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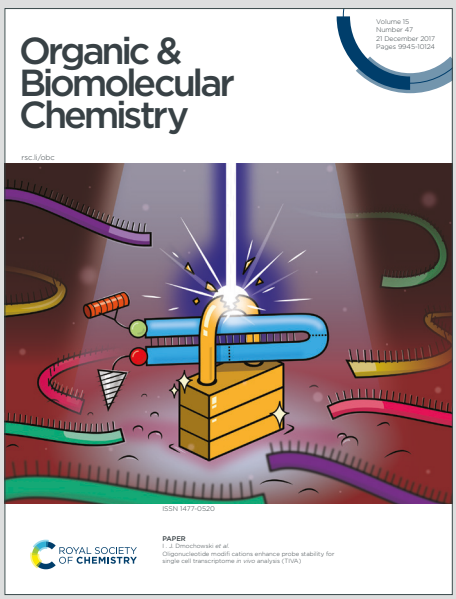

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RESEARCH ARTICLE

Selective Functionalization of the 1,6-Anhydro Moiety and of the Double Bond of Levoglucosenone

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Through a very efficient, step-economical (only 4 steps) and diastereoselective-chemoselective procedure, bio-based levoglucosenone has been converted into a versatile azide, which may be regarded as a synthetic equivalent of a 6-amino-6-deoxysugar. This procedure involves: a) reduction of the ketone of LGO; b) opening of the 1,6-anhydro moiety with acetic anhydride and a protic acid to give a triacetate; c) biocatalytic deacetylation of the primary alcohol; d) substitution of the alcohol with the azide. The overall yield from LGO is 59%. This azide has been employed in two diversity-generating protocols: Huisgen-Sharpless 1,3-dipolar cycloaddition with alkynes (also derived from bio-based phenols), and the Ugi multicomponent reaction. Furthermore, the double bond has been dihydroxylated with nearly complete diastereoselection both at the azide level or on the triazoles derived from Huisgen cycloadditions, furnishing compounds with the rare D-*altro* configuration. The chemistry described in this work may help in devising synthetic applications of levoglucosenone, a densely functionalised product of pyrolysis of lignocellulosic matter.

Introduction

Nowadays, oil is the main source of fine chemicals, but it is a non-renewable carbon source, destined to end by 50-100 years. Therefore, renewable biomass is entitled to become the oil of the future.[1] However, until now, it has been mainly used for the production of high volume, low value chemicals (polymers, solvents),[2] whereas its exploitation for the synthesis of more complex fine chemicals,[3] also through a diversity-oriented approach,[4] is still relatively underexplored. In this context, during the last years, our research group has studied the use of various bio-based derived components in multicomponent reactions such as the Passerini,[5-7] the Ugi,[8, 9] the Ugi-Joullié,[10] and the Hosomi-Sakurai[11] reactions.

Building blocks from biomass are often very challenging from the point of view of organic synthesis, being densely functionalized. On the other hand, they may offer the advantage to be chiral and enantiomerically pure. One such example is levoglucosenone **1** (LGO)[12] (Scheme 1). LGO is the main product of acid catalysed pyrolysis of cellulose containing products, including low value materials such as waste or lignocellulosic matters.[13-16] If one consider that 180 billion tons of non-food lignocellulosic biomass are produced annually, the potential of LGO as starting material is very high.

Several transformations (including total syntheses)[17] have been accomplished starting from this building block,[12, 18] and its derivatives have been often employed in the field of drug discovery.[19] Anyway, we think that there is still ample room for further investigation. In particular, to our knowledge, only one example of multicomponent reaction has been reported so far on LGO (or better on its saturated derivative).[20] Thus, at the outset of this work, we wanted to study new possible applications of MCRs or other diversity generation processes, such as the azide-alkyne cycloaddition ("click" reaction),[21, 22] employing this bio-based building block.

