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Solvent-Free 1,3-Dipolar Cycloadditions of Nitrones for a More Sustainable Synthesis of Glycomimetics

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Abstract: 1,3-Dipolar cycloadditions on nitrone dipoles are key reactions to access five-membered heterocycles, which are useful intermediates in the synthesis of biologically relevant glycomimetics. The good atomic balance and high stereoselectivity characteristic of such reactions make them good candidates for the development of green protocols. In the present work, these features were maximized by avoiding the use of organic solvents and considering starting materials derived from biomass. Reactions involving (acyclic and cyclic) carbohydrate-derived nitrones as dipoles and levoglucosenone as dipolarophile were considered. Performing selected 1,3-dipolar cycloadditions in neat conditions showed reduced reaction times, maintaining similar selectivity and yields with respect to the classical protocols. The use of microwave irradiation and orbital shaking were also exploited to increase the sustainability of the synthetic protocols. The collected results highlight the potential of solvent-free 1,3-dipolar cycloadditions in the design of efficient synthetic routes according to green chemistry principles, such as prevention, atom economy, safer solvents and auxiliaries, and use of renewable feedstocks.

Keywords: 1,3-dipolar cycloadditions; nitrones; glycomimetics; carbohydrates; levoglucosenone; stereoselective syntheses; neat; solvent-free conditions

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1. Introduction

1,3-Dipolar cycloadditions provide one of the most useful methods to access five-membered ring heterocycles [1,2], as attested by the vast research conducted in this field in the past 50 years (see selected Reviews [3–9]) and the widespread use of this type of reaction in nearly all chemistry areas, ranging from materials chemistry [10] to drug discovery [11].

A general 1,3-dipolar cycloaddition (1,3-DC) involves a 1,3-dipole compound (4π system) which reacts with a dipolarophile (2π system) in a [4π + 2π] cycloaddition thermally allowed by the Woodward–Hoffmann rules [12]. 1,3-Dipoles are usually classified into two classes: allyl type, in which the central atom can be nitrogen (e.g., azomethine ylides, azomethine imines, nitrones, etc.) or oxygen (carbonyl ylides, carbonyl imines, carbonyl oxides, etc.), and propargyl-allenyl type (e.g., nitrile ylides, nitrile oxides, azides, etc.) [13]. The structural variety of dipolarophiles, which can, in principle, be any compound containing a double or triple bond, isolated or conjugated, is responsible for the high versatility of 1,3-dipolar cycloadditions [14].

Although the mechanism of the 1,3-DC was widely debated in the 1960s, the idea of a concerted but asynchronous process for the formation of the new σ-bonds has been broadly accepted to date. Nevertheless, cycloadditions are commonly represented using a transition state involving the 4π-electron component of the 1,3-dipole that interacts

with the 2π-electron component of the dipolarophile [3]. One of the main advantages of 1,3-dipolar cycloadditions is represented by the high regio- and stereoselectivity of the reactions. The regioselectivity of a 1,3-DC can be predicted on the basis of the frontier orbitals theory because the nature of the substituents on both the 1,3-dipole and the dipolarophile (i.e., the presence of electron-donating or electron-withdrawing groups) affects the frontier molecular orbital (FMO) energies determining the dominant HOMO-LUMO interaction(s) of the transition state, as well as the orbital coefficient values at the connecting atoms determining the preferred orientation of reagents [15]. On the other hand, the high stereoselectivity of 1,3-DC reactions for alkene dipolarophiles and ally-type dipoles is strongly related to the concerted nature of the reaction mechanism, which results in the retention of the relative configuration of the original dipolarophile in the final adduct. In addition, since the cycloaddition is usually faster than the eventual 1,3-dipole isomerization and *exo*/*endo* selectivity is often high, the reaction is stereoselective also respect to the 1,3-dipole.

A key role in the vast scenario of 1,3-dipolar cycloadditions is played by 1,3-DC of nitrones **1** with alkenes **2** to access isoxazolidines **3** (Figure 1) [16], bearing up to three new contiguous stereocentres, which depend both on the stereochemistry of the dipolarophile and on the *exo*/*endo* approach of the two partners of the cycloaddition. The isoxazolidines **3** can then be easily converted into attractive compounds such as γ-amino alcohols, valuable building blocks in the total synthesis of natural products [17], and glycomimetics, an important family of biologically active compounds including polyhydroxylated and aminopolyhydroxylated carbocycles, azasugars, amino sugars, and polyhydroxylated alkaloids with pyrrolidine, indolizidine, and pyrrolizidine structure [18], also called iminosugars [19].

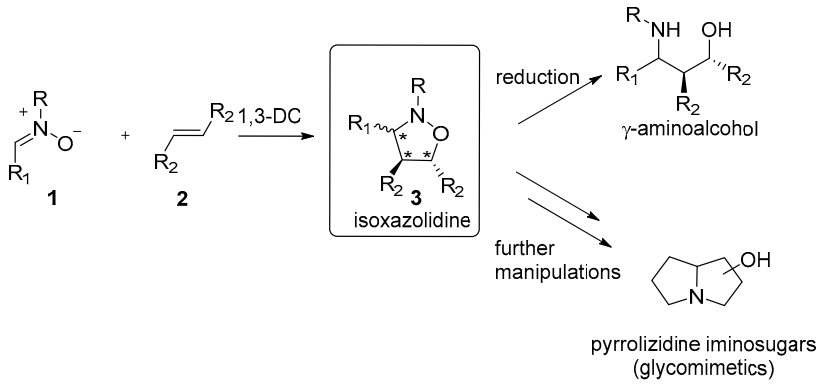


Figure 1. General scheme of 1,3-DC of nitrones with alkenes to form isoxazolidines, valuable intermediates for the synthesis of biological relevant compounds such as γ-aminoalcohols and glycomimetics (a pyrrolizidine iminosugar is reported as general example). * Denotes a stereogenic carbon atom.

There is no class of glycomimetics that has not been efficiently prepared through the essential mediation of acyclic [20] or cyclic [21] nitrones. A general method for the straightforward synthesis of indolizidine and pyrrolizidine iminosugars was developed by Brandi, Goti, and co-workers, by means of highly stereoselective 1,3-DC of cyclic nitrones (namely polyhydroxylated pyrroline *N*-oxides) followed by simple transformations of isoxazolidine adducts [22]. In particular, carbohydrate-derived nitrones have proven to be useful tools for a stereoselective approach towards stereochemically complex carbocycles and heterocycles, not only due to the presence of several contiguous stereogenic centers with a well-defined configuration, but also due to the possibility of temporarily adding a variety of moieties to the hydroxyl groups of carbohydrates (for examples, see: [23–26]). Moreover, the increasing attention of the scientific community towards the use of renewable sources makes carbohydrates, readily obtained from biomass, ideal candidates as sustainable

starting materials [27]. This aspect, combined with the intrinsic high atom economy and selectivity of 1,3-DC reactions, prompted us to revise the conditions usually employed for the obtainment of isoxazolidine intermediates in order to maximize the sustainability of the synthetic processes exploited to access glycomimetics. Since cycloaddition reactions are characterized by a negative volume of activation, previous studies conducted in our group demonstrated that the use of high pressure strongly accelerates and improves the yield of 1,3-DC reactions, as reported for the cycloaddition of enantiopure hydroxylated nitrones to glycals to access pseudo aza-*C*-disaccharides [28]. Conversely, no attention had been paid previously to the type of solvents used in such reactions, which are usually volatile organic solvents. Many efforts have been recently devoted to replacing organic solvents with non-flammable, non-volatile, non-toxic, and inexpensive green solvents, thus performing 1,3-DC reactions in ionic liquid, fluorinated solvents and water [29]. However, due to the early transition states characteristic of concerted cycloaddition reactions, it is reported that the choice of solvent has very little influence on the rate of the 1,3-DC [1]. Therefore, performing the reactions in neat conditions represents the ideal choice from the green chemistry perspective, since it avoids the use of conventional volatile solvents and can minimize the overall waste production, even though scarcely explored until now [30–34].

