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Stereoselective synthesis of 3-glycosyl-5-methoxycarbonyl-isoxazolidines from D-galactose and D-glucose

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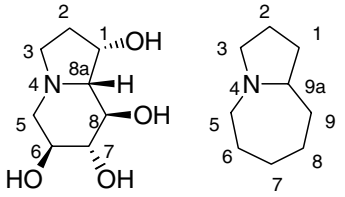
Abstract—Regio- and stereoselective cycloaddition of methyl acrylate to *C*-glycosyl nitrones derived from D-galactose and D-glucose, giving 5-methoxycarbonyl-3-(pentoglycos-5-yl or pentitol-1-yl)isoxazolidines, is reported. Transformation of one of them into a 4-hydroxy-2-(pentoglycos-5-yl)pyrrolidine derivative, potentially useful in a route to polyhydroxy-perhydroazaazulenes, was achieved.

Castanospermine (**1**) and other indolizidine derivatives are glycomimetics that show, among others, antimalarial, antiviral, immunosuppressor, and antidiabetic activities, probably as a consequence of their glycosidase inhibitory properties.[1,2] This is the main reason why many synthetic routes have been developed to obtain **1**,[1] as well as a diversity of stereoisomers and analogues of **1**,[3,4] since even a change of configuration at a single hydroxy group could alter the inhibitory properties.[4] Readily available monosaccharide derivatives have frequently been used[5] as starting materials to obtain this kind of compound, thus taking advantage from the configurational variety of sugars and their ability to exert asymmetric induction in the formation of new stereogenic centers.

It is known that, in the 1,3-dipolar cycloaddition of *C*-glycosyl nitrones, including cyclic nitrones, with diverse olefins, glycosyl-isoxazolidines are formed, a reaction that occurs with high regio- and stereoselectivity. We have reported the reactions of conveniently protected *C*-glycosyl nitrones, derived from D-galactose, D-xylose, and D-ribose, with nitroalkenes[6] and vinyl trimethylsilane,[7] in which *C*-glycosyl-isoxazolidines were regio- and stereoselectively obtained. In the case of vinyl trimethylsilane as the dipolarophile, the obtained cycloadducts were transformed into C_7 and C_8 aminodialdoses, direct precursors of higher-chain glycosamino acids.



A possible route to new potential glycosidase inhibitors derived from the perhydroazaazulene system (**2**), which can be considered as heterocyclic-system homologues of castanospermine and other related indolizidine derivatives, may start from the isoxazolidines that we obtained (Scheme 1) in the [3+2] cycloaddition reaction of the nitrones **3** and **4**, prepared from D-galactose and

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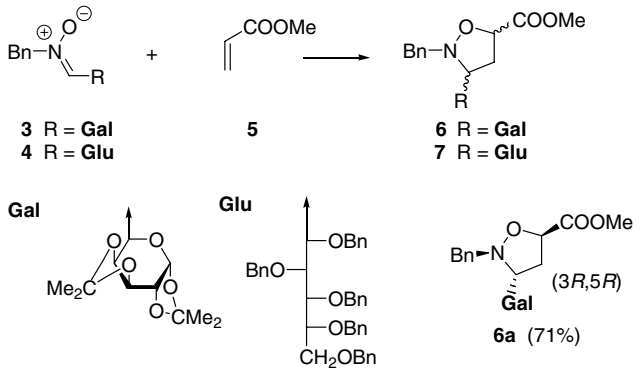


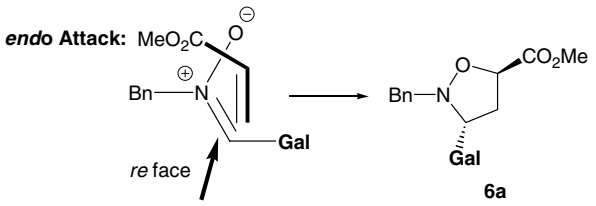
Scheme 1. Regioselective reaction of the nitrones **3** and **4** with methyl acrylate (**5**).

