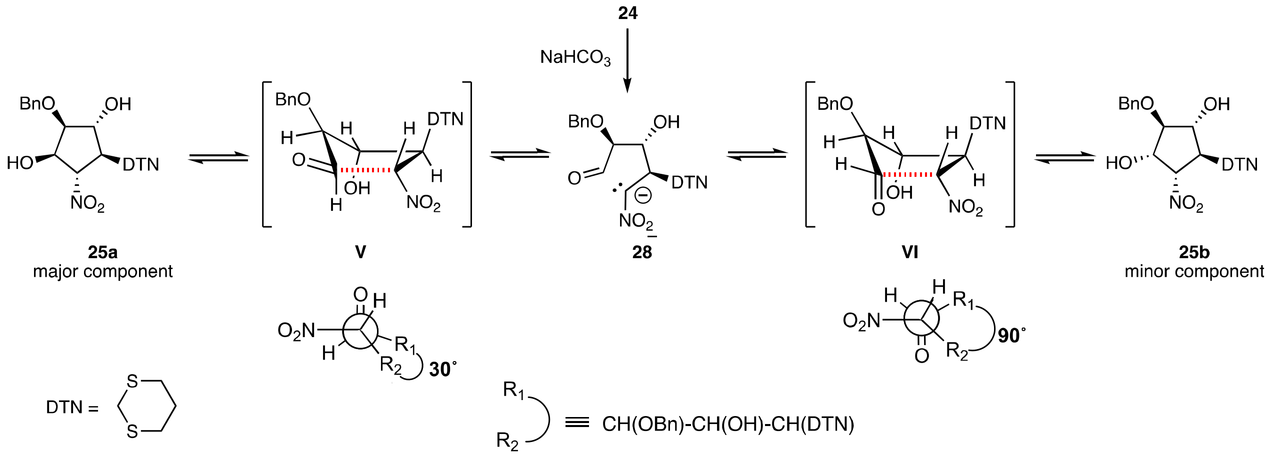
The reaction of **20a**+**20b** with 2,2-dimethoxypropane and *p*-TsOH, formed a separable mixture of the two acetonides **21a**+**21b** (10:2), from which the major component **21a** was partially isolated (59% yield) by column chromatography and unambiguously characterized by X-ray crystallographic analysis (Fig. 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 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 3:1 AcOH/water afforded the lactols **23**, which upon oxidation with lead tetraacetate gave nitroaldehyde **24** (Scheme 5).



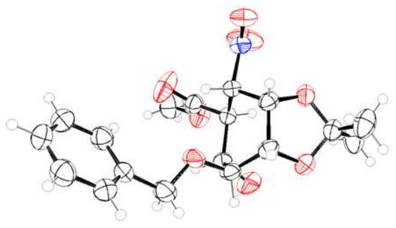
Scheme 5. *Reagents and conditions:* i) 3:1 AcOH/water, reflux, 2.5 h. ii) $Pb(OAc)_4$, benzene, rt, 2 h. iii) 2% aq. $NaHCO_3$, rt, 24 h. (**25a**+**25b**: 82%, 3 steps). iv) $CH_2(OCH_3)_2$, P_2O_5, CH_2Cl_2, reflux, 12 h (**26a**+**26b**: 89%, 3 steps). v) a. $BF_3.OEt_2$, HgO, TFH, water, rt, 1.5 h. b. 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, 3:1 MeOH/water, rt, 1 h. c. Trimethylsilyldiazomethane, 7:2 Et_2O/MeOH, rt, 15 min. (**27a**+**27b**: 67%, 3 steps) vi) a. H_2, 10% Pd/C, citric acid, MeOH, rt, 2 days. b. saturated aq. $NaHCO_3$, CbzCl, MeOH, rt, 3 h. (**6a**: 47%, **6b**: 24%).



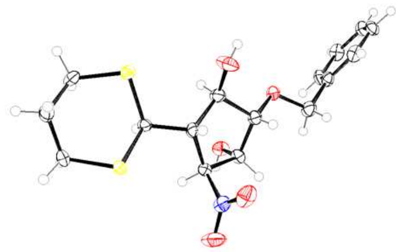
Scheme 6. Mechanistic proposal for the selective transformation of compound **24** into the mixture **25a**+**25b**

Upon treatment with 2% aqueous sodium bicarbonate compound **24** cyclized to give an inseparable mixture of cyclopentanes **25a** and **25b** (89% yield) in an approximately 10:6 ratio as indicated by the ^{13}C 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 containing the same mixture of compounds **25a** and **25b**, whose structures were unequivocally established by X-ray crystallographic analysis (Fig. 3).[40] 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 thermodynamically more stable epimer) occur *via* **V** (the thermodynamically less stable transition state, due to stereoelectronic reasons).