Herein, we report our attempts to optimize 1-3-DC reactions using carbohydrate-derived dipolarophiles or carbohydrate-derived nitrones (cyclic or acyclic), as well as a combination of both, in neat conditions.

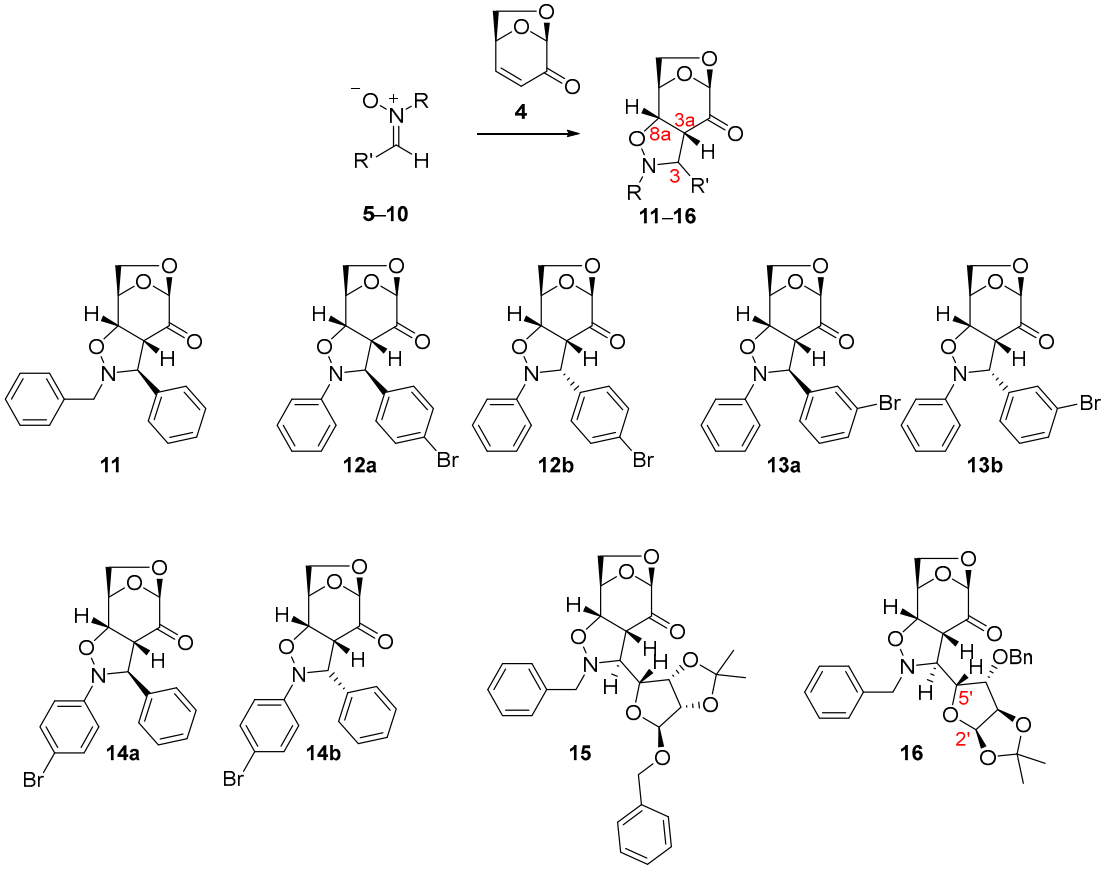
2. Results

With the aim of probing the efficacy of solvent-free conditions in 1,3-dipolar cycloadditions of biomass-derived compounds, cycloadditions with a single reagent (1,3-dipole or dipolarophile) derived from biomass or cycloadditions that involve a 1,3-dipole and a dipolarophile both derived from biomass were explored in our experiments. In particular, levoglucosenone (**4**, Scheme 1) and *N*,*N*-dimethylacrylamide were chosen as dipolarophiles, while different acyclic and cyclic nitrones (derived from sugars or tartaric acid) were employed as 1,3-dipoles.

Levoglucosenone (**4**) is a highly functionalized chiral synthon that can be produced by pyrolysis of cellulose-containing industrial residual materials such as waste paper [35], and it is a promising 1,6-anhydrosugar for obtaining highly added-value chemicals in various applications including pharmaceutics [36–38] and material chemistry [39–41]. Although the interest in this valuable compound has grown a lot in recent years, some of its functionalities have not yet been deeply explored. In the literature, there are few examples in which levoglucosenone is used as a dipolarophile in 1,3-dipolar cycloadditions with nitrones, but no example of solvent-free cycloadditions has been reported, to the best of our knowledge. For this reason, we decided to fill this gap by reproducing already reported 1,3-dipolar cycloadditions with levoglucosenone in neat conditions. First of all, cycloadditions of levoglucosenone with the diversely substituted acyclic nitrones **5**–**10** to form the corresponding isoxazolidine adducts **11**–**16** were studied, as shown in Scheme 1.

As the model reaction, we considered the 1,3-DC reaction of levoglucosenone (**4**) and *N*-benzyl-*C*-phenylnitrone **5**, described by Paton and collaborators [42]. The authors reported that the reaction proceeded completely regio- and stereoselectively with the obtainment of cycloadduct **11** as the sole product in 87% yield by refluxing in dry toluene for 48 h (Table 1, Entry 1). The complete regioselectivity observed for **11** is in agreement with a qualitative FMO analysis for a 1,3-dipole of type II. In the cycloaddition with a 1,2-disubstituted alkene with an electron-donating (alkyl) and an electron-withdrawing (ketone) substituent, [13] as in levoglucosenone, both $LUMO_{dipole}$-$HOMO_{dipolarophile}$ and $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interactions are to be considered. In both the interactions

the coefficients of the orbitals at C and O of the nitrone and those at sp^2-C of alkene converge to place the EDG group at C-5 and the EWG at C-4 of isoxazolidine. Regarding the steroselectivity, the cycloadduct **11** derived from an *endo* approach of nitrone **5** to levoglucosenone and *anti* with respect to the 1,6-anhydro bridge.



