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A New Synthesis of Polyhydroxylated Cyclopentane β-Amino Acids from Nitro Sugars †

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Abstract: The design and synthesis of new amino acids a has attracted considerable attention in recent times. Particular attention has been devoted to b-amino acids, on account of the metabolic and conformational stability of b-peptides. Among them, cyclopentane b-amino acids have become attractive candidates for the stabilization of bioactive peptides, due to the high propensity of their homopolymers to fold in rigid secondary structures in short peptide sequences. Nitro compounds are very versatile in organic synthesis. In particular, nitroalkenes can act as potent Michael acceptors and, in fact, Michael addition of nucleophiles to nitroolefins is an important tool for the creation of carbon-carbon bonds and heteroatom-carbon bonds. After employing this powerful method for carbon-carbon bond construction, the nitro group can be transformed into a wide variety of functionalities, including amino groups, by reduction. In connection with our continuing interest in nitro compounds and cycloalkane b-amino acids, we report here the unexplored Michael addition of tris(phenylthio)methane (a synthetic equivalent of the carboxyl group) to a cyclopentane sugar nitroolefin derived from D-glucose ([1*R*, 2*R*)-2-(benzyloxy)-4-nitrocyclopent-3-en-1-yl formate], this being the key step in a synthetic sequence that allowed new access to a cyclopentane b-amino acid [methyl (1*S*,2*R*,3*R*,5*R*)-2-(benzyloxy)-5-((*tert*-butoxycarbonyl)amino)-3-hydroxycyclopentane-1-carboxylate]. This approach is shorter and more efficient than a previous synthesis of this b-amino acid, also obtained from D-glucose.

Keywords: carbohydrates, sugar nitro olefins, cyclopetane beta-amino acids

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1. Background and Working Plan

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 given to β-amino acids, due to 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 propensity of their homopolymers to fold in rigid secondary structures in short peptide sequences [3].

Nitro compounds are very versatile in organic synthesis, due to their easy availability and ease of transformation into a wide variety of functionalities [4]. The chemistry of these compounds is dominated by the electron-withdrawing character of the nitro group. In particular, nitroalkenes can act as potent Michael acceptors and, in fact, Michael addition of nucleophiles to nitroolefins is an important tool for the creation of carbon-carbon and heteroatom-carbon bonds. After employing this powerful method for carbon-carbon bond

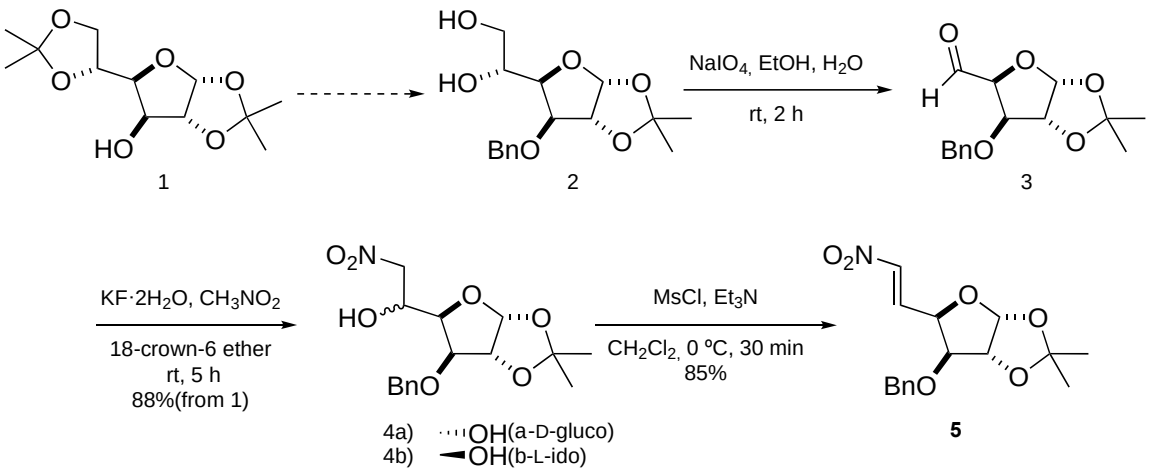
construction, the nitro group can be transformed into a wide variety of functionalities, including amino groups, by reduction.