D-glucose derivatives, respectively, with methyl acrylate (**5**). This dipolarophile is known to react with nitrones very regioselectively, so that, with few exceptions, the unique, or at least the main, product is the 5-methoxycarbonyl regioisomer.[8,9] Aiming different target molecules, other authors have used the reaction of sugar nitrones with **5**; thus, the isoxazolidine obtained[10] from the *N*-benzyl-*C*-glycosyl nitrone derived from 2,3-*O*-isopropylidene-D-glyceraldehyde was used in a discussion about the structure of leptospherin. More recently, starting from a protected L-fucose-derived cyclic nitrone and methyl acrylate, some indolizidine derivatives have been obtained and their α-L-fucosidase inhibitory activity measured.[11]

The synthesis we report herein presents the novelty that the acyclic nitrones employed were hexose derivatives, which in their reaction with **5**, regio- and stereoselectively afforded isoxazolidines with a C_5 sugar chain at C(3) and the methoxycarbonyl group at C(5), so that subsequent intermediates having a long enough sugar chain, might undergo annellation to give polyhydroxyperhydroazaazulenes. The configurations of the isoxazolidine new stereogenic centers C(3) and C(5) would be transferred to C(9a) and C(2) of the perhydroazazulene, respectively.

The (*Z*)-*N*-benzyl-nitrone **3** was easily prepared as described,[6] while **4**, to our knowledge, has not been described. Therefore, we obtained **4** (52% yield, after column chromatography) by treatment of 2,3,4,5,6-penta-*O*-benzyl-*aldehydo*-D-glucose[12] with *N*-benzylhydroxylamine, following a procedure similar to that used[6] to obtain **3**. [Nitrone **4**: oil; HRCIMS: *m*/*z* 736.3631 (calcd for $C_{48}H_{49}NO_6$+H: 736.3638). Selected spectral data: ^{1}H NMR δ 6.90 (d, 1H, $J_{1,2} = 7.1$, *H*C=N); ^{13}C NMR δ 138.0 (H*C*=N)].

The reaction of **3** with **5** in toluene at 35 °C led with total regioselectivity to only one of the four possible diastereomeric 5-methoxycarbonyl-isoxazolidines, which was isolated as a crystalline compound and recrystallized (abs ethanol) [71%, mp 102–104 °C; $[\alpha]_D^{25} - 44$ (*c* 1.0, CH_2Cl_2)]; its X-ray crystallographic analysis[13] unambiguously showed its (2*R*,3*R*,5*R*) absolute configuration,



Scheme 2. Reagent approach leading to the diastereomer **6a**.

as formulated (**6a**, Scheme 1). Anal. Calcd for $C_{23}H_{31}NO_8$: C, 61.46; H, 6.95; N, 3.12. Found: C, 61.38; H, 6.78; N, 3.25. HRCIMS: *m*/*z* 450.2130 (calcd for $C_{23}H_{31}NO_8$+H: 450.2128).† From the C(3) and C(5) (*R*,*R*) configurations assigned for compound **6a**, both high *endo*/*exo* diastereoselectivity and *re*/*si* (nitrone **3**) facial diastereoselectivity were evidenced for the reaction (Scheme 2).

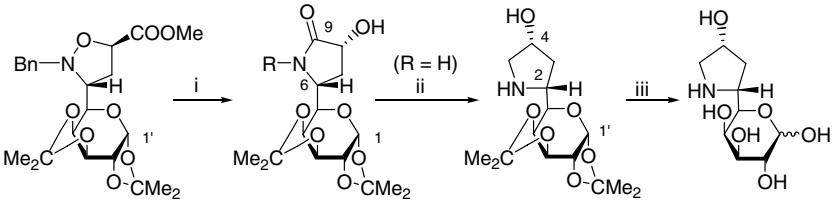
Scheme 3 summarizes the transformations performed on **6a**. Isoxazolidine-ring cleavage was achieved by treatment with hexacarbonylmolybdenum,[14,15] affording the 6-benzylamino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*threo* α-D-*galacto*-nonopyranosurono-9,6-lactam **7** and its *N*-deprotected derivative **8** in 18% and 62% yield, respectively, after column chromatography. Compound **7**: $[\alpha]_D^{20} - 50$ (*c* 2.7, $CHCl_3$).‡ Compound **8**: $[\alpha]_D^{20} - 16$ (*c* 1.0, $CHCl_3$).§ The mass spectral data agree with the presence of the benzyl group for **7** and its absence for **8**, also corroborated by the ^{1}H and ^{13}C NMR spectra.