Scheme 1. Compounds **11**–**16** obtained from 1,3-dipolar cycloaddition of acyclic nitrones **5**–**10** and levoglucosenone (**4**).

N-benzyl-*C*-phenylnitrone **5** was synthesized as described in the literature [43], and several solvent-free attempts were carried out using a slight excess of dipolarophile (1.2 equivalents) at different temperatures. While at room temperature no desired product could be observed even after more than 7 days, more encouraging results were obtained by heating the reaction mixture in an oven (Table 1, Entry 2–4). In fact, it was possible to obtain the cycloadduct **11** in 57–58% yield, both at 40 °C and at 60 °C, with reaction times strongly decreased (17 h vs. 96 h), by increasing the temperature (Table 1, Entry 3 vs. Entry 2). By carrying out the cycloaddition reaction at the temperature reported in the literature (110 °C), it was possible to obtain the desired cycloadduct **11** in only 3 h with satisfactory yield (63%, Table 1, Entry 4). Given the promising results, we envisaged that heating via microwave irradiation could further reduce reaction times (Table 1, Entry 5–6). The best results were obtained by heating in microwave at 110 °C with a power of 300 W, accessing cycloadduct **11** in 68% yield in only 1 h (Table 1, Entry 6).

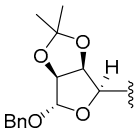
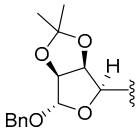
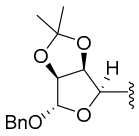
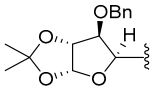
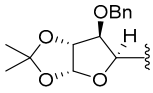
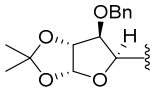
Another interesting example of 1,3-dipolar cycloadditions involving levoglucosenone for synthesis of potential enzymatic inhibitors is that reported by Peri and coworkers [44]. In particular, they explored the cycloaddition with three differently substituted nitrones (**6**–**8**) in dry dichloromethane at room temperature for 8 h in the presence of zinc chloride as Lewis acid promoter. In all cases, two different cycloadducts, resulting from the *endo-anti* (3*S*) and the *exo-anti* (3*R*) approaches (separable by column chromatography) were

obtained in different ratios, with total yields between 69–84% (Table 1, Entry 7,10,13). As shown in Table 1, it was possible to reduce the reaction times found in the literature (8 h) and increase yields by replicating the different cycloadditions under neat conditions by heating at 80 °C. At lower temperatures, the reaction times did not decrease considerably. *N*-Phenyl-*C*-4-bromophenylnitrone **6** [45], *N*-phenyl-*C*-3-bromophenylnitrone **7** [46], and *N*-4-bromophenyl-*C*-phenylnitrone **8** [47] were synthesized as described in the literature and reacted with a slight excess of levoglucosenone. Under solvent-free conditions, by heating at 80 °C, the cycloaddition of levoglucosenone to nitrone **6** led to the two desired cycloadducts **12a** and **12b** in 3*S*:3*R* 1:1.2 ratio after 2.5 h and in 81% total yield (compared to the 3*S*:3*R* 1:1 ratio and 77% yield reported in the literature, Table 1, Entry 8 vs. Entry 7). By using microwave heating, the reaction completed in only 45 min with a total yield of 79% (Table 1, Entry 9). Applying solvent-free conditions and conventional heating at 80 °C to *N*-phenyl-*C*-3-bromophenylnitrone **7**, the corresponding cycloadducts **13a** and **13b** were obtained in 3*S*:3*R* 1:2.2 ratio after 3 h in 69% total yield (compared to the 3*S*:3*R* 1:3.5 ratio and 69% yield reported in the literature, Table 1, Entry 11 vs. Entry 10). The yield was slightly increased (72%) by using microwave irradiation at 80 °C, which also allowed the reaction time to be decreased to only 45 min (Table 1, Entry 12). With *N*-4-bromophenyl-*C*-phenylnitrone **8**, the use of neat conditions allowed the reaction times to be reduced, but did not increase the reaction yield. Heating at 80 °C provided cycloadducts **14a** and **14b** in a 3*S*:3*R* 1:1 ratio and 75% total yield (compared to the 3*S*:3*R* 1:1.5 and 84% yield reported in the literature, Table 1, Entry 14 vs. Entry 13). Even in this case, the yield was slightly increased (81%) by using microwave irradiation at 80 °C, decreasing the reaction time to only 45 min as well (Table 1, Entry 15).

Table 1. 1,3-DC reactions of acyclic nitrones **5**–**10** and levoglucosenone (**4**) (1.2 equivalents).

Entry	Nitrone	R	R′	Reaction Conditions	Heating	Temperature	Time	Product (Yield) [a]
1 [b]	**5**	*-benzyl*	*-phenyl*	dry toluene	standard	110 °C	48 h	**11** (87%)
2	**5**	*-benzyl*	*-phenyl*	solvent-free	standard	40 °C	96 h	**11** (57%)
3	**5**	*-benzyl*	*-phenyl*	solvent-free	standard	60 °C	17 h	**11** (58%)
4	**5**	*-benzyl*	*-phenyl*	solvent free	standard	110 °C	3 h	**11** (63%)
5	**5**	*-benzyl*	*-phenyl*	solvent-free	microwaves (150 W)	110 °C	1.5 h	**11** (63%)
6	**5**	*-benzyl*	*-phenyl*	solvent-free	microwaves (300 W)	110 °C	1 h	**11** (68%)
7 [c]	**6**	*-phenyl*	*-4-bromophenyl*	dry $CH_2Cl_2ZnCl_2 \cdot Et_2O$	-	r.t.	8 h	**12** (77%)
8	**6**	*-phenyl*	*-4-bromophenyl*	solvent-free	standard	80 °C	2.5 h	**12** (81%)
9	**6**	*-phenyl*	*-4-bromophenyl*	solvent-free	microwaves (150 W)	80 °C	45 min	**12** (79%)
10 [c]	**7**	*-phenyl*	*-3-bromophenyl*	dry $CH_2Cl_2ZnCl_2 \cdot Et_2O$	-	r.t.	8 h	**13** (69%)
11	**7**	*-phenyl*	*-3-bromophenyl*	solvent-free	standard	80 °C	3 h	**13** (69%)
12	**7**	*-phenyl*	*-3-bromophenyl*	solvent-free	microwaves (150 W)	80 °C	45 min	**13** (72%)
13 [c]	**8**	*-4-Br-phenyl*	*-phenyl*	dry $CH_2Cl_2ZnCl_2 \cdot Et_2O$	-	r.t.	8 h	**14** (84%)

