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Stereocontrolled transformation of nitrohexofuranoses into cyclopentylamines via 2-oxabicyclo[2.2.1]heptanes. Part 6: synthesis and incorporation into peptides of the first reported 2,3-dihydroxycyclopentanecarboxylic acid

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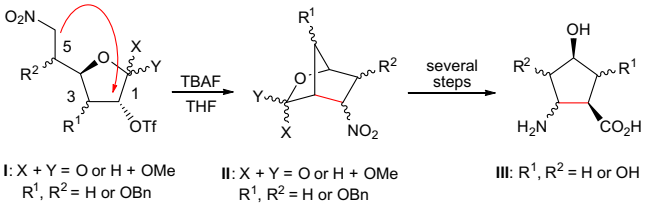
ABSTRACT

Herein we report the intramolecular alkylation of nitronates of methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-β-D-glucofuranoside and methyl-5-*O*-benzyl-3,6-deoxy-6-nitro-α-D-glucofuranoside into the corresponding 2-oxabicyclo[2.2.1]heptane derivatives. Similarly, methyl-3-*O*-benzyl-5-deoxy-5-nitromethyl-β-D-xylofuranoside and methyl-3-*O*-benzyl-5-deoxy-5-nitromethyl-α-D-xylofuranoside were cyclized to (1*R*,3*R*,4*S*,5*R*,7*R*)-7-benzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane and (1*R*,3*S*,4*S*,5*R*,7*R*)-7-benzyloxy-3-methoxy-5-nitro-2-oxabicyclo[2.2.1]heptane, respectively. These 2-oxabicyclo[2.2.1]heptane derivatives were eventually transformed into enantiopure methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-2-amino-2,3-dihydroxycyclopentanecarboxylate and this novel β-amino acid was incorporated into peptides.

1. Introduction

The design and synthesis of new amino acids and peptidomimetics has attracted considerable attention in recent times, due to the pharmacological limitations of bioactive peptides, which have been related to their conformational flexibility and their metabolic instability.[1] Particular attention has been devoted to β-amino acids, on account of the metabolic and conformational stability of β-peptides.[2] Among them, cyclopentane β-amino acids have become attractive candidates for the stabilization of bioactive peptides, due to the high tendency of their homopolymers to fold in rigid secondary structures in short peptide sequences.[3]

Carbohydrates are an abundant source of useful scaffolds for the stereoselective synthesis of functionalized carbo- and heterocycles.[4] One of the approaches developed for this purpose involves the generation of a bicyclic derivative constituted by the original sugar ring and a new ring, followed by the opening of the sugar ring (*approach a*). Alternatively, a new ring results from the cyclization of an open chain carbohydrate derivative (*approach b*). Among the variants of the *approach a* that have been developed, the one involving an intramolecular alkylation of nitronates of sugar derivatives **I** to give bicyclic compounds **II** has allowed us to develop the first approach for the synthesis of polyhydroxylated cyclopentane β-amino acids **III** (Scheme 1).[5] Stereocontrolled access to these richly functionalized alicyclic β-amino acids is limited to hexoses that fit the stereochemical requirements for the intramolecular displacement of –OTf leaving groups at C-2 by nitronates at C-6 (D-glucose, D-idose, D-allose, D-talose, and their respective L-hexose enantiomers). Moreover, our previous studies in this field allowed us to recognize that the efficiency of the key cyclization leading to compounds **II** depends on a number of structural factors of their precursors **I**: the sp^2 or sp^3 character of the carbon atom at C-1, the configuration of the stereogenic centers at C-1(sp^3), C-3 and C-5, and the nature of the substituents at C-3 and C-5.[5]



I: X + Y = O or H + OMe
R^1, R^2 = H or OBn

II: X + Y = O or H + OMe
R^1, R^2 = H or OBn

III: R^1, R^2 = H or OH

Scheme 1.

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In order to gain more insight into the factors influencing the key cyclization involved in this synthesis of polysubstituted cyclopentane β-aminoacids, we herein report its extension to additional nitro sugars **I**.

2. Results and discussion

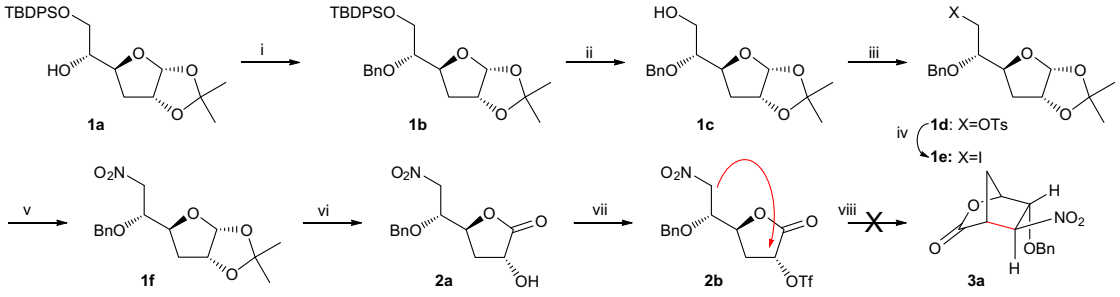
At first, we studied the cyclization of 6-nitro-3,6-dideoxy-2-*O*-triflyl-D-gluconolactone **2b**, which was obtained in seven steps and 17.3% overall yield from the known D-glucose derivative **1a**,[7] following a protocol previously developed in our group for the preparation of 6-nitro-6-dehydro-D-hexofuranosides (Scheme 2).[5a]