In connection with our continuing interest in nitro compounds and cycloalkane β-amino acids [5–8], we report here the unexplored Michael addition of tris(phenylthio)methane (a synthetic equivalent of the carboxyl group) to a cyclopentane sugar nitroolefin derived from D-glucose [(1*R*, 2*R*)-2-(benzyloxy)-4-nitrocyclopent-3-en-1-yl formate], this being the key step in a synthetic sequence that allowed new access to a cyclopentane β-amino acid [methyl (1*S*,2*R*,3*R*,5*R*)-2-(benzyloxy)-5-((*tert*-butoxycarbonyl)amino)-3-hydroxycyclopentane-1-carboxylate]. This approach is shorter and more efficient than a previous synthesis of this β-amino acid, also obtained from D-glucose.

2. Results and Discussion

According to our working plan, the transformation of diacetone-*α*-D-glucose (**1**) into nitroolefin **5** was carried out following a procedure described in the literature (Scheme 1) [9].

First, the reaction of diol **2** (obtained from **1**) with sodium periodate gave rise, by oxidative cleavage, to aldehyde **3**, which was treated directly with nitromethane and potassium fluoride, in the presence of 18-crown-6 ether, to give rise to a Henry reaction leading to an epimeric mixture of the nitro derivatives **4a** + **4b** in 88% yield for the two steps and an 8:1 ratio.



Scheme 1. Synthesis of sugar nitroolefin **5.**

This mixture was characterized on the basis of its spectroscopic properties. Thus, its ^{1}H NMR spectrum shows, among others, four signals at 71.5, 71.7, 77.5 and 78.5 ppm, corresponding to the two methylene groups of each of the epimers that make up the mixture. The IR spectrum shows two bands at 1554 and 1377cm^{-1}, characteristic of the nitro group. The 8:1 ratio at which the components of the **4a** + **4b** mixture were obtained, was easily established from its ^{1}H NMR, by comparison of the relative intensities of the signals corresponding to their respective anomeric protons, which appear as two doublets at 5.74 ppm ($J_{1,2}$ = 3.5 Hz) and at 5.82 ppm ($J_{1,2}$ = 3.8 Hz), as can be seen in Figure 1.

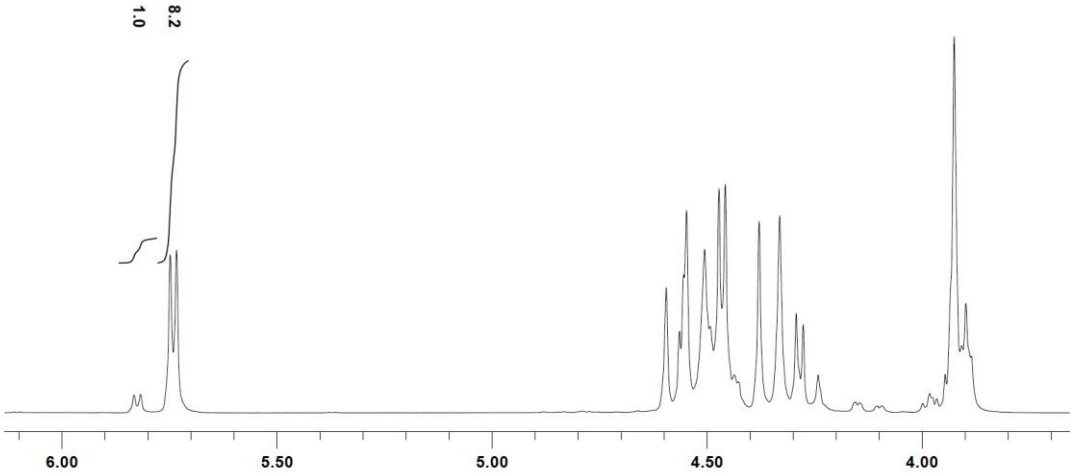
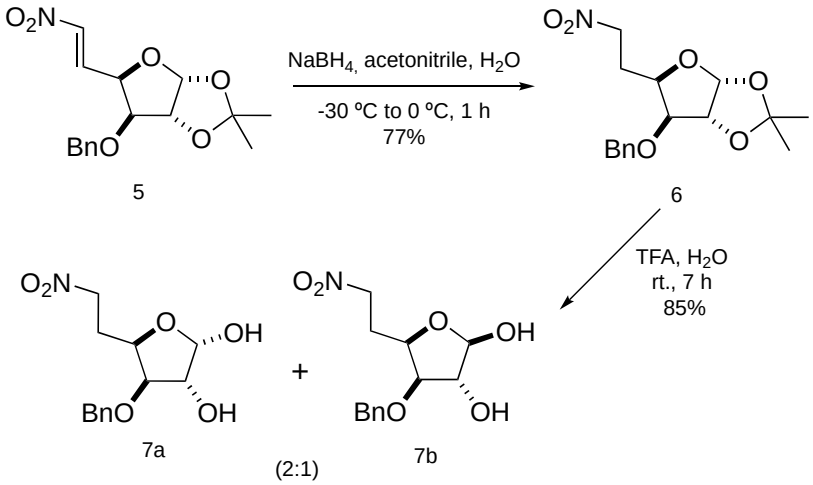


Figure 1. ^{1}H NMR spectrum of the mixture **4a** + **4b**.