Table 1. *Cont.*

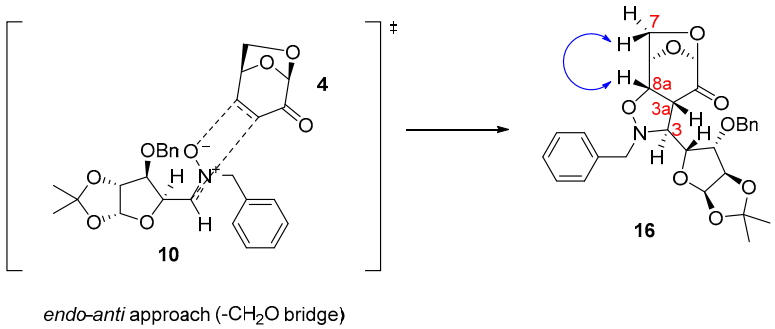
Entry	Nitrone	R	R′	Reaction Conditions	Heating	Temperature	Time	Product (Yield) [a]
14	**8**	*-4-Br-phenyl*	*-phenyl*	solvent-free	standard	80 °C	3 h	**14** (75%)
15	**8**	*-4-Br-phenyl*	*-phenyl*	solvent-free	microwaves (150 W)	80 °C	45 min	**14** (81%)
16 [d]	**9**	*-benzyl*		dry toluene	standard	60 °C	24 h	**15** (78%)
17 [e]	**9**	*-benzyl*		solvent-free	standard	60 °C	6 h	**15** (61%)
18 [e]	**9**	*-benzyl*		solvent-free	microwaves (150 W)	60 °C	4 h	**15** (62%)
19	**10**	*-benzyl*		dry toluene	standard	60 °C	18 h	**16** (60%)
20	**10**	*-benzyl*		solvent-free	standard	60 °C	6 h	**16** (62%)
21	**AG**	*-benzyl*		solvent-free	microwaves (150 W)	60 °C	3 h	**16** (57%)

[a] Isolated yield after flash column chromatography. [b] Reference [42]. [c] Reference [44]. [d] Reference [38]. [e] Reactions performed using 2.0 equivalents of levoglucosenone.

In 2020, exploring the functions of levoglucosenone to obtain new glycomimetics as carbonic anhydrase inhibitors [38], we investigated the 1,3-DC reaction of levoglucosenone with nitrone **9**, which can be obtained from D-mannose in five steps [48–50]. We were delighted to observe that the reaction occurred in a completely regio- and stereoselective manner, leading to the *endo-anti* cycloadduct **15** as the sole product in 78% yield, by heating at 60 °C in dry toluene for 24 h (Table 1, Entry 16). To obtain the desired product in a reasonable time, it was necessary to carry out the reaction at high concentration (2M), thus minimizing the solvent amount. For this reason, we thought that it would be of great interest to also try this reaction in solvent-free conditions. We initially heated nitrone **9** with the usual slight excess of levoglucosenone (1.2 equivalents) at 60 °C (same temperature as in the literature) in neat conditions, and cycloadduct **15** was obtained in a time frame comparable with classical conditions (18 h vs. 24 h). Using a larger amount of levoglucosenone (2 equivalents), the cycloadduct **15** was obtained in good yield (61%) in 6 h (Table 1, Entry 17). Performing the reaction in the same conditions by replacing conventional heating with microwave irradiation led to adduct **15** in 62% yield in only 4 h (Table 1, Entry 18).

Considering the interest in studying cycloadditions that involve both the dipole and the dipolarophile derived from biomass, a new 1,3-dipolar cycloaddition between levoglucosenone and nitrone **10** obtained from D-glucose [51] was studied. The first attempt was carried out by heating in dry toluene at 60 °C, and cycloadduct **16** was obtained as

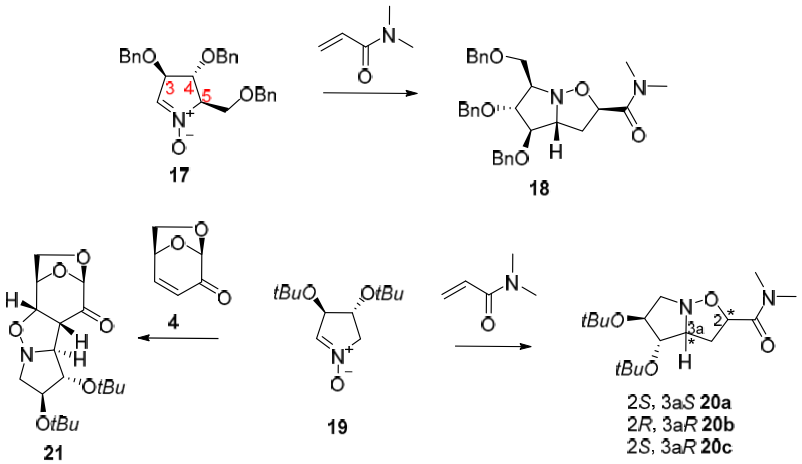
the sole product in 18 h and 60% yield (Table 1, Entry 19). Through NOESY and ^{1}H NMR experiments, it was possible to unequivocally determine the absolute configuration of the newly formed stereogenic centres of the adduct, which derived from an *endo-anti* approach (Scheme 2, and Supplementary Materials for ^{1}H NMR and NOESY spectra). Indeed, the NOESY coupling between proton H-7 and proton H-8a confirmed the *anti* approach of the nitrone **10** to the 1,6-bridge of levoglucosenone. On the other hand, the small value of the coupling constant between H-3 and H-3a (J = 3.7 Hz) confirmed the *endo* approach of nitrone **10**. Under solvent-free conditions, the cycloadduct **16** was obtained with complete regio- and stereoselectivity in 62% yield by heating at 60 °C (same temperature as in dry toluene) for 6 h (Table 1, Entry 20). The reaction time was also halved in this case (only 3 h) by heating to 60 °C via microwave irradiation, obtaining the new cycloadduct **16** in a similar 57% yield. (Table 1, Entry 21).



Scheme 2. *Endo-anti* approach of 1,3-dipolar cycloaddition of nitrone **10** and levoglucosenone to obtain the cycloadduct **16**. ‡ Indicates a transition state.

To investigate the influence of neat conditions on 1,3-DC reactions with enantiopure cyclic nitrones, key intermediates for the synthesis of pyrrolizidine iminosugars [22], we initially replaced levoglucosenone **4** with the commercially available dipolarophile *N*,*N*-dimethylacrylamide.

Nitrone **17**, easily obtained from D-arabinose [52,53], was successfully employed in 1,3-DC reactions with suitable dipolarophiles, providing bicyclic isoxazolidines with an excellent selectivity which can be ascribed to the peculiar "all-*trans*" disposition of the benzyloxy groups in nitrone **17** (Scheme 3). Indeed, the substituents at C-3 and C-5 allow exclusively *anti* cycloadducts to be obtained, and the steric bulk of substituent at C-4 ensures an excellent *exo* selectivity [52,54].



Scheme 3. Synthesis of cycloadduct **18** obtained from nitrone **17** and *N*,*N*-dimethylacrylamide and cycloadducts **20** and **21** starting from cyclic nitrone **19** with *N*,*N*-dimethylacrylamide and levoglucosenone **4**. * Denotes a stereogenic carbon atom.