Results and discussion

As shown in Scheme 1, our initial project involved ring-opening of the bicyclic acetal of **1** with isocyanides or other *C*- or *O*-nucleophiles, to give polyfunctionalised building-blocks **6** or **7**. Before opening the bicyclic acetal, we chose to convert LGO **1** into the corresponding alcohol **2**. Although this process, using Luche's reduction,[23] was already described,[24, 25] in our hands the reported work-up conditions turned out to be not user-friendly. Because of the hydrophilicity of **2**, the standard aqueous work-up involved indeed many extractions, leading anyway to a significative loss of product. We eventually found out that the best procedure involves quenching with solid citric acid followed by filtration through celite, evaporation, and direct chromatography.[26] In this way alcohol **2** could be obtained in 90% yield and 94:6 diastereomeric ratio. The minor diastereomer (slower running in TLC) is slightly separated and thus we were able to obtain **2** in up to 98:2 d.r. by

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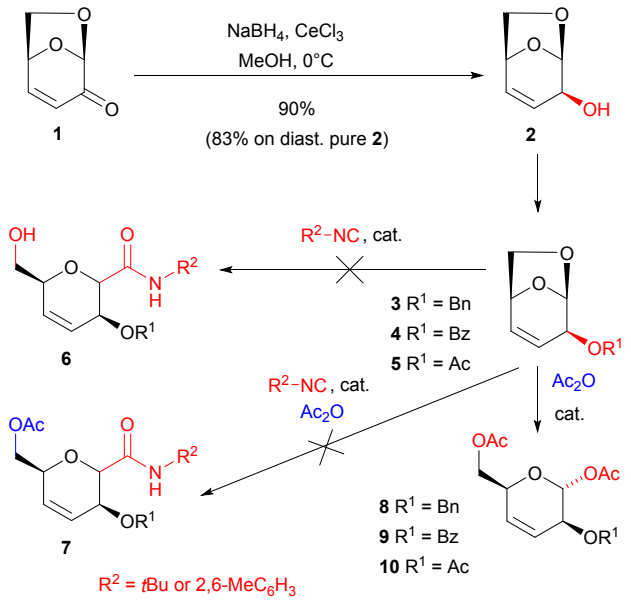
chromatography. This alcohol was protected to give known compounds **3**,[27] **4**,[27] and **5**.[26]



Scheme 1. Initial strategy

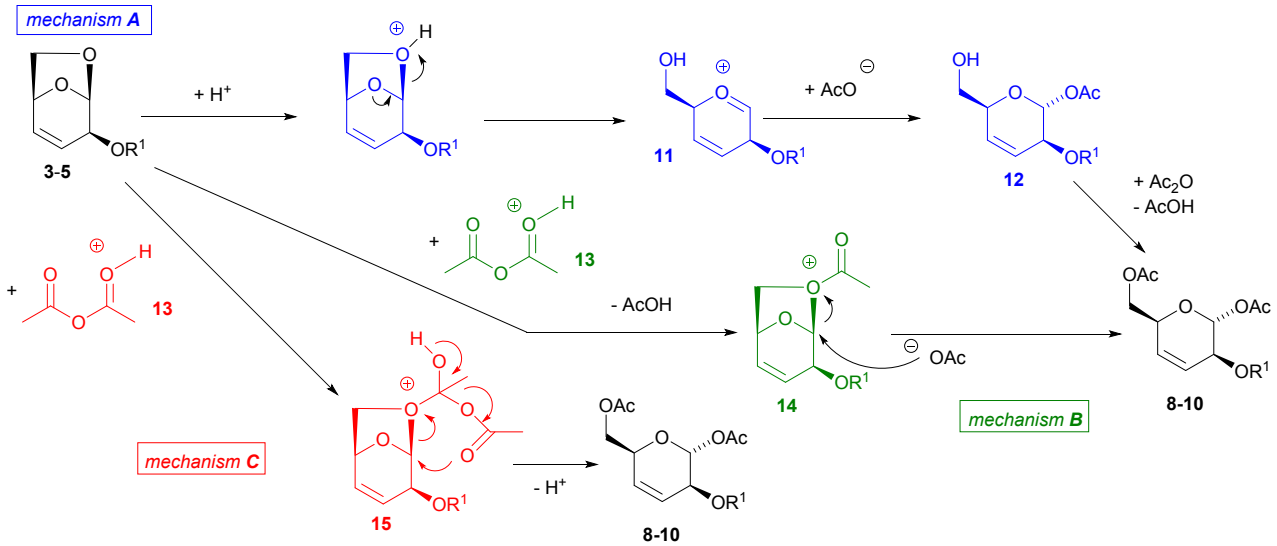
On these protected compounds, we investigated the possible reaction with isocyanides, under the catalysis of Lewis acids or TMS-OTfn (trimethylsilyl trifluoromethanesulphonate).

