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Stable Ditriflates of D-Glucose in the Synthesis of Iminosugars and Polyhydroxylated Pipecolic Acids

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A synthesis of the five membered iminosugar DAB and a divergent synthesis of the six membered iminosugar 1-dehydromannojirimycin (DMJ) and the corresponding sugar imino acid are reported. They involve double nucleophilic displacements of a D-xylose ditriflate by benzyl carbazate and a D-glucose ditriflate by allyl amine, respectively. They are followed by a similar protocol consisting of hydrolysis and oxidation or reduction of the resulting bicyclic glycosides. This allowed DMJ to be obtained from the cheap sugar D-glucose.

Introduction

Iminosugars are natural and synthetic polyhydroxylated monocyclic (pyrrolidine, piperidine, azepane) and bicyclic (pyrrolizidine, indolizidine, nortropane) nitrogenated compounds that can be considered sugar mimetics resulting from the replacement of the oxygen ring by nitrogen.[1,2] Past and current interest in these compounds lie on their capacity to act as strong inhibitors of both glycosidases and glycoxyltransferases,[3] and the consequent potential for the treatment of diverse diseases,[4–6] including diabetes, viral infections, tumor metastases and lysosomal storage disorders.[7] Hence, since the isolation of D-nojirimycin in 1996, iminosugars have received considerable attention, from both chemical and biological point of view. In fact, its *N*-alkylated derivatives Miglustat[8] (**2**) and Miglitol[9] (**3**), are clinically approved drugs used for the treatment of Gaucher's disease and type II diabetes, respectively. D-deoxymannojirimycin (DMJ, **4**, Figure 1) exhibits promising mammalian α-fucosidase activity.[10] And a representative polyhydroxylated pyrrolidine is iminocyclopentitol l,4-dideoxy-l,4-imino-D-arabinitol (DAB, **5**, Figure 1), a natural product that has shown to be an efficient inhibitor of α-glucosidases.[11]

Carbohydrate diols are a suitable source for the synthesis of iminosugars. Sequential approaches require multistep procedures, involving the reduction of nitro or azido sugars to amino sugars, from which the second C–N bond is generated by intramolecular displacement of a OMs, OTs or OTf leaving group.[12] An alternative approach to this targets involve the simultaneous generation of the two C–N bonds by a double displacement of open chain sugar dimesylates, ditosylates or dihalides by amines.[13,14] Recently a more attractive preparation of iminosugars from stable sugar ditriflates was reported, a variant that takes advantage of the use weak nitrogen nucleophiles. The first reported example consisted of an efficient synthesis of azetidines.[15–20] More recently this approach has been applied to a divergent synthesis of iminocyclopentitols and 3,4-dihydroxyprolines.[21] This paper reports the application of this methodology to a new synthesis of DAB (**5**) from a D-xylose ditriflates **8α** and **8β** (Scheme 1), together with a divergent synthesis of 1-deoxymannojirimycin (DMJ, **4**) and the corresponding polyhydroxylated pipecolic acid **24** from D-glucose ditriflates **16αβ** (Scheme 2 and Scheme 3).

Results and Discussion

Ditriflates **8α** and **8β** were obtained as previously,[21] as a 1:1 anomeric separable mixture, by treatment of D-xylose derivative mixture **7αβ** with Tf_2O and DIEA, and this mixture and its components were separately transformed into DAB (**5**), as shown in Scheme 1. Thus, reaction of ditriflate **8α** with benzyl carbazate provided the azabicycle glycoside **9α** in 83% yield, as established from the presence in its ^{1}H NMR of a broad singlet at 6.84 ppm and a singlet at 5.11 ppm, due to the NH and the CH_2 groups of the carbazate substituent. In addition, the α configuration of its anomeric center was deduced from a singlet at 4.79 ppm, corresponding to its anomeric proton. When the reaction was carried out with the anomer **8β**, the bicyclic compound **9β** was obtained in 32% yield. The configuration of its anomeric center was established from the presence in its ^{1}H NMR of a doublet at 5.01 ppm ($J = 1.9$ Hz), due to the anomeric proton. The low yield achieved for anomer **8β** was attributed to