In particular, nitrone **17** reacted with *N*,*N*-dimethylacrylamide to obtain the *exo-anti* cycloadduct **18** in a totally regio- and stereoselective manner; cycloadduct **18** is the precursor of 7-deoxycasuarine, a potent inhibitor of glycosidases [53]. In this case, the regioselectivity of the cycloaddition may be dominated by the higher differentiation of the carbon and oxygen coefficients in the LUMO orbital of the nitrone, while the low orbital coefficients difference in its HOMO [21] makes the preferred $HOMO_{dipole}$-$LUMO_{dipolarophile}$ orbital interaction unable to exert any regioselectivity. Thus, the regioselectivity, especially with moderately electron-deficient substituted alkenes such as esters and amides, is shown to be controlled by the higher energy $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interaction, which favors the formation of 5-substituted isoxazolidines. Steric effects may also play a relevant role in determining the observed selectivity. The cycloaddition was performed in dichloromethane at room temperature and provided **18** in 72 h and 85% yield (Table 2, Entry 1). The attempts in solvent-free conditions gave the desired adduct **18** both at room temperature (54 h, 60% yield, Table 2, Entry 2), and by heating at 40 °C (18 h, 59% yield, Table 2, Entry 4). Interestingly, the use of an orbital shaker to perform the reaction allowed **18** to be obtained at a higher 71% yield at room temperature in 15 h (Table 2, Entry 3).

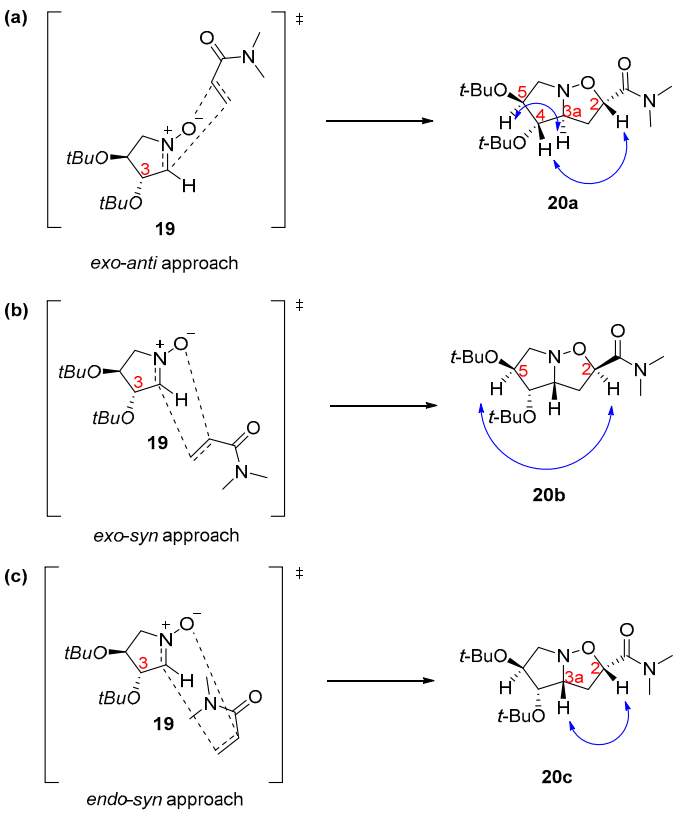
Table 2. 1,3-DC reactions of cyclic nitrones **17** and **19** with *N*,*N*-dimethylacrylamide and levoglucosenone (**4**).

Entry	Nitrones	Dipolarophile	Reaction Conditions	Heating	Temperature	Time	Product (Yield)
1 [a]	**17**	*N*,*N*-dimethylacrylamide	CH_2Cl_2	-	r.t.	72 h	**18** (85%)
2	**17**	*N*,*N*-dimethylacrylamide	solvent-free	-	r.t.	54 h	**18** (60%)
3	**17**	*N*,*N*-dimethylacrylamide	solvent-free	- (orbital shaker)	r.t.	15 h	**18** (71%)
4	**17**	*N*,*N*-dimethylacrylamide	solvent-free	standard	40 °C	18 h	**18** (59%)
5	**17**	levoglucosenon	dry toluene	standard	60 °C	96 h	-
6	**19**	*N*,*N*-dimethylacrylamide	toluene	-	r. t.	2.5 h	**20** (65%)
7	**19**	*N*,*N*-dimethylacrylamide	solvent-free	- (orbital shaker)	r.t.	1 h	**20** (70%)
8 [b]	**19**	levoglucosenone	dry toluene	-	r.t.	2 h	**21** (88%)
9	**19**	levoglucosenone	solvent-free	standard	80 °C	2 h	**21** (80%)
10	**19**	levoglucosenone	solvent-free	microwaves (150 W)	80 °C	45 min	**21** (76%)

[a] Reference [53]. [b] Reference [55].

Encouraged by these results, we explored the unprecedented cycloaddition of nitrone **17** to levoglucosenone. Unfortunately, a complex mixture of cycloadducts, which were impossible separate and characterize, were obtained in dry toluene by heating at 60 °C for 96 h (Table 2, Entry 5). This result was partially predictable since a 'mismatched' double asymmetric induction occurs in this case. Therefore, no trials in solvent-free conditions were carried out.

However, as a final attempt, we turned to another enantiopure cyclic nitrone (**19**, Scheme 3) which was previously employed by some of us in 1,3-DC reaction with levoglucosenone [55]. Nitrone **19**, obtained from L-tartaric acid [56], was initially reacted with *N*,*N*-dimethylacrylamide in toluene at room temperature (Table 2, Entry 6). After 2.5 h, three different cycloadducts, **20a**, **20b**, and **20c**, were obtained in a 1:0.4:0.1 molar ratio, as attested by the ^{1}H NMR analysis of the crude reaction mixture. Purification by flash column chromatography allowed pure **20a** to be isolated, with compounds **20b** and **20c** as an inseparable mixture, in 65% overall yield. The complete regioselectivity of the reaction was confirmed by bidimensional NMR experiments performed on the purified cycloadducts. As previously mentioned for nitrone **17**, in this case the regioselectivity of the cycloaddition is dictated by the less energetically favorable $LUMO_{dipole}$–$HOMO_{dipolarophile}$ interaction, leading to the formation of the 5-isoxazolidine with the electron-poor alkene [21]. NOESY and ^{1}H NMR experiments performed on isolated compound **20a** allowed the stereochemistry of the adduct to be determined; it derived from an *exo-anti* approach (Scheme 4a, see Supplementary Materials for NOESY spectra). Indeed, the NOESY coupling of the proton H-3a with the proton H-5 confirmed the *anti* approach of the dipolarophile relative to the hindering group (-O*t*Bu) on C-3 of the nitrone **19**, and the NOESY correlation between H-2 and H-4 confirmed the *exo* approach. Although compounds **20b** and **20c** were obtained as an inseparable mixture, all signals in the ^{1}H and ^{13}C NMR spectra were successfully assigned. This enabled the execution of NOESY experiments to elucidate the structures of the cycloadducts: the presence of NOESY correlation between H-5 and H-2 along with the absence of correlation between H-3a and H-5, confirmed an *exo-syn* approach of the dipolarophile (Scheme 4b) for the major cycloadduct of the two-component mixture **20b**, while the *endo-syn* diastereoselectivity for the minor cycloadduct **20c** was confirmed by selective irradiation of H-3a, which showed a NOESY correlation with H-2 but not with H-5 (Scheme 4c).