Although very few examples of reactions of isocyanides with acetals are reported in the literature,[28-30] we hoped to be able to open the bicyclic system introducing a new C-C bond in order to obtain interesting *C*-glycosides containing a secondary amide function. A search in the literature revealed very few examples regarding opening of **2** or its protected derivatives with *O*-nucleophiles,[31-33] and none with *C*-nucleophiles.

However, as better described in the S.I., despite several attempts, we never succeeded in introducing isocyanides as nucleophiles onto protected derivatives **3**-**5**. During these attempts, we reasoned that this failure might be due to reversible additions of the isocyanides and that trapping the liberated primary alcohol in **6** could be beneficial. Hoping to be able to obtain adducts **7**, we thus added Ac_2O to the reaction mixture. To our surprise, starting from **4**, and using TMS-OTf or Lewis acids as catalysts, we isolated, with excellent diastereoselectivity (> 10:1), diacetate **9.** The same result was obtained with protic acids. This was somehow unexpected, because, in standard Passerini reactions, it is always the isocyanide to act as the nucleophile, and not the carboxylate anion.

Scheme 2 show possible mechanisms of this opening reaction with Ac_2O. For the sake of clarity, protic catalysis is shown, but similar mechanisms can be envisaged using Lewis acids or TMSOTf. In mechanism A, the acid promotes opening of the ring to give oxocarbenium ion **11**, which may be attacked by a nucleophile. This mechanism does not seem very likely to us. First of all, we do not understand why **11** should not be attacked by the isocyanide, but by the carboxylate anion instead. Then, addition of acetate anion does not improve the process. Free alcohol **12** was never detected. Finally, according to this mechanism, the reaction should be poorly stereoselective or even give the other stereoisomer, as in other reported acid-catalysed opening of LGO with *O*-nucleophiles.[33]

Other possible mechanisms are B or C, where acylation of the bridge oxygen precedes the opening of the ring. In mechanism B, an intermolecular substitution by the acetoxy anion either through a S_N1 (*via* oxocarbenium ion) or S_N2 process should then take place. Once again, it is not clear why other added nucleophiles, such as isocyanides, do not participate.



Scheme 2. Possible mechanisms for conversion of **3**-**5** into **8**-**10**. Similar mechanisms may be envisaged using a Lewis acid or TMSOTf.

Thus, we think (although we do not have definitive proofs about that) that the reaction may proceed through the concerted mechanism C, with simultaneous entrance of both acetoxy groups starting from cation **15**. This mechanism, involving a 6-membered cyclic T.S., may also explain the high diastereoselectivity observed, and the preferred diastereomer.

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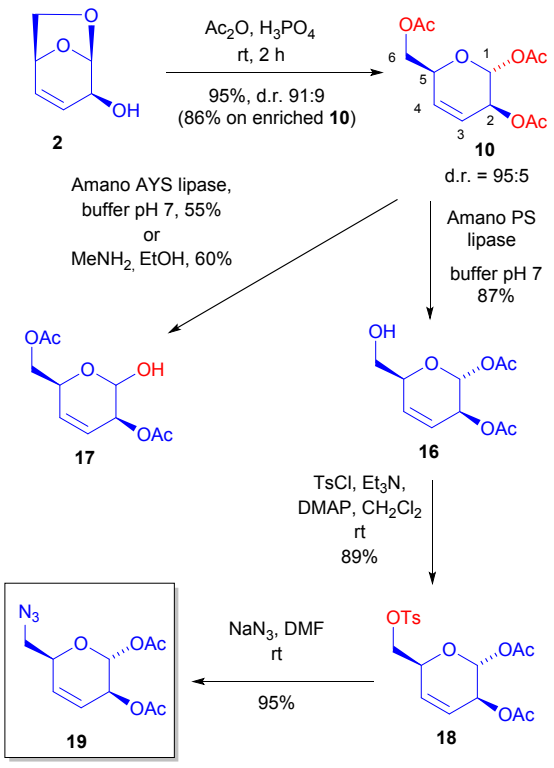
Reactions passing through an oxocarbenium ion should be less stereoselective (or even favour the other isomer), [33] and d.r.s should strongly depend on the nature of protecting group (because of anchimeric assistance), whereas in our case we did not observe significant differences.