The carbonyl group of **8** was reduced by the action of lithium aluminum hydride to give (2*R*,4*R*)-4-hydroxy-2-

† Selected spectral data for **6a**: IR (KBr) ν_{max} 1753 cm^{-1} (ester C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (locant numerals for the sugar moiety are maintained, but primed, such as for the starting sugar derivative) 5.48 (d, 1H, $J_{1',2'} = 5.0$, H-1′), 4.48 (dd, 1H, $J_{4a,5} \approx J_{4b,5} = 8.4$, H-5), 3.76 (s, 3H, MeOCO), 3.66 (m, 1H, H-3), 3.56 (dd, 1H, $J_{3,5'} = 9.9$, H-5′), 2.86 (ddd, 1H, $J_{4a,4b} = 12.3$, $J_{3,4a} = 1.7$, H-4a), 2.62 (ddd, 1H, $J_{3,4b} = 7.0$, H-4b); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.0 (*C*OOMe), 96.4 (C-1′), 77.0 (C-5), 66.6 (C-5′), 63.8 (C-3), 52.2 (COO*Me*), 34.0 (C-4). HRCIMS: *m*/*z* 450.2130 (calcd for $C_{23}H_{31}NO_8$+H: 450.2128).

‡ Selected spectral data for **7**: IR (KBr) ν_{max} 1686 cm^{-1} (amide C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.12 (m, 5H, Ph), 5.55 (d, 1H, $J_{1,2} = 5.2$, H-1), 5.18, 3.96 (each d, each 1H, $J_{gem} = 15.1$, CH_2Ph), 4.27 (dd, 1H, $J_{7a,8} = 6.8$, $J_{7b,8} = 5.2$, H-8), 3.98 (dd, 1H, $J_{5,6} = 3.4$, H-5), 3.72 (br m, 1H, HO), 3.60 (ddd, 1H, $J_{6,7a} = 5.1$, $J_{6,7b} = 7.1$, H-6), 2.29 (m, 2H, 2H-7); NOE contacts (1D NOESY): H-6, H-5, H-4, H-8; H-8, HO, H-6; HO, H-8, H-1; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.2 (*C*=O), 135.9 (*ipso*-C of Ph), 128.6, 127.6, 127.4 (Ph), 96.4 (C-1), 69.5 (C-8), 64.7 (C-5), 55.3 (C-6), 43.8 (*C*H$_2$Ph), 30.0 (C-7). HRCIMS: *m*/*z* 420.2008 (calcd for $C_{22}H_{29}NO_7$+H: 420.2022).

§ Selected spectral data for **8**: IR (KBr) ν_{max} 1707 cm^{-1} (amide C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (br s, 1H, NH), 5.49 (d, 1H, $J_{1,2} = 5.0$, H-1), 4.24 (m, overlapped signal, H-8), 3.68 (dd, 1H, $J_{5,6} = 2.3$, H-5), 3.68 (m, overlapped signal, H-6), 3.34 (br m, 1H, HO), 2.62 (m, 1H, H-7a), 1.98 (m, 1H, H-7b); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.4 (*C*=O), 96.0 (C-1), 70.5 (C-5), 69.1 (C-8), 51.1 (C-6), 33.5 (C-7). HREIMS: *m*/*z* 329.1475 (calcd for $C_{15}H_{23}NO_7$: 329.1475).



Scheme 3. Reagents and conditions: (i) $Mo(CO)_6$, $MeCN/H_2O$, reflux; (ii) $LiAlH_4$; (iii) 80% TFA.

(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)pyrrolidine (**9**) in 96% yield, after column chromatography. Compound **9**: $[\alpha]_D^{20} - 30$ (*c* 1.0, $CHCl_3$).[¶] The HRCIMS data were in agreement with its structure, also corroborated by the absences of any carbonyl IR band and ^{13}C signal (NMR spectrum).