Scheme 4. Different approaches of 1,3-dipolar cycloaddition of nitrone **19** and *N*,*N*-dimethylacrylamide to obtain: (**a**) cycloadduct **20a**; (**b**) cycloadduct **20b**; (**c**) cycloadduct **20c.** ‡ Indicates a transition state.

Performing the 1,3-DC without solvent at room temperature with the orbital shaker, cycloadduct **20a** and a mixture of **20b** and **20c** were obtained with the same selectivity and a slightly higher and shorted reaction time (70% yield, 1 h vs. 65% 2.5 h, Table 2, Entry 7 vs. Entry 6).

These results prompted us to apply the solvent-free conditions to the 1,3-dipolar cycloaddition of nitrone **19** with levoglucosenone, previously reported in dry toluene [55]. In this case, thanks to the high facial selectivity of levoglucosenone, a single *exo-anti* cycloadduct **21** was obtained at room temperature in 2 h with 88% yield (Table 2, Entry 8). Neat conditions at room temperature did not provide the desired product even after 7 days. Conversely, by heating at 80 °C, the sole cycloadduct **21** was obtained with similar reaction times and yields to that of the reaction in toluene reported in the literature (2 h, 80% yield, Table 2, Entry 9). At temperatures lower than 80 °C, the reaction times did not significantly decrease with respect to the literature. Using microwaves irradiation at 80 °C, the reaction time decreased to only 45 min, and similar 76% yield was obtained (Table 2, Entry 10).

3. Discussion

In this work, a more sustainable version of 1,3-dipolar cycloadditions of nitrones for the synthesis of glycomimetics was investigated. Considering that cycloadditions are favored by a volume contraction, we envisaged that solvent-free conditions could decrease the reaction times. In order to develop greener protocols, we also focused on the use of starting materials obtainable from biomass, such as carbohydrate-derived nitrones as dipoles and levoglucosenone, derived from cellulose-containing waste material, as dipolarophile.

First, 1,3-dipolar cycloadditions previously reported in the literature between levoglucosenone and acyclic nitrones were replicated in neat conditions (Table 1). From the first experiments with *N*-benzyl-*C*-phenylnitrone **5**, it was clear that heating in neat conditions could achieve the desired cycloadduct **11** faster than under solvent conditions. In addition, using microwave heating made it possible to further reduce the reaction time, selectively obtaining the desired product in only 1 h (vs. 48 h in solvent), with a good 68% yield.

Given the first promising results, other 1,3-dipolar cycloadditions were replicated between levoglucosenone and the differently substituted *N*-phenyl-*C*-phenylnitrones **6**–**8**. With *N*-4-bromophenyl-*C*-phenylnitrone **6**, no reaction occurred without solvent at room temperature. Conversely, the couple of cycloadducts **12a** and **12b** was obtained in solvent-free conditions in 2.5 h by heating in an oven at 80 °C, or in 45 min (vs. 8 h) by microwave irradiation at 80 °C, with slightly higher yields compared to the literature. Also, with *N*-phenyl-*C*-3-bromophenylnitrone **7**, it was possible to reduce the reaction time (3 h with standard heating or 45 min with microwave irradiation) for the synthesis of the cycloadducts **13a** and **13b**, obtained with slightly higher yields with respect to the reaction performed in classical conditions. Considering that the literature procedure involved the use of a zinc complex to improve the diastereoisomeric ratio (vide supra), in most cases, our reaction conditions led to similar results in terms of selectivity and yields, avoiding the use of metals and with reduced reaction times, thus providing a more sustainable protocol.

Moreover, the replication under solvent-free conditions of cycloadditions of levoglucosenone with the nitrone **9** derived from D-mannose led to the formation of the desired adduct **15** in shorter time (4 h vs. 24 h) and comparable yields. During this work, a 1,3-dipolar cycloaddition between levoglucosenone and the nitrone **10** derived from D-glucose was explored that had not been previously reported. When performed in dry toluene (18 h), the reaction led to the formation of a single cycloadduct **16** whose stereochemistry was interpreted thanks to NOESY and ^{1}H NMR studies. Under solvent-free conditions the cycloadduct was obtained with the same yield and shorter reaction time (3 h vs. 18 h).

To complete the work, attempts of cycloaddition with enantiopure cyclic nitrones were also repeated (Table 2). Nitrone **17** derived from D-arabinose and *N*,*N*-dimethylacrylamide efficiently reacted in solvent-free conditions, affording cycloadduct **18** stereoselectively at room temperature with a very good 71% yield when an orbital shaker was employed. Additional experiments were conducted between nitrone **19** derived from L-tartaric acid and *N*,*N*-dimethylacrylamide, leading to the formation of novel cycloadducts **20a**, **20b**, and **20c** (the latter two obtained as an inseparable mixture). When performed in toluene (2.5 h), the reaction yielded three cycloadducts whose stereochemistry was assigned on the basis of NOESY and ^{1}H NMR studies. Under neat conditions and orbital shaking, the cycloadducts were obtained with the same stereoselectivity with higher yield and shorter reaction time (1 h vs. 2.5 h), even at room temperature.

Finally, 1,3-DC of nitrone **19** with levoglucosenone led to cycloadduct **21** as the sole product, heating at 80 °C, with reaction times and yield comparable to the previous literature (dry toluene). The reaction time was lowered by using microwave heating (45 min vs. 2 h).

The collected results shed light on a new procedure for performing 1,3-dipolar cycloadditions as solvent-free and catalyst-free reactions, thus aligning with some of the 12 principles of green chemistry (prevention, atom economy, safer solvents and auxiliaries, use of renewable feedstocks) [57]. We have also further explored the great potential of levoglucosenone, a biomass-derived highly functionalized compound that can be involved in more sustainable procedures to synthesize new glycomimetics. In general, it has been observed that, under solvent-free conditions, the reaction times of cycloadditions are shorter than in solvent. Further studies are required to broaden the range of reactions replicated under neat conditions.

4. Materials and Methods

4.1. General Details

Commercial reagents were used as received. All reactions were monitored by TLC on 0.25 mm silica gel plates (Merck F254, Merk Life Science S.r.l., Merck KGaA, Darmstadt, Germany). Column chromatographies were carried out on Silica Gel 60 (32–63 μm) or on silica gel (230–400 mesh, Merck). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. Melting points were obtained with a Stuart Scientific melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz, a Varian Mercury 400 MHz, or a Varian INOVA 400 MHz instrument at 25 °C. Chemical shifts are reported relative to $CDCl_3$ (^{13}C: δ = 77.0 ppm). Integrals are in accordance with assignments, and coupling constants are given in Hz. For detailed peak assignments, 2D spectra were carried out (COSY, HSQC, NOESY, and NOE as necessary). Small scale microwave-assisted syntheses were carried out in a microwave apparatus for synthesis (CEM Discover, CEM Corporation, Matthews, NC, USA) with a septum-sealed reaction vessel, and the reaction mixture temperature was monitored by an infrared temperature sensor. IR spectra were recorded with a BX FTIR Perkin-Elmer system spectrophotometer and an IRAffinity-1S Shimadzu spectrophotometer. ESI-MS spectra were recorded with a Thermo Scientific™ (Thermo Fisher Scientific, Waltham, MA, USA) LCQ fleet ion trap mass spectrometer. Optical rotation measurements were performed on a JASCO DIP-370 polarimeter.