Continuing with our work plan, this mixture **4a** + **4b** was treated with mesyl chloride and triethylamine in dichloromethane, isolating nitroolefin **5** in 85% yield, as clearly shown by its spectroscopic properties, identical to those described in the literature [10], including the presence in its ^{13}C NMR spectrum of two signals at 135. 8 and 140.4 ppm, corresponding to the -CH- of the C-5 and C-6 positions, as well as the presence in its IR spectrum of a band at 1661 cm^{-1}, due the double bond formed.

Once nitroolefin **5** was obtained, we proceeded with reaction protocol foreseen to generate nitrocyclopentene **10**, the key compound of our synthetic routes (Schemes 2 and 3).



Scheme 2. Synthesis of nitrosugar **7**$\alpha\beta$ (anomeric mixture).

Thus, firstly, the reduction of the double bond of the derivative **5** with sodium borohydride in acetonitrile, which was carried out at low temperature and acidic pH (~3–4), efficiently led to the nitro compound **6** in 77% yield, as evidenced by its spectroscopic data. In its ^{13}C NMR spectrum we can highlight the signals at 26.1, 71.7 and 72.3 ppm, corresponding to three -CH_2- groups. In its-^{1}H NMR spectrum a multiplet is observed between 2.22–2.50 ppm, corresponding to the two protons at the C-5 position. In addition, its mass spectrum shows a peak with a ratio m/z = 324, corresponding to the $(M+H)^+$ ion.

Next, when derivative **6** was dissolved in a trifluoroacetic acid/water mixture and the resulting solution was stirred at room temperature for seven hours, hydrolysis of the acetonide group occurred, yielding lactols **7**α and **7**β in 85% yield and a 2:1 ratio. This ratio

was determined from the ^{1}H NMR of their mixture, by comparison of the signals corresponding to the respective anomeric protons, which appear as doublets at 5.34 ppm ($J_{1,2}$ = 3.5 Hz) and at 5.09 ppm ($J_{1,2}$ 9.0 Hz), as can be seen in Figure 2.

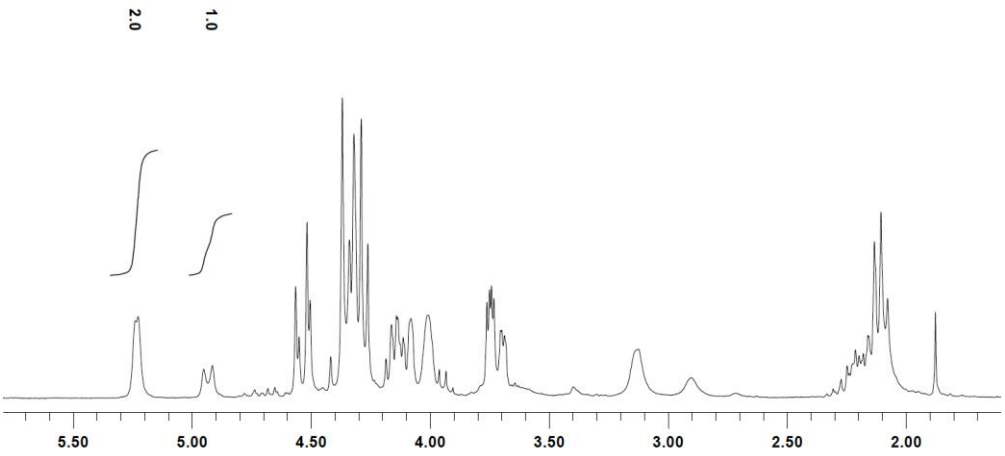
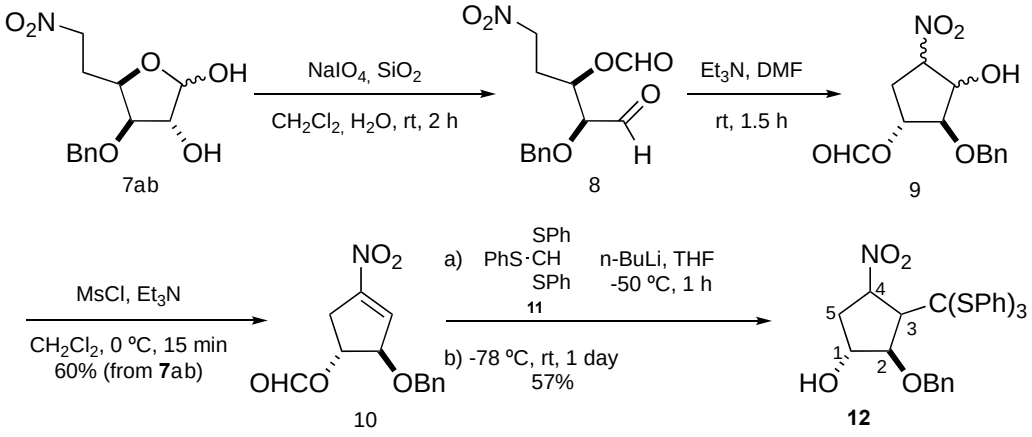