Apart from the mechanistic rationalisations, we reasoned that diacetates **8**-**9** or triacetate **10** could be useful building blocks for diversity-oriented processes using glycomimetic fragments. This opening reaction was thus optimized (see S.I.). To make a long story short, we eventually found that: a) protic acids, especially phosphoric acid, behave better than Lewis acids or TMSOTf, being also more sustainable; b) previous protection of the allylic alcohol was not really necessary, and the reaction could be carried out directly on alcohol **2**, affording triacetate **10** in just 2 steps from LGO, with nearly complete stereocontrol for the stereocenter at position 1 (sugar numbering).

Although in this way we obtained a triacetate, we were confident to be able to differentiate the three groups by chemoenzymatic means. This was indeed the case. After screening various lipases, we found out that Amano P lipase was highly chemoselective, allowing hydrolysis of the primary acetate in **10** to give **16** (Scheme 3). Other enzymes (see S.I.) were less selective, whereas Amano AYS lipase preferred to hydrolyse the anomeric acetate to give **17**. Selective hydrolysis of the latter can be also achieved chemically, using $MeNH_2$ in EtOH.



Scheme 3. Conversion of triacetate **10** into azide **19.**

Thus alcohol **16** could be obtained in just three steps from LGO **1**, in overall 62% yield, and with an operationally simple and "green" procedure.

In order to get a nitrogen containing building block, we then converted **16** into azide **19**, through the tosylate **18**, by a classical S_N2 substitution.

A comment on diastereomeric purity of alcohol **16**, tosylate **18** and azide **19** is worthy. We started from nearly pure (d.r.: 98:2) alcohol **2** and performed diastereoselective opening to **10** (91:9) and finally chemoselective enzymatic hydrolysis to **16**. These two last steps are highly, but not completely, selective and thus small amounts of isomers could be present. These could be eliminated by careful chromatographies at the level of **10**, **16** and **19**. However, tosylate **18** is a white solid, and we found out that, working on a larger scale, it is also possible to be less accurate in chromatography of intermediates, since a single trituration at the level of **18** can afford a very pure compound.

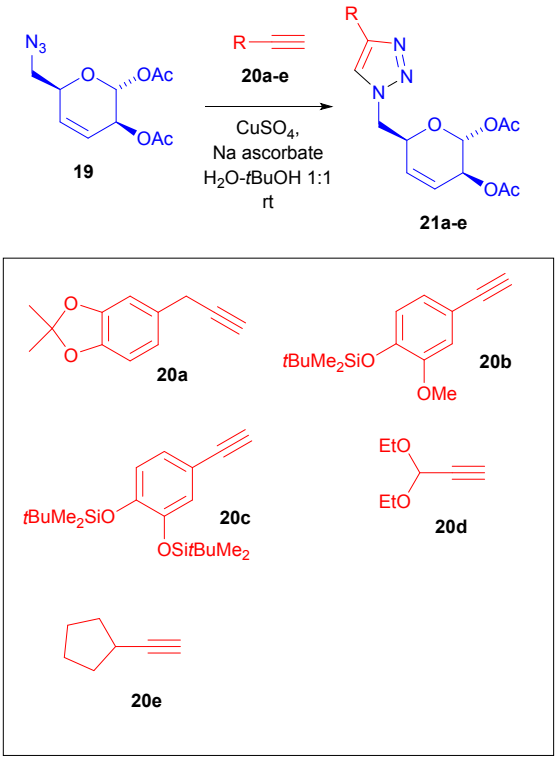
Azide **19** may be considered a synthetic equivalent of a 6-aminosugar, taking into account the possibility to convert the double bond into a diol, as described below. Although quite rare, 6-aminosugars are endowed with interesting biological activities.[34-36]

As a first application we employed azide **19** in a series of 1,3-dipolar cycloadditions with alkynes ("click" reactions).[21]. The alkynes used are shown in Scheme 4, whereas the results are listed in Table 1. As already previously observed by us in another work,[37] when using very small amounts of catalysts (0.01 equivalents of $CuSO_4$ and 0.1 equivalents of Na ascorbate) (see Table 1), these 1,3-dipolar cycloadditions tended to stop, probably because of inactivation of Cu(I). Therefore, initially we used to add a second or even a third portion of both catalysts when the reaction appeared to stop. [37] In the last experiments, we preferred to add a higher catalyst quantity (especially ascorbate) from the beginning in order to have more complete reactions.