4.2. General Procedure for Solvent-Free 1,3-Dipolar Cycloaddition of Nitrones and Dipolarophiles

Nitrone **5–10**, **17**, and **19** (1 equiv) were added to levoglucosenone **4** (1.2 or 2 equiv) or *N*,*N*-dimethylacrylamide (1.2 equiv). The reaction was left, or shaken at room temperature, or heated in an oven, or heated via microwave irradiation (see Tables 1 and 2 for

temperature and reaction time). The end of the reaction was confirmed by TLC, and the crude was purified by flash column chromatography purification on silica gel, obtaining the compounds **11**–**16**, **18**, **20a**–**c**, and **21** with yields between 57–81%.

For all the obtained products that are known compounds reported in the literature (**11**–**15**, **18**, **21**), ^{1}H NMR spectral data and m.p. when solid are reported in the Supplementary Materials and are in agreement with the literature.

4.3. Synthesis of Cycloadduct **16**

Nitrone **10** [51] (50.4 mg, 0.131 mmol) was added to a solution of levoglucosenone (**4**) (16.6 mg, 0.131 mmol) in dry toluene (0.150 mL) under nitrogen atmosphere. The reaction was heated at 60 °C for 18 h. The end of the reaction was confirmed by TLC (eluent hexane:AcOEt 2:1). The reaction crude was purified by flash column chromatography purification on silica gel (eluent hexane:AcOEt 7:3) obtaining the compound **16** (39.4 mg, 0.077 mmol) as colourless oil with 60% yield.

According to the General Procedure, compound **16** (33.8 mg, 0.066 mmol, 62%) was obtained as colourless oil from the reaction of nitrone **10** [51] (41 mg, 0.107 mmol) and levoglucosenone (**4**) (16.2 mg, 0.128 mmol) at 60 °C in an oven for 6 h, followed by flash column chromatography purification on silica gel (eluent hexane:AcOEt 7:3, R_f: 0.2).

According to the General Procedure, compound **16** (35.2 mg, 0.069 mmol, 57%) was obtained as colourless oil from the reaction of nitrone **10** [51] (46.6 mg, 0.121 mmol) and levoglucosenone (**4**) (18.4 mg, 0.146 mmol) at 60 °C for 3 h under microwave irradiation (150 W), followed by flash column chromatography purification on silica gel (eluent hexane:AcOEt 7:3, R_f: 0.2). $[\alpha]^{20}_D$ = −124.4 (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): 3020, 2916, 2849, 1756, 1456, 1379, 1163, 1115, 1076, 941 cm^{-1}. $C_{28}H_{31}NO_8$: MS-ESI (*m*/*z*, %) = 1040.8 (100, $[2M+Na]^+$), 532.1 (85, $[M+Na]^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 10H, *Ar*), 5.97 (d, *J* = 3.9 Hz, 1H, H-2′), 5.18 (s, 1H, H-5), 4.70–4.66 (m, 3H, H-3′, H-8, -OCH_2), 4.50 (d, *J* = 11.1 Hz, 1H, -OCH_2), 4.21 (d, *J* = 6.7 Hz, 1H, H-8a), 4.06–4.00 (m, 4H, H-4′, H-5′, -NCH_2), 3.93 (dd, *J* = 3.7, 6.1 Hz, 1H, H-3), 3.75 (dd, *J* = 5.6, 7.7 Hz, 1H, Ha-7), 3.47 (d, *J* = 7.7 Hz, 1H, Hb-7), 3.32 (dd, *J* = 3.7, 6.7 Hz, 1H, H-3a), 1.41 (s, 3H, -CH_3), 1.32 (s, 3H, -CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8 (s, 1C, CO), 137.1 (s, 1C, *Ar*), 137.0 (s, 1C, *Ar*), 130.4, 129.2, 128.9, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.3 (d, 10C, *Ar*), 111.9 (s, 1C, O-C-O), 105.0 (d, 1C, C-2′), 100.6 (d, 1C, C-5), 82.5 (d, 1C, C-4′), 81.8 (d, 1C, C-8), 80.1 (d, 1C, C-5′), 78.8 (d, 1C, C-8a), 72.8 (d, 1C, C-3′), 71.6 (t, 1C, -OCH_2), 65.5 (d, 1C, C-3), 65.6 (t, 1C, C-7), 62.8 (t, 1C, -NCH_2), 52.1 (d, 1C, C-3a), 26.8 (q, 1C, -CH_3), 26.4 (q, 1C, -CH_3) ppm.

4.4. Synthesis of Cycloadducts **20a**, **20b** *and* **20c**

Compounds **20a** (brown oil) and a mixture of **20b** and **20c** 1:0.7 (pale yellow oil) were obtained in a ratio of 1:0.4:0.1 with 65% of total yield from the reaction of nitrone **19** [56] (40.0 mg, 0.174 mmol) and *N*,*N*-dimethylacrylamide (0.209 mmol, 22 µL) in toluene (0.087 mL) at room temperature for 2.5 h, followed by flash column chromatography purification on silica gel (eluent AcOEt, **20a** R_f: 0.2 and **20b** + **20c** R_f: 0.1).

According to the General Procedure, compounds **20a** (brown oil) and a mixture of **20b** and **20c** 1:0.7 (pale yellow oil) were obtained in a ratio of 1:0.4:0.1 with 70% of total yield from the reaction of nitrone **19** [56] (40.0 mg, 0.174 mmol) and *N*,*N*-dimethylacrylamide (0.209 mmol, 22 µL) in an orbital shaker at room temperature for 1 h, followed by flash column chromatography purification on silica gel (eluent AcOEt, **20a** R_f: 0.2 and 20b + **20c** R_f: 0.1).