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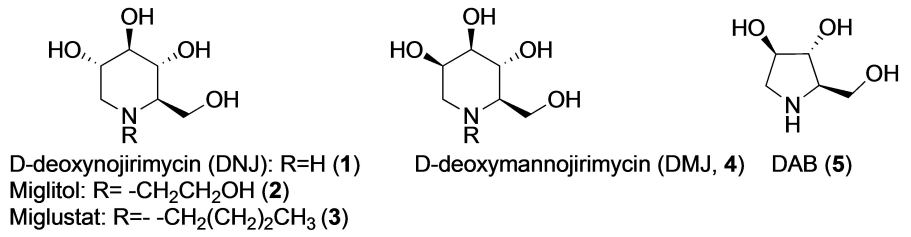
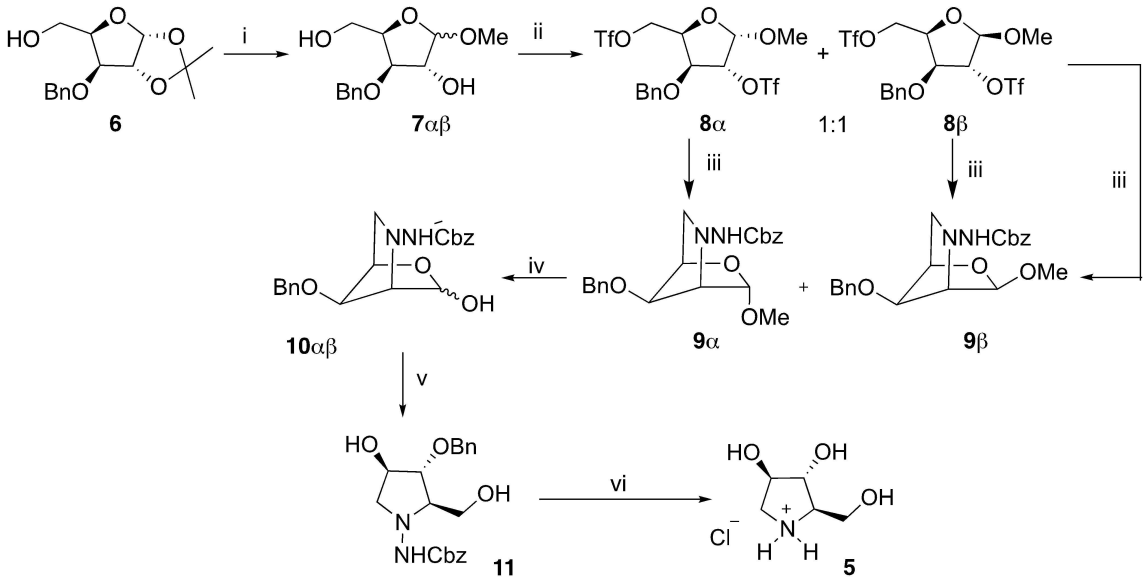
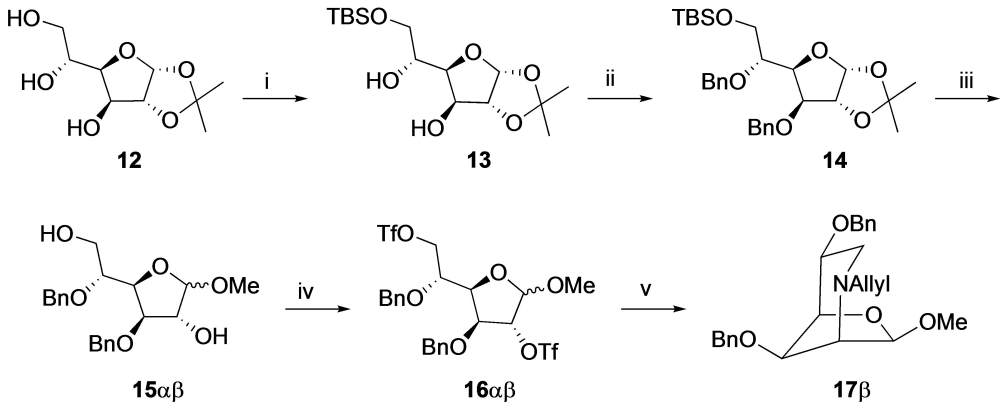