Compounds **7** and **8** should keep the (6*R*,8*R*) configuration, coming from that of isoxazolidine C(3) and C(5) atoms, respectively. No epimerization at C(3) of **6a** is to be expected, so that **7** and **8** must have the (6*R*) configuration. However, the C(5) of **6a** might have undergone epimerization. For compound **7**, the C(6)H/C(8)H and C(8)H/C(6)H contacts (1D NOESY experiments) and the absence of HO/C(6)H and C(6)H/OH contacts are in agreement with a 6,8-*cis* relationship, and therefore corroborate the expected (8*R*) configuration. The overlapping between some signals in the ^1H NMR spectrum of **8** did not allow us to perform similar 1D NOESY experiments, but it was possible for its reduction product **9**, for which the C(3a)H/C(2)H, C(3a)H/C(4)H, C(5b)H/C(2)H, and C(5b)H/C(4)H contacts observed as well as the absence of both C(3b)H/C(2)H and C(3b)H/C(4)H contacts indicate the 2,4-*cis* relationship again, so that the (2*R*,4*R*) configuration is assigned for **9** and (6*R*,8*R*) for **8**.

Deprotection of **9** with aqueous 80% trifluoroacetic acid almost quantitatively yielded (2*R*,4*R*)-4-hydroxy-2-(α-D-*galacto*-pentopyranos-5-yl)pyrrolidine (**10**, 98%), after cation-exchange chromatography; it showed mutarotation: $[\alpha]_D^{20} - 7$ to -43.6 (24 h; *c* 0.3, MeOH), in agreement with its hemiacetal structure, and high-resolution mass spectrometry corroborated the loss of both isopropylidene protecting groups.[**]

Some conformational features for **6a** and its derivatives (**7**–**10**) can be deduced from the spectral data. Thus, the C(5′)H/C(azol ring)H coupling constant takes the values 9.9, 3.4, 2.3, 6.5, and 10.0 Hz, respectively, for **6a**, **7**, **8**, **9**, and **10**; among them, first and last high values are indicative of a preferential *anti* relationship in solution between these protons (compounds **6a** and **10**), while for compounds **7** and **8**, the low values of *J* suggest that these protons have a preferential *gauche* relationship in solution, and the medium *J* value for **9** may indicate no conformational preference in solution.

In view of the foregoing, fairly good results, we planned to extend the 1,3-cycloaddtion reaction with the same dipolarophile **5** to the nitrone **4**, which has a primary hydroxy group at the terminal carbon atom, and thus should allow us to save a reduction step of the synthetic route to polyhydroxy-perhydroazazulenes. A first assay of its reaction with **5** at 50 °C led to a mixture of products. Two diastereomeric 3-(penta-*O*-benzyl-D-*gluco*-pentitol-1-yl)isoxazolidines (**11a**[††] and **11b**[‡‡]) were

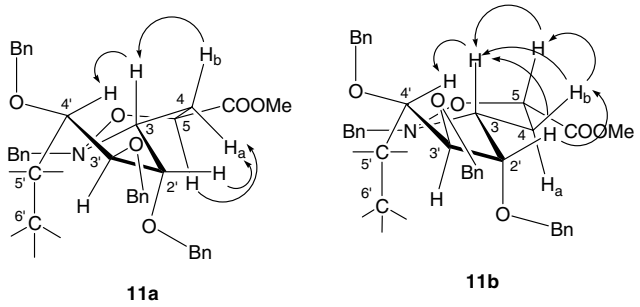
[¶] Selected spectral data for **9**: IR (KBr) ν_{max} 3183 (OH and NH), and 1067 cm^{-1} (C–OH); ^1H NMR (300 MHz, $CDCl_3$) δ (locant numerals for the sugar moiety are maintained, but primed, such as for the starting sugar derivative) 5.51 (d, 1H, $J_{1',2'} = 5.0$, H-1′), 4.27 (m, overlapped signal, H-4), 3.70 (dd, 1H, $J_{2,5'} = 6.5$, H-5′), 3.34 (ddd, 1H, $J_{2,3a} = 9.2$, $J_{2,3b} = 5.4$, H-2), 2.95 (ddd, 1H, $J_{5a,5b} = 11.3$, $J_{4,5a} = 1.8$, $^4J_{3b,5a} = 1.8$, H-5a), 2.82 (dd, 1H, $J_{4,5b} = 4.1$, H-5b), ~2.5 (br s, 2H, NH and OH), 2.14 (ddd, 1H, $J_{3a,3b} = 14.6$, $J_{3a,4} = 5.8$, H-3a), 1.83 (dddd, $J_{3b,4} = 5.2$, H-3b); NOE contacts (1D NOESY): H-3a, H-2, H-4; H-2, H-3a, H-5b, H-5′, H-4′; H-5b, H-2, H-4; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 96.3 (C-1′), 71.9 (C-4), 70.2 (C-5′), 56.9 (C-2), 55.2 (C-5), 37.7 (C-3). HRCIMS: *m*/*z* 316.1757 (calcd for $C_{15}H_{25}NO_6$+H: 316.1760).