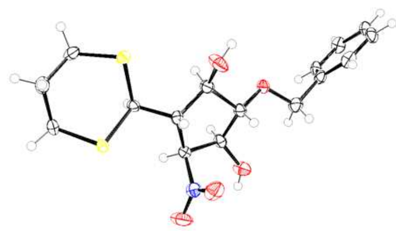
Protection of the hydroxy groups of the epimeric mixture **25a**+**25b** by formaldehyde dimethyl acetal and phosphorous pentoxide gave an inseparable mixture of cyclopentanes **26a**+**26b** (89% yield), which was subjected to the same three steps sequence as for the transformation of the dithianyl group of compound **18** into the methoxycarbonyl group of 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), which were separable by column chromatography.



ORTEP diagram of compound **21a**



ORTEP diagram of compound **25a**



ORTEP diagram of compound **25b**

Figure 3.

3. Conclusion

In summary, we have synthesized 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 *via* the 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. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 250 (250 MHz for ^{1}H and 62.5 MHz for ^{13}C) and Varian Inova 400 (400 MHz for ^{1}H 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**[40] and **18**[43] were prepared according to known procedures.

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

Acetyl chloride (0.81 mL, 6.4 mmol) was added to a cooled (0 ºC) solution of compound **10a** (0.72 g, 1.89 mmol) in dry methanol (12 mL) and the solution was stirred at 0 ºC 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**: $[\alpha]_D^{20}$: —70 (*c* 0.7, $CHCl_3$). ^{1}H 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, -C<u>H</u>HPh); 4.56 (d, 1 H, *J*=6.8 Hz, -C<u>H</u>HPh); 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, -C<u>H</u>HNO$_2$); 4.87 (dd, 1 H, *J*=7.1 Hz, *J*=14.3 Hz, -C<u>H</u>HNO$_2$); 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 (υ, cm^{-1}): 3528 (OH); 1741 (CO); 1557 (NO_2); 1377 (NO_2). MS-CI (m/z, %): 324 (3, $[M-CH_3O]^+$); 169 (75, $[M-C_7H_9N0_5]^+$); 91 (100, $[PhCH_2]^+$). Elemental analysis: calculated for $C_{16}H_{21}NO_8$: C: 54.08; H: 5.96; N: 3.94.; found: C: 54.32; H: 6.08; N: 4.07. **Compound 11b**: $[\alpha]_D^{20}$: +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_2); 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 (υ, cm^{-1}): 3528 (OH); 1752 (CO); 1565 (NO_2); 1380 (NO_2). MS-CI (m/z, %): 324 (5, $[M-CH_3O]^+$); 169 (40, $[M-C_7H_9N0_5]^+$); 91 (100, $[PhCH_2]^+$). Elemental analysis: calculated for $C_{16}H_{21}NO_8$: 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 ºC) solution of a recently obtained anomeric mixture **11a**+**11b** in dry dichloromethane (13.8 mL). The new solution was stirred at -30 ºC 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**: $[\alpha]_D^{20}$: —49 (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz, ppm): 3.33 (s, 3 H, $-CH_3$); 3.68—3.73 (m, 1 H, H-6); 3.79 (s, 3 H, $-CH_3$); 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, -CHHPh); 4.50 (d, 1 H, *J*=6.5 Hz, -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 (υ, cm^{-1}): 1750 (s, CO); 1565 (NO_2); 1383 (NO_2). MS-CI (m/z, %): 338 (42, $[M+H]^+$); 121 (100, $[MH-C_{12}H_{13}N0_3]^+$); 91 (95, $[PhCH_2]^+$). Analysis: calculated for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15; found C, 57.13; H, 5.83; N, 4.20. **Compound 13b**: $[a]_D^{20}$: +23 (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz, ppm): 3.36 (s, 3 H, $-CH_3$); 3.56—3.59 (m, 1 H, H-4); 3.80 (s, 3 H, $-CH_3$); 3.97—4.02 (m, 1 H, H-6); 4.34 (d, 1 H, *J*=6.5 Hz, -CHHPh); 4.43—4.53 (m, 3 H, -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 (υ, cm^{-1}): 1745 (CO); 1548 (NO_2); 1376 (NO_2). MS-CI (m/z, %): 338 (30, $[M+H]^+$); 121 (100, $[MH-C_{12}H_{13}N0_3]^+$); 91 (90, $[PhCH_2]^+$). Analysis: calculated for $C_{16}H_{19}NO_7$: 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 ºC), 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. $[\alpha]_D^{20}$: +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, $-CH_3$); 3.74 (s, 3 H, $-CH_3$); 4.11—4.15 (m, 1 H, H-7); 4.45-4.60 (m, 3 H, $-CH_2Ph$, H-1); 4.92 (d, 1 H, $J_{3,4}$=2.5 Hz, H-3); 5.03—5.22 (m, 3 H, $-CH_2Ph$, H-5); 5.48 (d, 1 H, *J*=9.9 Hz, -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 (υ, cm^{-1}): 3433 (NH); 1747 (CO); 1726 (CO). MS-CI (m/z, %): 442 (65, $[M+H]^+$); 334 (100, $[M-C_7H_70]^+$); 291 (25, $[M-C_8H_8N0_2]^+$). Analysis: calculated for $C_{24}H_{27}NO_7$: 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. $[\alpha]_D^{20}$: +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, $-CH_3$); 3.74 (s, 3 H, $-CH_3$); 4.37—4.56 (m, 5 H, H-1, H-5, H-7, $-CH_2Ph$); 4.62 (bs, 1 H, H-3); 5.09 (ABq, 2 H, *J*=12.35 Hz, $-CH_2Ph$); 5.38 (d, 1 H, *J*=9.6 Hz, -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 (υ, cm^{-1}): 3425 (NH); 1743 (CO); 1728 (CO). MS-CI (m/z, %): 442 (47, $[M+H]^+$); 334 (100, $[M-C_7H_70]^+$); 291 (5, $[M-C_8H_8N0_2]^+$). Analysis: calculated for $C_{24}H_{27}NO_7$: 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, $CHCl_3$). ^1H NMR ($CDCl_3$, 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, CH_3O-); 4.95—5.30 (m, 4 H, H-2, H-5, $-CH_2Ph$); 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, -C<u>H</u>O). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 52.2 (CH_3); 54.5 (CH); 56.2 (CH); 66.7 (CH_2); 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 (υ, cm^{-1}): 3352 (OH + NH); 1694 (CO). MS-CI (m/z, **%):** 320 (85, $[M+H]^+$); 276 (99, $[MH-CO_2]^+$); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{16}H_{17}NO_6$: 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 $NaBH_4$ (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 Na_2SO_4), 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 ($CDCl_3$, 250 MHz, ppm): 3.15—3.30 (2 H, m, H-1, -OH); 3.74 (s, 3 H, CH_3O-); 4.05—4.17 (m, 2 H, -C<u>H</u>$_2$OH); 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, $-CH_2Ph$); 5.81—5.86 (m, 1 H, H-4); 7.30—7.38 (m, 5 H, 5xAr-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 52.2 (CH_3); 55.7 (CH); 57.5 (CH); 58.8 (CH_2); 67.1 (CH_2); 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 (υ, cm^{-1}): 3315 (OH + NH); 1735 (CO); 1694 (CO). MS-CI (m/z, %): 340 (1, $[M+H]^+$); 322 (22, $[M-OH]^+$); 280 (15, $[M-C_2\ H_30_2]^+$); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{16}H_{19}NO_6$: 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. NH_4Cl (4x20 mL), dried (anhydrous Na_2SO_4) and concentrated to dryness in a rotary evaporator. After, 2-methyl-2-butene (0.8 mL, 6.93 mmol), $NaClO_2$ (0.14 g, 1.29 mmol) and $NaH_2PO_4.2H_2O$ (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 Na_2SO_4), 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 (Et_2O/hexane). $[\alpha]_D^{20}$: —43.0 (*c* 1.40, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz, ppm): 1.33 (s, 3 H, CH_3); 1.50 (s, 3 H, CH_3); 3.66 (s, 3 H, OCH_3); 3.88-3.96 (m, 2 H, H-3 + H-5); 4.38 (d, 1H, *J*=11.4 Hz, CH_2Ph); 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, CH_2Ph); 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). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 26.1 (CH_3); 26.7 (CH_3); 42.5 (CH); 52.6 (OCH_3); 71.8 (CH_2); 71.9 (CH_2); 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 ($\bar{\upsilon}$, cm^{-1}): 1740 (CO); 1554 (NO_2); 1380 (NO_2). MS-CI (m/z, %): 382 (6, MH^+); 335 (8, $[M-NO_2]^+$); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{18}H_{23}NO_8$: 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. $NaHCO_3$ (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 $CuSO_4$ (0.21 g, 1.32 mmol) and *p*-TsOH.H_2O (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. $NaHCO_3$, 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 Na_2SO_4), 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, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 1.37 (s, 3 H, CH_3); 1.49 (s, 3 H, CH_3); 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, OCH_3); 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, CH_2 Ph); 4.81 (d, 1 H, *J*=11.7 Hz, CH_2 Ph); 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). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 25.2 (CH_3); 27.1 (CH_3); 45.7 (CH); 52.8 (OCH_3); 70.4 (CH); 73.0 (CH_2); 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 (ῡ, cm^{-1}): 3488 (OH); 1725 (CO); 1549 (s, NO_2); 1381 (m, NO_2). MS-CI (m/z, %): 382 (4, MH^+); 366 (3, $[M-CH_3]^+$); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{18}H_{23}NO_8$: 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-benzyloxycarbonylamino-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. $NaHCO_3$ (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 Na_2SO_4), 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. $[\alpha]_D^{20}$: —8.8 (*c*, 2.36, acetone). ^{1}H NMR (CD_3COCD_3, 250 MHz, ppm): 1.29 (s, 3 H, CH_3); 1.46 (s, 3 H, CH_3); 3.50-3.70 (m, 2 H, H-1 + H-2); 3.58 (s, 3 H, OCH_3); 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, CH_2Ph); 7.31-7.41 (m, 5 H, 5 x H-Ph). ^{13}C NMR (CD_3COCD_3 , 62.5 MHz, ppm): 27.5 (CH_3); 29.5 (CH_3); 51.1 (CH); 52.1 (CH); 52.9 (CH_3); 67.6 (CH_2); 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 (ῡ, cm^{-1}): 3442 (OH); 3358 (NH); 1735 (CO). MS-CI (m/z, %): 396 (2%, MH^+); 338 (24%, $[MH-C_2H_3O_2]^+$); 91 (100%, $[PhCH_2]^+$). Analysis: calculated for $C_{19}H_{25}NO_8$: 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.