Figure 1. A selection of iminocyclohexitols and iminocyclopentitols.



Scheme 1. Synthesis of the iminosugar DAB (**5**). *Conditions*: i) AcCl, MeOH/H_2O, rt, 2 h. ii) Tf_2O, DIEA, CH_2Cl_2, −30 °C, 2 h (85%). iii) $CbzNHNH_2$, DIEA, MeCN, 50 °C, 19 h (83% for **9α**, 32% for **9β**). iv) TFA/H_2O (1 : 1), rt, 2 h. v) $NaBH_4$, EtOH/H_2O (3 : 1), rt, 2 h (41%, two steps). vi) a. H_2, 10% Pd/C, MeOH, rt, 4 h. b. 1 M HCl, Et_2O (99%, 2 steps)



Scheme 2. Synthesis of **17β**, a precursor of iminosugar of iminosugar **4** and polyhydroxylated pipecolic acid **24**. *Conditions*: i) TBSCl, imidazole, DMF, −20 °C, 4 h (89%). ii) a. NaH, nBu_4NI, THF, 0 °C, 10 min; b. BnBr, 50 °C, 40 h (79%). iii) H_2SO_4, MeOH, 0 °C- > rt, 26 h (90%). iv) Tf_2O, pyr, CH_2Cl_2, −30 °C, 3 h. v) allylamine, DEA, CH_3CN, 50 °C, 23 h (55%, two steps).

steric reasons. The orientation of its methoxy substituent could interfere with the approach of the carbazate nucleophile to the carbon at C-2, bearing the OTf leaving group. On the other hand, when the anomeric mixture **8α + 8β** was subjected to the conditions for the transformation of **8α** into **9α**, a mixture of **9α + 9β** resulted.

According to our plan, the acidic hydrolysis of the glycoside subunit of the mixture **9α + 9β** with TFA provided the anomeric mixture **10αβ**, which was directly reacted with $NaBH_4$, to provide prolinol **11** in 41% yield, as established from its spectroscopic and analytical data, mainly from the presence in its ^1H NMR of a doublet at 3.58 ppm ($J = 12.4$ Hz) and a doublet