20a: $[\alpha]^{20}_D$ = 84.1 (c 1.0, $CHCl_3$). IR (neat) ν = 2972, 2936, 2872, 1651, 1393, 1192, 1061 cm^{-1}. $C_{17}H_{32}N_2O_4$: MS-ESI (*m*/*z*, %) = 351.08 (100, $[M+Na]^+$), 678.92 (83, $[2M+Na]^+$), 329.08 (75, $[M+H]^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (t, *J* = 7.0 Hz, 1H, H-2), 3.92–3.88

(m, 1H, H-5), 3.76 (t, *J* = 3.8 Hz, 1H H-4), 3.56 (ddd, *J* = 9.0, 5.6, 3.4 Hz, 1H, H-3a), 3.45 (dd, *J* = 10.9, 5.9 Hz, 1H, Ha-6), 3.08 (s, 3H, *Me*), 3.00 (ddd, *J* = 12.6, 9.0, 7.0 Hz, 1H, Ha-3), 2.92 (s, 3H, *Me*), 2.87 (dd, J = 10.9, 7.3, Hz, 1H, Hb-6), 2.25 (m, 1H, Hb-3), 1.16 (s, 9H, -O*tBu*), 1.16 (s, 9H, -O*tBu*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (s, 1C, C=O), 82.1 (d, 1C, C-4), 77.1 (d, 1C, H-5), 74.7 (d, 1C, H-2), 74.1 (s, 2C, *Cq*), 71.0 (d, 1C, C-3a), 60.7 (t, 1C, C-6), 37.2 (q, 1C, *Me*), 36.5 (t, 1C, C-6), 35.98 (q, 1C, *Me*), 28.75 (q, 3C, -O*tBu*), 28.6 (q, 3C-O*tBu*) ppm.

20b + **20c**: IR (neat) ν = 2972, 2934, 1649, 1366, 1111 cm^{-1}. $C_{17}H_{32}N_2O_4$: MS-ESI (*m*/*z*, %) = 329.18 (100, $[M+H]^+$), 351.15 (44, $[M+Na]^+$), 679.09 (69, $[2M+Na]^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (dd, *J* = 7.4, 4.5 Hz, 1H, H-2, **20b**), 4.60 (dd, *J* = 7.4, 4.5 Hz, 1H, H-2, **20c**), 4.13 (q, *J* = 7.4 Hz, 1H, H-5, **20c**), 4.04 (dd, *J* = 8.0, 6.4 Hz, 1H, H-5, **20b**), 3.96 (t, *J* = 7.4 Hz, 1H, H-4, **20c**), 3.92–3.89 (m, 1H, H-4, **20b**), 3.87–3.84 (m, 1H, H-3a, **20b**), 3.82–3.78 (m, 1H, H-3a, **20c**), 3.37 (dd, *J* = 13.5, 7.4 Hz, 1H, Ha-6, **20c**), 3.31 (dd, *J* = 13.7, 6.4 Hz, 1H, Ha-6, **20b**), 3.10 (s, 3H, *Me*, **20b**), 3.09 (s, 3H, *Me*, **20c**), 2.96 (s, 3H, *Me*, **20c**), 2.94 (s, 3H, *Me*, **20b**), 2.92–2.87 (m, 3H, Hb-6, **20b**, Ha-3, Hb-6, **20c**), 2.74 (ddd, *J* = 12.8, 8.7, 4.5 Hz, 1H, Ha-3, **20b**), 2.54 (ddd, *J* = 12.8, 7.4, 4.7 Hz, 1H, Hb-3, **20b**), 2.19 (ddd, *J* = 12.9, 8.4, 7.4 Hz, 1H, Hb-3, **20c**), 1.18 (s, 9H, -O*tBu*, **20b**), 1.16 (s, 18H, -O*tBu*, **20b** and **20c**), 1.14 (s, 9H, -O*tBu*, **20c**) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8 (s, 1C, C=O, **20b**), 168.5 (s, 1C, C=O, **20c**), 77.6 (d, 1C, C-4, **20b**), 77.4 (d, 1C, C-4, **20c**), 76.8 (d, 1C, C-2, **20c**), 75.9 (d, 1C, C-2, **20b**), 75.8 (d, 1C, C-5, **20b**), 74.3 (d, 1C, C-5, **20c**), 74.2 (s, 1C, *Cq*, **20b**), 73.9 (s, 1C, *Cq*, **20c**), 73.8 (s, 1C, *Cq*, **20c**), 73.7 (s, 1C, *Cq*, **20b**), 66.6 (d, 1C, C-3a, **20c**), 65.8 (d, 1C, C-3a, **20b**), 59.8 (t, 1C, C-6, **20c**), 59.7 (t, 1C, C-6, **20b**), 37.4 (q, 1C, *Me*, **20b**), 37.2 (q, 1C, *Me*, **20c**), 36.2 (q, 1C, *Me*, **20b**), 36.0 (q, 1C, *Me*, **20c**), 33.9 (t, 1C, C-3, **20c**), 33.1 (t, 1C, C-3, **20b**), 28.7 (q, 6C, -O*tBu*, **20b** and **20c**), 28.6 (q, 6C, -O*tBu*, **20b** and **20c**) ppm.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions6020036/s1, Figure S1: ^{1}H NMR of compound **16** (400 MHz, $CDCl_3$); Figure S2: ^{13}C NMR of compound **16** (100 MHz, $CDCl_3$); Figure S3: 1D NOESY of compound **16** (irradiation of H-8a at 4.21 ppm, 400 MHz, $CDCl_3$); Figure S4: 1D NOESY of compound **16** (irradiation of Hb-7 at 3.47 ppm, 400 MHz, $CDCl_3$); Figure S5: ^{1}H NMR spectrum of **20a** (400 MHz, $CDCl_3$); Figure S6: ^{13}C NMR spectrum of **20a** (400 MHz, $CDCl_3$); Figure S7: 1D NOESY spectrum of **20a** (irradiation of H-2 at 4.90 ppm, 400 MHz, $CDCl_3$); Figure S8: 1D NOESY spectrum of **20a** (irradiation of H-4 at 3.76 ppm, 400 MHz, $CDCl_3$); Figure S9: 1D NOESY spectrum of **20a** (irradiation of H-3a at 3.56 ppm, 400 MHz, $CDCl_3$); Figure S10: 1D NOESY spectrum of **20a** (irradiation of H-5 at 3.92–3.88 ppm, 400 MHz, $CDCl_3$); Figure S11: ^{1}H NMR spectrum of **20b + 20c** (400 MHz, $CDCl_3$); Figure S12: ^{13}C NMR spectrum of **20b + 20c** (400 MHz, $CDCl_3$); Figure S13: 1D NOESY spectrum of **20b + 20c** (irradiation of H-2 of **20b** at 4.71 ppm, 400 MHz, $CDCl_3$); Figure S14: 1D NOESY spectrum of **20b + 20c** (irradiation of H-5 of **20b** at 4.04 ppm, 400 MHz, $CDCl_3$); Figure S15: 1D NOESY spectrum of **20b + 20c** (irradiation of H-3a of **20c** at 3.82–3.78 ppm, 400 MHz, $CDCl_3$); Figure S16: 1D NOESY spectrum of **20b + 20c** (irradiation of H-2 of **20c** at 4.60 ppm, 400 MHz, $CDCl_3$). For all the obtained products that are known compounds reported in the literature (**11**–**15**, **18**, **21**) ^{1}H NMR spectral data and m.p. when solid are reported in the Supplementary Materials and are in agreement with the literature. For all obtained new compounds (**16** and **20a**–**c**) ^{1}H NMR, ^{13}C NMR, 1D NOESY spectra are reported in the Supplementary Materials. Refs. [38,42–50,52,53,55,56] are mentioned in the Supplementary Materials.

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