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Synthesis of Enantiopure Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-Amino-3,4,5-trihydroxycyclopentanecarboxylate.

Fernando Fernández[a], Juan C. Estévez*,[a] and Ramón J. Estévez*,[a]

[a]*Departamento de Química Orgánica, Universidade de Santiago de Compostela*

15782 Santiago de Compostela, SPAIN

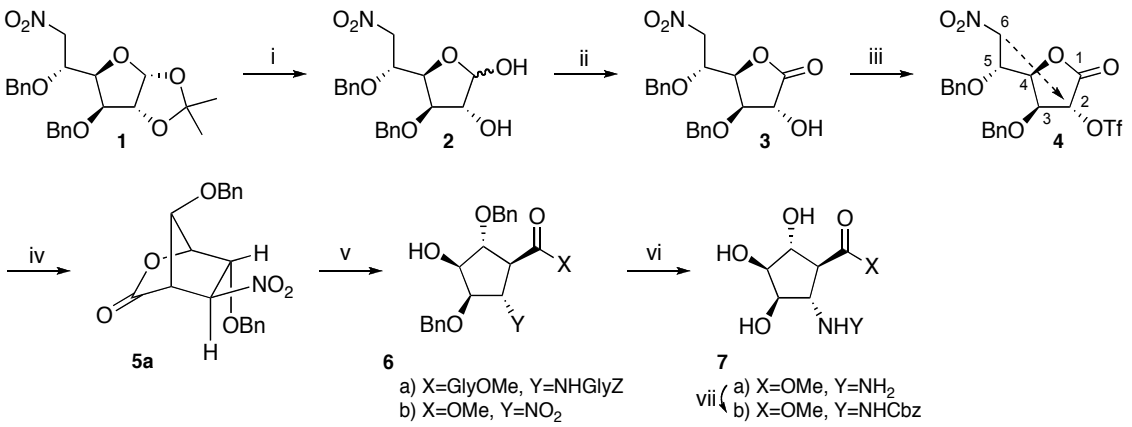
Corresponding author e-mail: ramon.estevez@usc.eS

1. ABSTRACT.

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

2. INTRODUCTION.

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

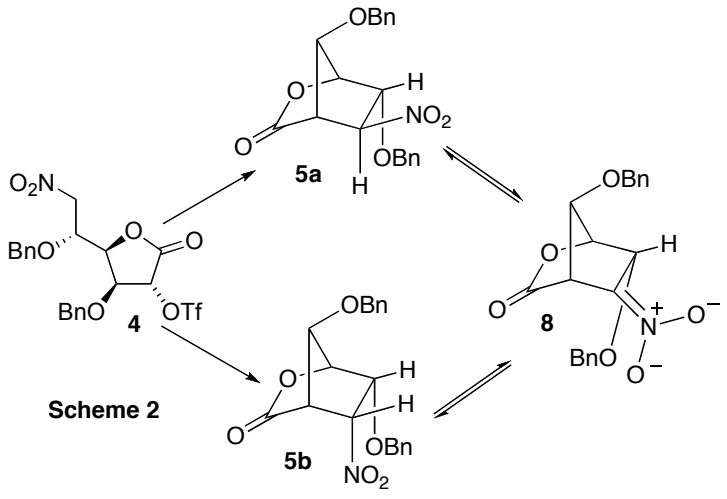


Scheme 1.- Conditions: i) TFA/H_2O (1:1), rt, 19 h; ii) Br_2, $BaCO_3$, dioxane/H_2O (2:1), rt, 36 h (94% from **1**); iii) Tf_2O, pyridine, CH_2Cl_2, -30˚C, 1.5 h; iv) TBAF, THF, rt, 6 h (75% from **3**); v) MeONa/MeOH (0.5 M), rt, 1.5 h, 65%; vi) H_2, Pd/C, MeOH, citric acid, 50 h; vii) CbzCl, $NaHCO_3$,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

3. RESULTS AND DISCUSSION.

Reaction of the easily prepared nitroglucofuranose derivative **1** with trifluoroacetic acid and water, followed by anomeric oxidation of the resulting hydroxy lactol **2** with bromine and barium carbonate afforded the lactone **3** as a yellow oil (94% yield from **1**). Reaction of **3** with triflic anhydride in pyridine furnished the corresponding triflate **4**, which when treated with TBAF in THF readily underwent an intramolecular displacement of the triflate group by the carbanion α to the nitro group, affording the bicyclic β-nitrolactone **5a** only, in a 75% yield for the last two steps (previous yield, 41%). This substantial yield improvement was achieved when the concentration of triflate **4** in the reaction mixture was raised from 0.10 M to 0.11 M and this compound was allowed to stand *in vacuum* for 12 hours just before its transformation.