Benzylation of the free OH group of **1a** by treatment with NaH and BnBr was followed by a TBAF mediated removal of the TBDPS protecting group of the resulting derivative **1b**. This afforded compound **1c**, which in turn easily provided its *O*-tosyl derivative **1d** upon treatment with TsCl for 10 h, in the presence of pyridine.[6] The reaction of this compound with NaI resulted in the efficient formation of iodo derivative **1e**,[6] which yielded the key nitrosugar **1f**, after reaction with $NaNO_2$ and trihydroxybenzene (phloroglucinol),[5a] a scavenger that avoids nitrite ester formation. Removal of the isopropylidene protecting group of **1f** with aqueous TFA, followed by oxidation of the anomeric position of the resulting 3-deoxy furanose with Br_2 and $BaCO_3$, furnished the expected sugar lactone **2a**, which was directly converted into its –OTf derivative **2b**, when reacted with Tf_2O and pyridine (Scheme 2).[5c] Finally, compound **2b** was directly allowed to react with TBAF in dry THF, but the expected cyclization leading the bicyclic lactone **3a** did not occur. This unsuccessful result allowed us to confirm that a substituent at the C-3 position of type **2b** substrates is required for the success of these cyclizations.[5c]

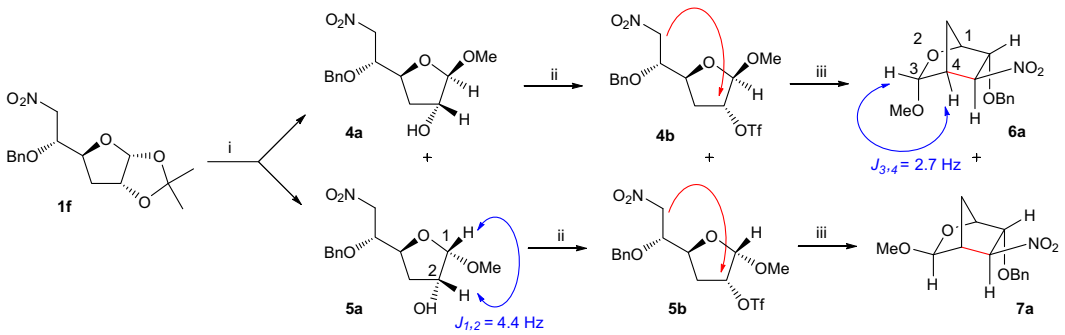
However, satisfactory results were achieved when we explored the alternative nitronate alkylation route depicted in Scheme 3.[5c] Thus, when nitroglucofuranose derivative **1f** was now reacted with AcCl in MeOH, a 6:1 ratio of an inseparable anomeric mixture of **4a** and **5a** was obtained. This ratio was established from the relative intensities of the two singlets that appear in its ^1H NMR at 3.34 ppm and 3.46 ppm, due to the anomeric methoxy substituents of **4a** and **5a**, respectively. On the other hand, the configuration at the anomeric stereogenic center of **5a** was deduced from a doublet at 4.83, ppm due to its anomeric proton, which is coupled with the proton at C-2. The coupling constant value ($J_{1,2}$ = 4.4 Hz) requires a *cis*-configuration of both protons. This is in accordance with the configuration proposed for anomer **4a**. As expected, its anomeric proton showed a singlet (δ = 4.78 ppm), due to a *trans*-configuration of the protons H_1 and H_2.

The reaction of this mixture of compounds **4a** and **5a** with Tf_2O and pyridine, under the same conditions as for **2a**, provided the corresponding mixture of compounds **4b** and **5b**, which was treated directly with TBAF in THF. The intramolecular displacement of the triflate group at C-2 by the nitronate at C-6 resulted in the formation of a 20:1 mixture of bicyclic anomers **6a** and **7a**, which was separated by column chromatography and identified from their analytical and spectroscopic properties. The anomeric proton at 5.17 ppm of anomer **6a** showed a doublet with a coupling constant of $J_{3,4}$ = 2.7 Hz, due to an *endo* disposition of its methoxy group. On the other hand, the *exo* disposition of the methoxy group of its isomer **7a** was easily deduced from a singlet at 4.67 ppm, due to its anomeric proton.

The stereochemical outcome of the key step to compound **6a** can be explained by assuming that both bicyclic compounds **6a** and **6a′** should be formed from nitronate **4b′** (Scheme 4). Under the reaction conditions, however, compounds **6a** and **6a′** should be in equilibrium with their common nitronate **6a″**. At equilibrium, the thermodynamically more stable compound **6a** should be favoured over compound **6a′**, where the NO_2 and the OBn substituents are eclipsed. This explains the remarkably high stereoselectivity of the cyclization. A similar behavior could explain the selective transformation of compound **5b** into bicyclic compound **7a.**



Scheme 2. Reagents and conditions: (i) (a) NaH, NBu_4I, BnBr, DMF, 50 °C, 1 h; (b) MeOH, 50 °C, 2 h; (ii) TBAF, THF, rt, 4 h; (iii) TsCl, Py, rt, 10 h; (iv) NaI, acetone, reflux, 15 h; (v) $NaNO_2$, phloroglucinol, DMSO, rt, 96 h; (vi) (a) TFA, H_2O, rt, 12 h; (b) Br_2, $BaCO_3$, dioxane, H_2O, rt, 14 h; (vii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (viii) TBAF, THF, rt, 1.5 h.



Scheme 3. Reagents and conditions: (i) AcCl, MeOH, 0 °C, 14 h; (ii) Tf_2O, pyridine, CH_2Cl_2, −30 °C, 1.5 h; (iii) TBAF, THF, rt, 1.5 h.