In these click reactions, we have also used some alkynes containing the catechol structure typical of natural polyphenols. In order to gain access to hybrid peptidomimetics-glycomimetics, we also decided to employ azide **19** in Ugi multicomponent reactions.[38, 39] Our idea was to use azide **19** as a synthetic equivalent of a primary amine.

In the literature there are some examples[40-42] of one-pot Staudinger-aza-Wittig-Ugi sequence, where an azidoaldehyde is first reduced by a phosphine (Staudinger reduction) to form a phosphazene, followed by an intramolecular aza-Wittig reaction affording a cyclic imine. Finally, the latter is the substrate of a 3-component Ugi-Joullié reaction.

However, this protocol was always applied to azidoaldehydes, in an intramolecular way. We tried to transfer the same approach to an intermolecular process, thus applying a true 4-component Ugi reaction. We were pleased to find out that this was indeed possible, by treating azide **19** with PPh_3 in the presence of an aldehyde, followed by addition of an isocyanide and of a carboxylic acid. A series of Ugi products, shown in Scheme 5, were obtained. Unfortunately, diastereoselectivity was very low, as usual for this MCR, giving nearly 1:1 mixture of the possible diastereomers.



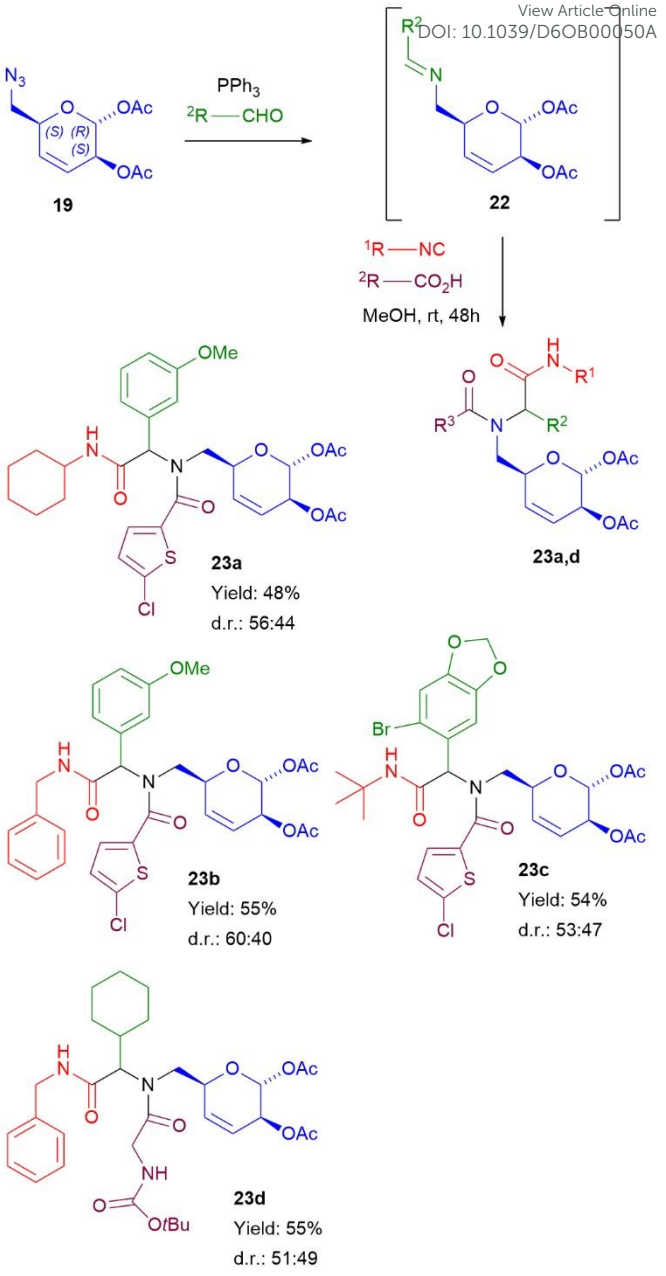
Scheme 4. Click reactions starting from azide **19**