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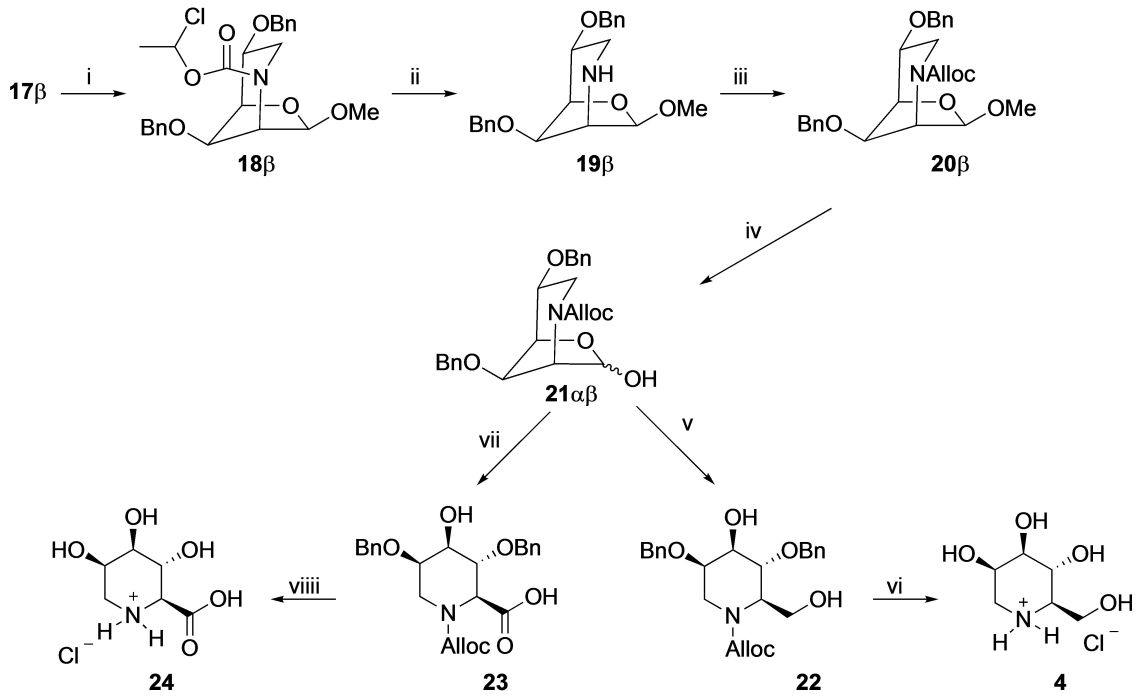

Scheme 3. Divergent synthesis of iminosugar **4** and polyhydroxylated pipecolic acid **24**. *Conditions:* i) $ClCO_2CHClCH_3$, $ClCH_2CH_2Cl_2$, reflux, 48 h. ii) MeOH, reflux, 24 h. iii) AllocCl, K_2CO_3, 18-crown-6, THF, 0 °C to rt, 15 h (81%, 3 steps). iv) THF/H_2O (3:1), rt, 4 h. v) $NaBH_4$, EtOH/H_2O (2:1), rt, 1 h (73%). vi) a. $Pd(Ph_3)_4$, Ph_3SiH, THF, rt, 90 min; b. H_2, 20% $Pd(OH)_2$/C, HCl, MeOH, rt, 14 h (79%, 2 steps). vii) $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, *t*BuOH/H_2O 1:1 (8.8 mL). viii) a. $Pd(Ph_3)_4$, Ph_3SiH, THF, rt, 23 h; b. H_2, 20% $Pd(OH)_2$/C, HCl, MeOH, rt, 14 h (77%, 2 steps).

of doublets at 3.72 ppm ($J = 12.4$ Hz and $J' = 2.7$ Hz), both corresponding to the CH_2 groups. Finally, catalytic hydrogenation of this 1-aminoprolinol **11** resulted in the hydrogenolysis of the N–N bond and the removal of the Bn group, thus providing the expected iminosugar DAB (**5**) quantitatively, which was isolated as its hydrochloride salt. This compound was identical to a sample previously obtained.[21]

This strategy for the synthesis of iminocyclitols from sugar ditriflates was extended to the hexose D-glucose. This required the preparation of sugar 2,6-ditriflates **16αβ**. They were obtained as an inseparable mixture from the known D-glucose derivative **14** (Scheme 2),[22] which was prepared by the new approach stated in Scheme 2. It involved the preparation of **12** from diacetone-D glucose, previously reported,[23] followed by treatment with TBSCl, for selective protection of the OH group at the C-6 position. This was followed by reaction of the resulting compound **13** with BnBr to protect the remaining OH groups, and finally treatment of compound **14** with H_2SO_4 provided a 1:1.5 anomeric mixture **15αβ .** Then, proceeding as for **8α + 8β**, treatment of **15αβ** [24] with Tf_2O and pyridine provided the expected ditriflate mixture **16αβ**, which was directly reacted with allyl amine and DIEA, the result being the formation of the bicyclic furanoside **17β** only. The 55% yield achieved led us to assume that **17β** arises from the major anomer **15β**, via ditriflate **16β**, and thus to assign the configuration of its anomeric position. This is in accordance with its ^{1}H NMR spectrum, which shows a doublet at 5.00 ppm ($J = 2.0$ Hz), due to its *endo* anomeric proton (coupled with the H-4 proton).