[**] Selected spectral data for **10**: IR (KBr) ν_{max} 3396 (OH and NH) and 1094 cm^{-1} (C–OH); ^1H NMR (500 MHz, CD_3OD) δ 4.77 (d, 1H, $J_{1',2'} = 6.0$, H-1′), 4.43 (dddd, 1H, $J_{3a,4} = 5.5$, $J_{3b,4} = 4.5$, $J_{4,5a} = 7.5$, $J_{4,5b} = 7.0$, H-4), 3.77 (dd, 1H, $J_{2,5'} = 10.0$, H-5′), 3.18 (dd, 1H, $J_{5a,5b} = 9.5$, $J_{4,5a} = 7.5$, H-5a), 3.06 (dd, 1H, $J_{4,5b} = 7.0$, H-5b), 3.00 (ddd, 1H, $J_{2,3a} = 8.5$, $J_{2,3b} = 2.5$, H-2), 2.35 (ddd, 1H, $J_{3a,3b} = 14.0$, H-3a), and 1.75 (ddd, 1H, H-3b); ^{13}C NMR (75.4 MHz, CD_3OD) δ 90.2 (C-1′), 71.4 (C-4), 68.4 (C-5′), 59.6 (C-2), 58.1 (C-5), and 39.2 (C-3). HRFABMS: *m*/*z* 258.0953 (calcd for $C_9H_{17}NO_6$+Na: 258.0954).

[††] Selected spectral data for **11a**: IR (film) ν_{max} 1751 cm^{-1} (ester C=O); ^1H NMR (500 MHz, $CDCl_3$) δ (locant numerals for the sugar moiety are maintained, but primed, such as for the starting sugar derivative) 4.38 (dd, 1H, $J_{4a,5} = 8.7$, $J_{4b,5} = 7.6$, H-5), 3.93 (dd, 1H, $J_{4',5'} \approx J_{3',4'} \approx 5.0$, H-4′), 3.73 (dd, 1H, $J_{2',3'} \approx J_{3',4'} \approx 5.0$, H-3′), 3.72 (s, 3H, COOMe), 3.68 (overlapped signal, 1H, H-2′), 3.39 (ddd, 1H, $J_{3,4a} = 3.8$, $J_{3,4b} = 7.7$, $J_{2',3} \approx 0$, H-3), 2.78 (ddd, 1H, $J_{4a,4b} = 12.7$, H-4a), and 2.46 (ddd, 1H, H-4b); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.9 (*C*OOMe), 78.5 (C-2′), 76.7 (C-5), 67.2 (C-3), 52.1 (COO*Me*), and 33.5 (C-4). HRCIMS: *m*/*z* 822.3989 (calcd for $C_{52}H_{55}NO_8$+H: 822.4006).

[‡‡] Selected spectral data for **11b**: IR (film) ν_{max} 1753 cm^{-1} (ester C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (overlapped signal, 1H, H-5), 3.99 (dd, 1H, $J_{3',4'} = 4.9$, $J_{4',5'} = 5.0$, H-4′), 3.89 (dd, 1H, $J_{5',6'a} = 3.7$, $J_{6'a,6'b} = 9.8$, H-6′a), 3.82 (dd, 1H, $J_{2',3'} = 1.4$, H-3′), 3.77 (dd, 1H, $J_{2',3} = 3.7$, H-2′), 3.73 (s, 3H, COOMe), 3.12 (ddd, 1H, $J_{3,4a} = 5.0$, $J_{3,4b} = 8.6$, H-3), 2.85 (ddd, 1H, $J_{4a,4b} = 13.0$, $J_{4a,5} = 3.7$, H-4a), and 2.61 (ddd, 1H, $J_{4b,5} = 9.9$, H-4b); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 77.7 (C-2′), 74.8 (C-5), 67.7 (C-3), 51.8 (COO*Me*), and 33.6 (C-4). HRCIMS: *m*/*z* 822.3995 (calcd for $C_{52}H_{55}NO_8$+H: 822.4006).