Table 1. Synthesis of triazoles **21**[a]

Alkyne	Triazole	Cat. amount (Ascorbate / $CuSO_4$)	Reaction time[b]	Yield[c]
20a	**21a**	0.1/0.01 equiv. x 2	4h + 1h	65%
20b	**21b**	0.1/0.01 equiv. x 2	3h + 2h	66%
20c	**21c**	0.1/0.01 equiv. x 2	2h + 1h	90%
20d	**21d**	0.1/0.01 equiv. x 3	2h + 2h + 1h	84%
20e	**21e**	0.5/0.2 equiv.	4 h	93%

[a] Conditions: azide **19** and alkyne **20** (1.2 equiv.) were treated, in *t*-BuOH/H_2O 1:1, at rt, with the indicated equiv. of Na ascorbate and of $CuSO_4$. The same amount of catalysts was added after the first time indicated in column 4. In some cases a third addition of catalysts was necessary. [b] For example (line 1), 4h + 1h means 4h, followed by a second addition of catalyst and then further reaction for 1h. [c] Isolated yields.

When using an aliphatic aldehyde (cyclohexanecarboxaldehyde to give **23d**) we surprisingly observed at the end of the process, the presence of starting azide **19**, notwithstanding the fact that PPh_3 was used in excess. We reasoned that the aldehyde could somehow inhibit the reduction of the azide. Therefore, in this case, we repeated the reaction treating the azide with PPh_3 before addition of the aldehyde and the yield was improved from 40% to 55%.

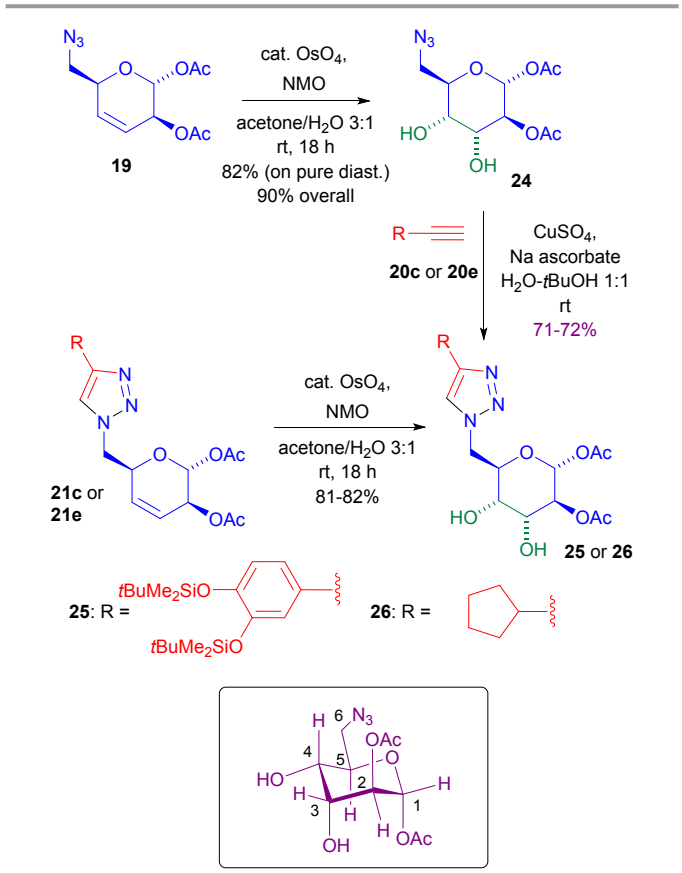


Scheme 5. Ugi reactions starting from azide **19**

In all the products shown in Schemes 4 and 5, the double bond of starting levoglucosenone is still present. This double bond can be seen as a synthetic equivalent of a diol. In order to prove this synthetic equivalence, we studied dihydroxylation of azide **19** using catalytic OsO_4 (3%) in the presence of stoichiometric *N*-methylmorpholine-*N*-oxide (NMO) (Scheme 6). With our surprise, this dihydroxylation was found to be highly diastereoselective and we could isolate diol **24** as a single diastereomer after chromatography. Careful examination of the crude and of some head fractions of chromatography allowed to detect two possible isomers, in quantities around 5% and 3%, relative to the major isomer. Osmium catalysed hydroxylation is known to be stereospecific and thus we were a little surprised

by the presence of two isomers. Due to the very low amount of them it was not possible to understand their structure.