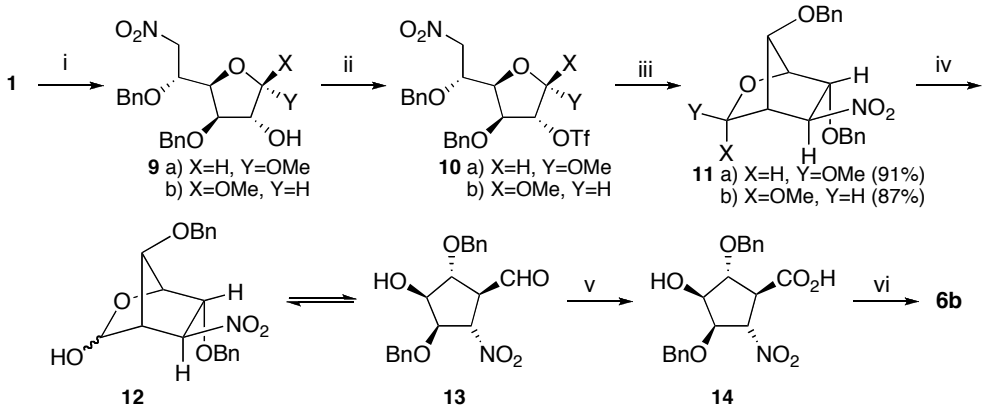
The stereochemical outcome of this key step leading to compound **5a** was explained assuming that both bicyclic compounds **5a** and **5b** should be formed from the nitronate of compound **4** (Scheme 2). Under the reaction conditions, however, compounds **5a** and **5b** should be in equilibrium with their common nitronate **8.** At equilibrium, the thermodynamically more stable compound **5a** should be favoured with respect to compound **5b**, where the NO_2 and the OBn substituents are eclipsed. This explains the highly remarkable stereoselectivity of the cyclization.



Scheme 2

In a modification of our previous synthetic route leading to **6a**, the reaction of this bicyclic lactone with sodium methoxide in MeOH followed by the hydrogenation of the resulting methyl 5-nitrocyclopentane carboxylate **6b** in an acidic medium, provided the desired β-amino acid ester **7a**, as a result of the reduction of the nitro group to the amine and the simultaneous removal of the benzyl protecting groups. Finally, **7a** was directly reacted with CbzCl in order to transform it into its derivative **7b** with its amino group protected by a Cbz moiety.

On the other hand, in the course of our previous work in this field, we obtained a cyclopentylamine based glycosidase inhibitor from D-glucose via the bicyclic pyranoside **11b** (Scheme 3).[4a] It is worth to point that the nitronate based cyclization of the epimeric mixture **10a**+**10b** led to the isolation of a single compound (**11b**) in a moderate yield (46%). Here we describe further studies on this route, that allowed us to clarify and improve the yield of this key cyclization, and to apply it to a new, longer but more efficient preparation of the above cyclopentane β-amino acid **7a**.



Scheme 3. i) AcCl, MeOH, 0˚C to rt, 13 h (49% for **9a**, 41% for **9b**); ii) Tf_2O, pyridine, CH_2Cl_2, -30˚C, 1.5 h; iii) TBAF, THF, rt, 14 h (91% for **11a** from **9a**, 87% for **11b** from **9b**); iv) TFA/H_2O (3:1), rt, 4 h; v) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, t-BuOH/H_2O (1:1); vi) $TMSCHN_2$, Et_2O/MeOH (7:2), rt, 15 min (75% from **11a** + **11b**)

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

According to our plan, hydrolisis of the mixture **11a**+**11b** followed by their immediate oxidation with sodium chlorite provided the desired 5-nitrocyclopentane-

carboxylic acid **14**, which was directly converted into the previously obtained methyl ester derivative **6b** when it was allowed to react with trimethylsilyldiazomethane. We asummed that the hydrolysis of the bicyclic glycoside mixture **11a**+**11b** produced the expected mixture of hemiacetals **12**, which is in equilibrium with its open aldehyde form **13**. Treatment of this mixture **12**+**13** with sodium chlorite resulted in the oxidation of **13** to **14**, a process that promotes a displacement of this equilibrium to compound **13**. This hypothesis was supported by the ^{1}H NMR of the mixture **12**+**13**.[8]

4. CONCLUSIONS.

To sum up, we have adapted our strategy for the tranformation of nitrosugars into carbasugars[4] to the development of two efficient alternative stereocontrolled tranformations of D-glucose into (1*S*,2*S*,3*R*,4*S*,5*R*)-2-amino-3,4,5-trihydroxy-cyclopentanecarboxylic acid derivative **7a**. The alternative via nitrosugarlactone **3** (Scheme 1), which consists of 13 steps, allowed us to obtain this polyhydroxylated cyclopentane β-amino acid **7b** in a 15% overall yield. On the other hand, the alternative via nitroglycosides **9a** and **9b** is longer but more efficient, because the target **7b** was now obtained in 20% yield after 14 steps (Scheme 3).

Work is now in progress aimed at extending of these studies to hexoses other than D-glucose, in order to prepare a pannel of polyhydroxylated cyclopentane β-amino acids as a previous stage for the study of the structural, physical and biological properties of their β-peptides.

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5. Noboru, O. In The Nitro Group in Organic Synthesis; Feuer, H., Ed. Organic Nitro Chemistry Series; Wiley-VCH, 2001.
6. Crystallographic data for the structure of compound **11a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-205610. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk).
7. The 1H-NMR spectrum of the epimeric mixture **11a+11b** displayed two singlets at 3.41 ppm and 3.49, both due to the anomeric OMe substituents of **11a** and **11b**, respectively. A ratio 1.1:1.0 for both anomers was deduced from these signals.
8. The 1H-NMR spectrum of the mixture 12+13 includes two signals at 4.70 ppm and at 4.85 ppm, corresponding to the H-3 protons of anomers 12. The signal displayed at 9.45 ppm was attributed to the aldehyde proton of compound 13.