Next, an attempt to hydrolyze the glycosidic moiety of bicyclic glycoside **17β** failed. This was attributed to the basic character of the nitrogen atom, because when the allyl group was replaced by an Alloc group, satisfactory results were achieved. Thus, as shown in Scheme 3, reaction of **17β** with $ClCO_2CHClCH_3$ provided the carbamate **18β** and methanolysis of this compound allowed the nitrogen protecting group to be removed, to give bicycle **19β**, which was finally reacted with alloc chloride and K_2CO_3 to furnish the desired *N*-Alloc protected bicycle **20β** in 81% yield (3 steps), as a rotamer mixture, as deduced from its ^{1}H NMR and ^{13}C NMR spectra, the latter showing signals of carbonyl groups at 155.7 and 156.3 ppm.

According to our plan, reaction of the *N*-Alloc bicycle **20β** with aqueous TFA led to the expected anomeric mixture **21αβ**, which upon direct oxidation with $NaClO_2$ gave the polysubstitutted pipecolic acid **23**. This compound was finally converted into the trihydroxylated pipecolic acid **24**,[25,26] by removing the Alloc group by reaction with PhSH and $Pd(Ph)_3$ and subsequent catalytic hydrogenation of the resulting debenzylated pipecolic acid, for removal of the Bn groups.

Moreover, treatment of the mixture **21αβ** with $NaBH_4$ provided the poysubstituted imnosugar **22** and removal of the Alloc and Bn groups of this compound, under the protocol for the transformation of **23** into **24**, gave the 1-deoximannojirimycin (**4**),[27–30] isolated as its hydrochloride salt. Iminohexitol **4** is well-known inhibitor of a bovine α-L-fucosidase and of mannosidase I of glycoprotein processing.[31,32]

Conclusions

To sum up, we have developed a second synthesis of the iminosugar DAB, which is shorter than our previous synthesis of this target, both starting from the same stable sugar ditriflates **8α** and **8β**.

As an additional example of the synthetical potential of sugar ditriflates, we have developed a new divergent synthesis of 1-deoxymannojirimycin (**4**) and the corresponding polyhydroxylated pipecolic acid **24**.The key step for the route leading to these targets involved a double displacement of sugar ditriflates **16αβ** by a primary amine, a process that was accompanied by the inversion of the configuration at C-2. This allowed to start from the cheap sugar D-glucose. An additional advantage this approach to **4** is that it is shorter than a previous synthesis of this target, which involved a sequential formation of the endocyclic C–N bonds.

Work is now in progress in order to extend this methodology to the preparation of other iminocyclopentitols and iminocyclohexitols, in order to establish the scope and limitation of this methodology for the access to iminosugars.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The experimental procedures, together with the ^{1}H, and ^{13}C NMR spectra for all compounds are available in the supplementary material of this article.

Keywords: Iminosugars · Pipecolic acids · Sugar diols · Stereoselective synthesis

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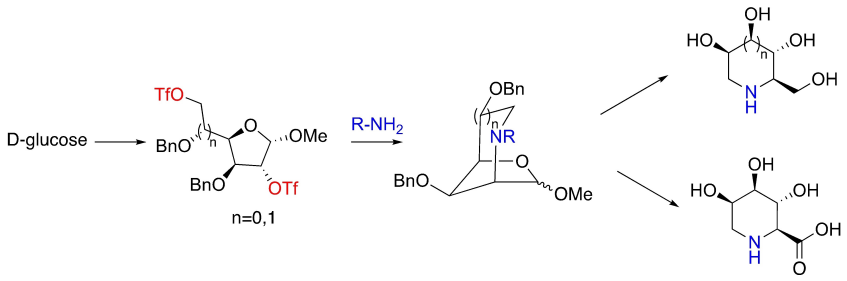

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