isolated as oils in 6.9% and 9.0% yield, respectively, after column chromatography. This poor yield of cycloadducts may be a consequence of the cycloaddition reversibility or of the lower reactivity of **4** as compared with **3**; nitrone decomposition gave appreciable amounts of the α,β-unsaturated aldehyde **12**, which was isolated in 7.2% yield. Other fractions eluted from the column were a mixture of **11a** and **11b** (4.6%), and a mixture of the starting nitrone and decomposition products (~33%). Configurational assignment for **11a** and **11b** was made on the basis of coupling constant values and, in particular, the NOE contacts (1D NOESY) observed. For the former compound, NOE contacts were observed, on the one hand between C(3)H and C(4)Hb, and on the other hand between C(4)Ha and C(5)H; hence, C(3)H and C(5)H should have a *trans* relationship with regard to the isoxazolidine ring, such as that shown in the formulae **11a** and **11d**. In order to discriminate between both formulae, the C(4)Ha/C(2′)H and C(3)H/C(4′)H contacts were considered, as well as the following coupling constant values: C(2′)H/C(3)H (≈0 Hz), C(2′)H/C(3′)H (≈5.0 Hz), and C(3′)H/C(4′)H (≈5.0 Hz); molecular models for **11a** and **11d** indicated that the best agreement with the foregoing observations corresponded to **11a** (Scheme 4). For the latter diastereomer, C(3)H and C(5)H should have a *cis* relationship, such as that shown in **11b** and **11c**, as deduced from the C(3)H/C(5)H, C(3)H/C(4)Hb, and C(4)Hb/C(5)H NOE contacts observed, while the assignment of one of these structures for it was decided taking into account the C(3)H/C(2′)H and C(3)H/C(4′)H contacts and the following coupling constant values: C(2′)H/C(3)H (3.7 Hz), C(2′)H/C(3′)H (1.4 Hz), and C(3′)H/C(4′)H (4.9 Hz); molecular models evidenced the best agreement of **11b** with these data (Scheme 4). No conclusion about regio- and stereoselectivity can be deduced for the cycloaddition reaction of **4** with **5** from the experimental data obtained in this first assay. However, the isolated products **11a** and **11b** are configurationally pure, thus making encouraging the search for better reaction conditions to increase the yields.



Scheme 4. NOE (1D NOESY) contacts for **11a** and **11b**.

In conclusion, the high stereoselectivity observed in the cycloaddition reaction of the nitrone **3** with methyl acrylate leading to a sole diastereomer of cycloadduct in good yield, is a very convenient feature to undertake a synthetic route toward stereochemically pure polyhydroxy-perhydroazaazulene derivatives, ring homologues of known, glycosidase inhibitor polyhydroxy-indolizidines, such as castanospermine (**1**). The here reported transformations of **6a**, leading to the partially protected, configurationally pure 4-hydroxy-2-(pentopyranos-5-yl)pyrrolidine **9** and its completely deprotected derivative **10**, will be used as a main part of such synthetic route. Subsequent steps will imply reduction of the potential aldehydic function to primary alcohol, transformation of the new hydroxyl group in a good leaving group, and annellation by nucleophilic attack of the pyrrolidine N atom. Previous protection of the amino function could be necessary. With regard to the reaction of nitrone **4** with **5**, we are now working on the optimization of conditions to achieve a substantial enhancement of yield, since the stereochemically pure products **11a** and **11b** should lead, after a similar sequence of synthesis, to pure diastereomeric 4-hydroxypyrrolidines having a primary alcohol function at the end of the sugar chain.

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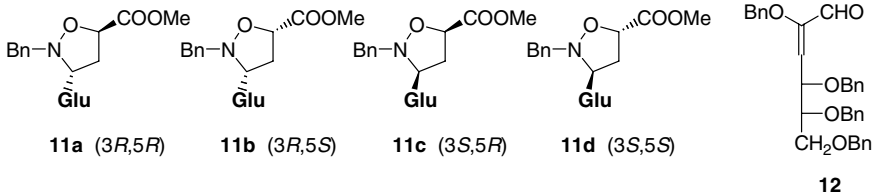

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