Anyway, the relative stereoinduction of the two *cis* diols is higher than 20:1, the yield is high and **24** can be easily isolated in pure form by chromatography. The relative configuration of this major product was easily assessed by examination of the coupling constants in ^{1}H NMR, which were compatible only with the $^4C_1$ conformation of the *altro* diastereomer, shown in Scheme 6 (sugar numbering). In particular, there is a $J_{4\text{-}5}$ equal to 9.7 Hz, indicating that *H*-4 and *H*-5 are both axial and *trans* to each other. On the other hand, $J_{3\text{-}4}$ and $J_{2\text{-}3}$, respectively 3.5 and 3.3 Hertz are in agreement with a *cis* (3-4) or a *trans* diequatorial (2-3) relationship. Neither conformation of the *talo* isomer fit with these coupling constants, because *H*-4 and *H*-5 would be *cis* and thus $J_{4\text{-}5}$ would be around 3 Hz. The preference for the $^4C_1$ conformation may be ascribed to the α effect. Although highly diastereoselective dihydroxylation of levoglucosenone from the bottom face is known,[24, 43] in that case the bridge causes a much higher shield of the upper face than in the case of **19** and thus this very high diastereoselectivity was unexpected to us.



Scheme 6. Highly diastereoselective dihydroxylation of azide **19** and triazoles **21**.

Compound **24** has the relative and absolute configuration of α-D-*altro*pyranose, a very rare sugar. Therefore, this building block may be very useful for the "click" assembly of glycomimetics having this unusual relative configuration.

Hydroxylated azide **24** was used in 1,3-dipolar cycloaddition with alkynes **20c** and **20e** to give triazoles **25**, **26**, which were isolated as pure diastereomers. Alternatively, triazoles **21c** and **21e** may be dihydroxylated, again with high diastereoselection, to afford the same *altro* derivatives **25**, **26**. In the case of **21c**, we obtained a d.r. of 98:2, whereas, with **21e**, stereoinduction was slightly lower (93:7). In these cases, a third isomer was again present, but in very little amount (< 1%).

Conclusions

In conclusion, we have developed an efficient transformation of levoglucosenone into azide **19**, which may be considered an useful building block for diversity-oriented synthesis of complex molecule containing a fragment corresponding to a 6-aminosugar. Azide **19** was synthesized thanks to a highly diastereoselective opening of the bridge with acetic anhydride and protic acids, followed by an enzymatic differentiation of the hydroxy group at carbon 6.

The suitability of azide **19** in diversity-oriented synthesis was demonstrated by a series of click reactions or of Ugi reactions starting from it.

We also demonstrated the synthetic equivalence of the double bond of levoglucosenone with a diol, by an OsO_4 catalysed dihydroxylation.

The use of azide **19** in Ugi and click reactions demonstrates its synthetic equivalence with rare 6-deoxy-6-aminosugars.[34-36] There are indeed very few examples of this kind of sugars in the literature, and none with the particular D-*altro* configuration that can be achieved by osmylation. While 1-aminosugars have been previously used as component in the Ugi reactions,[44] to our knowledge no example of use of 6-aminosugars in MCRs is known.

From the stereochemical point of view, it is worth noting that a series of 3 highly diastereoselective transformations has allowed to convert LGO (only 2 chirality centers) into stereopure compounds **24**-**26** (5 chirality centers).

Author Contributions

Conceptualization: LB, RR. Funding acquisition: LB, RR. Resources: CL. Data analysis: CL, LB, RR. Investigation: MR, JC, FR, DK. Supervision: CL, LB. Writing of draft: LB. Writing: editing and review: CL, RR, DK.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

Additional references were quoted within the Supporting Information.[45]

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DATA AVAILABILITY STATEMENT

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Selective Transformation of Levoglucosenone into a Versatile, Nitrogen-containing Building Block, and its Application in Diversity-Oriented Synthesis

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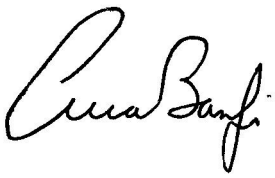
The data supporting this article have been included as part of the Supplementary Information.



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