Figure 2. ^{1}H RMN spectrum of the mixture **7αβ.**

Comparison of the ^{1}H NMR spectra of **6** and **7αβ** showed the absence of the signals corresponding to the methyls of the acetonide group present in the starting product **6**, confirming that the desired deprotection had taken place. In addition, the IR spectrum of **7αβ** shows a band at 3395 cm^{-1}, assignable to the free hydroxyls at the C-1 and C-2 positions.

Continuing with our work plan, the reaction of these nitro hexofuranoses **7αβ** with sodium periodate in dichloromethane and water, in the presence of silica gel [11], led to the oxidative cleavage of their 1,2-diol system, given rise to the desired nitro aldehyde **8** (Scheme 3). Its ^{1}H NMR spectrum shows a singlet at 8.00 ppm of one proton, corresponding to its formyloxy group, and a singlet at 9.62 ppm of one proton, corresponding to the aldehyde group.



Scheme 3. Synthesis of nitro carbasugar **12.**

Then, following a procedure described in the literature,[12] derivative **8** was treated with triethylamine in dimethylformamide, leading by an intramolecular Henry reaction to a mixture of the nitro cyclopentanes **9**, which was treated directly with mesyl chloride and triethylamine in dichloromethane, isolating nitro cyclopentene **10**, with a yield of 60% for the three steps. This mixture was characterized on the basis of its spectroscopic properties, among which we can highlight in its ^{1}H NMR spectrum a double triplet of one proton at 5.42 ppm ($J_{1,2}$ = $J_{1,5'}$ =3.5 Hz, $J_{1,5}$ = 7.0 Hz), corresponding to the -CH- bearing the

formyloxy group, a multiplet of one proton between 6.83–6.85 ppm, due to the olefinic -CH- at the C-3 position and a singlet of one proton at 8.04 ppm, corresponding to the formyloxy group. Its ^{13}C NMR spectrum shows at 35.1 ppm a signal corresponding to the methylene at the C-5 position. In addition, its IR spectrum shows the characteristic bands of the nitro group, at 1360 cm^{-1} and 1553 cm^{-1}, together with a band at 1726 cm^{-1}, corresponding to the -CO- of the formyloxy group.

Once the key nitro cyclopentene **10** was obtained, its transformation into the derivative **12** was carried out by adding a tris(phenylthio)methane group, as shown in Scheme 3 [13].

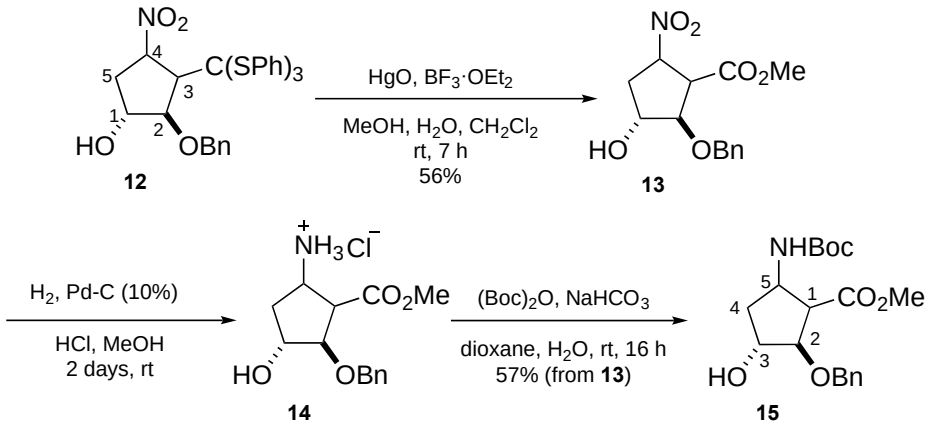
By adding *n*-butyllithium to a solution of tris(phenylthio)methane (**11**) in tetrahydrofuran, the corresponding lithium salt was obtained, to which the previously prepared nitroolefin **10** was then added. Compound **12** was thus obtained as the sole product, in 57% yield. As shown, under the reaction conditions the introduction of the tris(phenylthio)methane group was accompanied by the deprotection of the formyloxy group. The characterization of derivative **12** was made on the basis of its spectroscopic properties, including the presence in its ^{1}H NMR spectrum of two multiplets between 7.16–7.50 ppm, dues to twenty aromatic protons [five protons corresponding to the benzyloxy group and fifteen protons corresponding to the three phenyls of the tris(phenylthio)methane group], as well as the presence of a double triplet at 5.29 ppm ($J_{4,3} = J_{4,5} = 4.1$ Hz, $J_{.4,5'} = 8.2$ Hz), corresponding to the -CH- contiguous to the nitro group. Its ^{13}C NMR spectrum shows, among others, a signal at 58.1 ppm, corresponding to the -CH- linked to the tris(phenylthio)methane group, as well as a signal at 77.5 ppm, corresponding to the quaternary carbon of the newly introduced tris(phenylthio)methane group. A comparison of the spectra of **10** and **12** showed the absence of any signal corresponding to the formyloxy group of the starting **10**.

This Michael addition process took place with total selectivity, obtaining derivative **12** as the only product of the four possible isomers had to be determined in subsequent stages of our synthesis plan.

Next, a solution of the nitro derivative **12** in methanol, water and dichloromethane was treated with mercury (II) oxide and boron trifluoride etherate, obtaining a 56% yield of compound **13**, after seven hours of reaction at room temperature, as clearly shown by its spectroscopic properties. Its ^{1}H NMR spectrum shows a singlet of three protons at 3.76 ppm, corresponding to the -OCH$_3$ of the ester group. In its ^{13}C NMR spectrum we can observe, among others, a signal at 52.8 ppm, corresponding to the -CH- bearing the ester group, as well as a signal at 53.0 ppm, corresponding to the -OCH$_3$ group. In addition, a band at 1737 cm^{-1} due to the carbonyl group is observed in its IR spectrum.

However, from the spectroscopic data, it was not possible to determine the absolute configuration at the C-3 and C-4 positions of **13**

We continued our work on the synthesis of polyhydroxylated cyclopentane β-amino acids by catalytically hydrogenating nitro ester **13** in the presence of hydrochloric acid, which led to the reduction of its nitro group to amino (Scheme 4). The resulting compound **14** was directly treated with *tert*-butoxycarbonyl anhydride in basic medium, giving the β-amino ester **15** in 57% yield for the two steps.



Scheme 4. Synthesis of cyclopentane β-amino acid derivative **15.**

The absolute configuration at the C-1 and C-5 positions of the β-amino ester **15** could be established from NOE experiments (Figure 3).

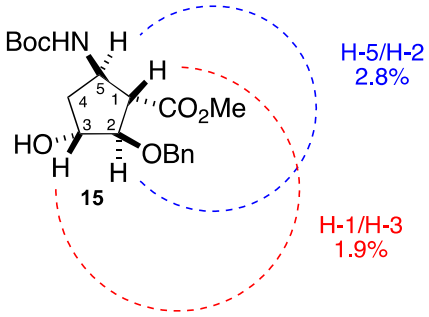


Figure 3

Thus, it was observed that H-1 shows NOE with H-3 (1.9%), which indicates that both protons are on the same face of the cyclopentane ring, allowing the configuration at the C-1 position to be established. Furthermore, H-5 presents NOE with H-2 (2.8%), which is only possible if both protons are arranged on the same side of the cyclopentane ring, which determines the configuration of the C-5 position.

Ultimately, the synthesis of the polyhydroxylated cyclopentane β-amino acid **15** was synthesized from D-glucose following a synthetic including an intramolecular Henry reaction that allowed to generate a nitroolefin **10**, to which lithium tris(phenylthio)methylene was enantioselectively added, to generate a polysubstituted cyclopentane **12**, two of whose substituents [NO_2 and $C(SPh)_3$] are the precursors of the amino and the ester functionalities of the derivative **15**.

This new synthetic strategy could be applied to the full panel of the sixteen hexoses. The research group is currently working on this.

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Conflicts of Interest:

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