$Pb(OAc)_4$ (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 Na_2SO_4), 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. ^{1}H NMR (CD_3OD, 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, 8 H, 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**). ^{13}C NMR (CD_3OD, 62.5 MHz, ppm): 26.2 (CH_2-**25a**); 26.3 (CH_2-**25b**); 28.9 (2 x CH_2-**25a**); 29.9 (CH_2□**23a**); 30.1 (CH_2-**25b**); 48.3 (CH-**25b**); 48.7 (CH-**25a**); 52.2 (CH-**25b**); 53.5 (CH-**25a**); 72.7 (CH_2□**22a**); 73.2 (CH_2-**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 (ῡ, cm□1): 3512 (OH); 3381 (OH); 1551 (NO_2); 1372 (NO_2). MS□CI (m/z, %): 371 (4, M^+); 174 (52); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{16}H_{21}NO_5S_2$: 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. ^{1}H NMR ($CDCl_3$, 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, 8 H, 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, OCH_3-**26b**); 3.31 (s, 3 H, OCH_3-**26a**); 3.37 (s, 3 H, OCH_3-**26a**); 3.39 (s, 3 H, OCH_3-**26b**); 3.70—3.96 (m, 4 H, H□**26a** + H-**26a** + H□**26b** + 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 CH_2OMe-**26a** + CH_2Ph-**26a** + 2 x CH_2OMe-**26b** + CH_2Ph□**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**). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 24.9 (CH_2-**26b**); 25.0 (CH_2-**26a**); 27.3 (CH_2-**26b**); 27.4 (CH_2□**26b**); 29.2 (CH_2-**26a**); 29.4 (CH_2-**26a**); 46.9 (CH-**26b**); 47.6 (CH-**26a**); 50.4 (CH-**26a**); 51.4 (CH□**26b**); 55.5 (OCH_3-**26b**); 55.6 (OCH_3-**26b**); 55.6 (OCH_3-**26a**); 55.7 (OCH_3-**26a**); 71.5 (CH_2-**26b**); 71.9 (CH_2-**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 (CH_2-**26b**); 96.0 (CH_2-**26a** + CH_2-**26b**); 96.5 (CH_2-**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 (ῡ, cm$^{□1}$): 1554 (NO_2); 1368 (NO_2). MS-CI (m/z, %): 459 (3, M^+); 119 (57, $[C_4H_7S_2]^+$); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{20}H_{29}NO_7S_2$: 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). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 3.29 (s, 3 H, OCH_3-**27b**); 3.30 (s, 3 H, OCH_3-**27a**); 3.33 (s, 3 H, OCH_3-**27b**); 3.36 (s, 3 H, OCH_3-**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, OCH_3-**27a**); 3.76 (s, 3 H, OCH_3-**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 CH_2OMe-**27a** + CH_2Ph-**27a** + H□3-**27b**+ 2 x CH_2OMe-**27b**+ CH_2Ph-**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**). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 50.4 (CH-**27b**); 52.0 (CH-**27a**); 52.5 (OCH_3-**27b**); 52.7 (OCH_3-**27a**); 55.4 (OCH_3-**27b**); 55.5 (OCH_3-**27a**); 55.6 (OCH_3-**27a**); 55.7 (OCH_3-**27b**); 71.7 (CH_2-**27a**); 71.8 (CH_2-**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 (CH_2-**27b**); 95.9 (CH_2-**27a**); 96.0 (CH_2-**27b**); 96.3 (CH_2-**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 (ῡ, cm$^{□1}$): 1741 (CO); 1558 (NO_2); 1377 (NO_2). MS-CI (m/z, %): 400 (7, MH^+); 354 (4, [M□C_2H_5 O]); 91 (100, $[PhCH_2\ ]^+$). Analysis: calculated for $C_{18}H_{25}NO_9$: 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** (0.08 g, 24% yield, yellow oil). **Compound 6a**: $[\alpha]_D^{20}$: —4.9 (*c* 2.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 2.80—2.86 (m, 1 H, H-1); 3.20 (s, 1 H, OH); 3.32 (s, 3 H, OCH_3); 3.34 (s, 3 H, OCH_3); 3.68 (s, 3 H, OCH_3); 4.04—4.22 (m, 4 H, H-2 + H-3 + H-4 + H-5); 4.65—4.75 (m, 4 H, 2 x CH_2OMe); 5.08 (s, 2 H, CH_2Ph); 5.69 (d, 1 H, *J*=7.7 Hz, NH); 7.31—7.33 (m, 5 H, 5 x H-Ph). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 51.5 (CH); 52.1 (OCH_3); 55.3 (OCH_3); 55.5 (OCH_3); 56.5 (CH); 66.5 (CH_2); 73.9 (CH); 79.6 (CH); 82.4 (CH); 95.9 (CH_2); 96.0 (CH_2); 127.9 (3 x CH); 128.3 (2 x CH); 136.1 (C); 155.5 (CO); 172.5 (CO). IR (ῡ, cm^{-1}): 3346 (OH + NH), 1731 (CO). MS-CI (m/z, %): 414 (13, MH^+); 354 (24, $[M\text{-}C_2H_3O_2]^+$); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{19}H_{27}NO_9$: C 55.20, H 6.58, N 3.39; found C 55.45, H 6.81, N 3.31. **Compound 6b**: $[\alpha]_D^{20}$: -19.1 (*c* 2.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 2.86—2.93 (m, 1 H, H-1); 3.37 (s, 3 H, OCH_3); 3.38 (s, 3 H, OCH_3); 3.42—4.42 (m, 5 H, OH + H-2 + H-3 + H-4 + H-5); 3.68 (s, 3 H, OCH_3); 4.64—4.76 (m, 4 H, 2 x CH_2OMe); 5.08 (s, 2 H, CH_2Ph); 5.51 (d, 1 H, *J*=7.6 Hz, NH); 7.31—7.35 (m, 5 H, 5 x H-Ph). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 52.2 (OCH_3); 52.4 (OCH_3); 53.6 (CH); 55.6 (OCH_3); 55.8 (CH); 66.7 (CH_2); 79.9 (CH); 80.1 (CH); 84.4 (CH); 96.1 (CH_2); 97.0 (CH_2); 128.0 (2 x CH); 128.0 (CH); 128.4 (2 x CH); 136.2 (C); 155.7 (CO); 172.5 (CO). IR (ῡ, cm^{-1}): 3438 (OH + NH), 1729 (CO); 1704 (CO). MS-CI (m/z, %): 414 (8, MH^+); 354 (16, $[M\text{-}C_2H_3O_2]^+$); 91 (100, $[PhCH_2]^+$). Analysis: calculated for $C_{19}H_{27}NO_9$: C 55.20, H 6.58, N 3.39; found C 55.38, H 6.72, N 3.21.

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Supplementary Material

- New contribution to the synthesis of sugar β–amino acids from sugar β–nitro acids.
- First two examples of a novel class of bicyclic β–amino acids.
- First example of a novel class of cyclopentene β–amino acids.
- Examples of a new polyhydroxylated cyclopentane β–amino acid and a new cyclohexane β–amino acid.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: