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Microreview

Asymmetric Synthesis

Levoglucosenone and Its New Applications: Valorization of Cellulose Residues

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Dedicated to Professor Madeleine M. Joullié, an outstanding scientist and a great mentor

Abstract: The need to find sustainable alternatives to reduce the dependence on fossil sources has led to significant research efforts on the conversion of biomass into platform chemicals. Modern organic chemistry requires easily obtainable chiral building blocks that show high chemical versatility for their application in the synthesis of enantiopure compounds. The selective pyrolytic conversion of cellulose or cellulose-containing materials produces levoglucosenone, a highly functionalized chiral structure. This compound has been innovatively used as a template for the synthesis of key intermediates of biologically active products and for the preparation of chiral auxiliaries, catalysts, and organocatalysts for their application in asymmetric synthesis.

1. Introduction

Around the world, significant actions are being undertaken to switch from today's fossil-based economy to a more sustainable bioeconomy. A key factor to achieve this goal will be the development of highly efficient and cost-effective processing of biological feedstock to a range of bio-based products which will allow bridging the gap between economic growth and environmental sustainability in the long term. Additionally, it is generally recognized that the resources of the world are limited and sustainability has become a crucial point for the development of chemical products. These circumstances impose a great urgency to find renewable sources for their transformation into useful products including chemicals, fuels, and materials for replacing the enormous demand for petroleum.

Biomass has received particular attention because it represents the only abundant source of renewable organic carbon. More importantly, its oxygenated nature, chemical diversity, and chirality render biomass a highly suitable raw material to

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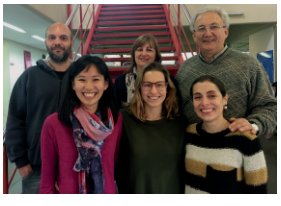

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manufacture a multitude of high-added-value compounds.[1] Chirality at the molecular level has emerged as one of the major issues in the development of chemical technology, especially in the areas of drug synthesis and advanced materials. Among the plethora of natural molecules, carbohydrates are the most prominent members of the chiral pool since they are main constituents of all foremost structural molecules in living systems. By far, carbohydrates are the annually leading renewable biofeedstock from which to develop viable organic chemicals that can compete or eventually replace those derived from fossil sources. Cellulose is the single most abundant organic compound on earth.[2] This biopolymer is based on cellobiose as monomer, formed by two units of D-glucose linked by a β(1→4) bond, which is a great source of chirality if appropriately treated.

Pyrolysis is one of the most promising technologies for biomass utilization. Solid biomass can be converted into charcoal, liquid bio-oil, and noncondensable gases.[3] Because of the advantages of universality, renewability, easy transport, and high energy density, bio-oil attracts a lot of attention.[4] Besides, bio-oils contain hundreds of organic compounds from which many of them could turn into specific value-added chemicals.[5] However, to solve the problem associated with complex mixtures, selective pyrolysis has been put forward to produce some specific chemicals by controlling the process properly, such as choosing suitable raw materials, adding specific catalysts, pretreating feedstock, and selecting appropriate pyrolysis conditions.[6]

Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose, **1**, Figure 1), is thus considered to be a promising biorenewable platform for both fine and commodity chemical industries.[7] Levoglucosenone has an advantage over other biomass platform chemicals because it can be directly produced by pyrolysis of cellulose-containing urban and industrial residual materials such as waste paper. The highly functionalized structure of **1** makes it an attractive chiral synthon for the synthesis of a wide variety of natural and unnatural compounds.[8] The 1,6-anhydro bridge locks the pyranose ring in the $^1C_4$ conformation and sterically hinders the β-face of the molecule providing an excellent facial selectivity. Since the first report on the preparation of levoglucosenone more than 4 decades years ago,[9] different research studies were conducted to develop a wide variety of applications of this chiral template. The synthesis of several chemical compounds, such as natural products, nucleosides, anticancer drugs, building blocks and green solvents have been reported.[10,11]

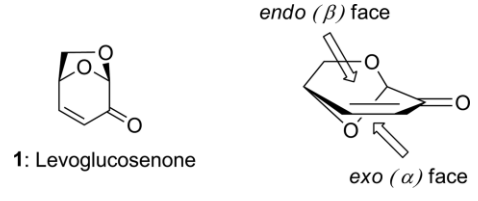


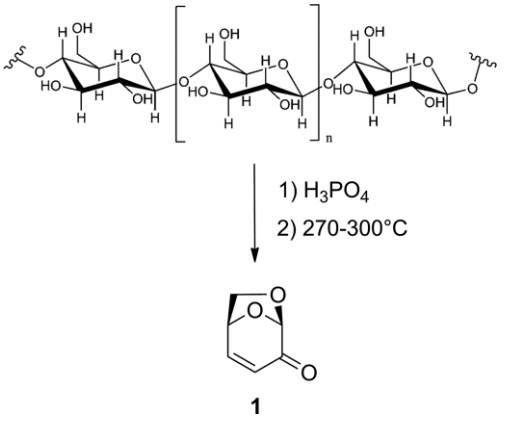
Figure 1. Levoglucosenone structure.

In the context of our ongoing interest in the development of new tools for the preparation of optically active compounds, we devoted a great deal of effort to the design and synthesis of original chiral synthons, inductors and biological active compounds derived from levoglucosenone. The novel compounds can enable the generation of new functional materials, thus broadening the existing portfolio of chiral chemicals. Furthermore, the current research attempts to incorporate the principles of sustainability and green chemistry in the preparation and application of the new chiral compounds. Particular focus is given to reviewing the status of levoglucosenone application in asymmetric synthesis and chiral amplification, highlighting recent results of its conversion towards high value-added chemicals.

2. Preparation of Levoglucosenone

There are different methodologies for the preparation of levoglucosenone; however, the shortest and most straightforward procedure is the pyrolysis of cellulose or cellulose containing materials. A thorough study of the relevant variables of the pyrolytic process has demonstrated that temperature, pressure and catalyst concentration, heat and mass transfer are the main factors. It has been reported that the acid-catalyzed pyrolysis process allows increasing the selectivity towards levoglucosenone, when using glucose, cellulose or birch and pine wood among different biomass sources, and phosphoric acid as a catalyst, under conventional thermal pyrolysis.[12,13] The use of solid superacids and zeolites as acid catalysts was also investigated,[14] as well as the effect of ionic liquids.[15] It was also demonstrated that the pyrolytic conversion of microcrystalline cellulose assisted by microwave irradiation generates **1** as the main product in the bio-oil.[16]

Although an alternative approach for the synthesis of **1** starting from D-galactose has been reported,[17] the most common method to obtain levoglucosenone in preparative scale is the pyrolysis of cellulosic materials[18] (Scheme 1). In a typical experiment for the pyrolytic conversion of microcrystalline cellulose, the acid pretreated sample with catalytic amounts of H_3PO_4 is introduced in an electric furnace at 270–300 °C affording a bio-oil which contains the desired enone as the main product, with 2-furfuraldehyde as the major impurity present in 5–10 %. Vacuum distillation allows to obtain levoglucosenone with sufficient purity for synthetic transformation.[17]



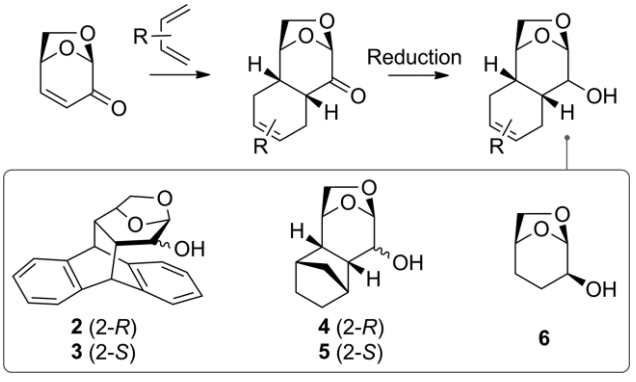
Scheme 1. Cellulose pyrolysis.

3. Levoglucosenone in Asymmetric Synthesis

Enantiomerically pure chiral molecules have deeply impacted different branches of science: drugs, optic and electronic systems, polymers with new properties and probes to evaluate biological functions represent just a few examples. Therefore, asymmetric synthesis emerges as a central discipline within modern organic chemistry.[19] Although the sophistication of this fascinating field has reached unsuspected limits, the development of new, effective and simple synthetic procedures to carry out chemo, regio- and enantioselective transformations continues to be a huge challenge in years to come. Moreover, the search of abundant and renewable supplies of chiral scaffolds for the development of new tools for asymmetric synthesis has received considerable attention in the recent past, highly motivated by the increasing awareness in environmental issues.[20] In this regard, our group has been interested in exploring the synthetic utility of levoglucosenone in the field of asymmetric synthesis, as will be discussed in this section.

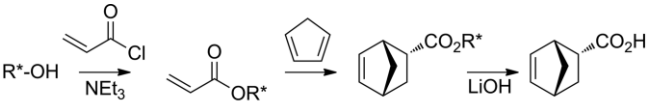
3.1. Chiral Auxiliaries

Our initial efforts were focused on the development of chiral auxiliaries for Diels–Alder reactions, one of the most valuable reactions to afford six-membered rings in high regio- and stereoselectivity. Taking advantage on the high dienophilicity exhibited by **1**, the first generation of chiral auxiliaries was synthesized following a Diels–Alder/reduction strategy. Hence, the [4+2] cycloaddition with suitable dienes allowed the introduction of elements of stereocontrol with different bulkiness at the α face of the molecule, whereas the reduction of the ketone group to the corresponding alcohol was thought to facilitate the covalent binding with the prochiral substrate. Following this approach, four different chiral auxiliaries were synthesized (**2**–**5**, Scheme 2) in order to determine the relationship between the absolute configuration at the carbinolic center and the steric hindrance exerted by the diene moiety with the asymmetric induction capacity of the corresponding alcohol.[21–23] Moreover, we also investigated saturated alcohol **6** (easily synthesized from **1** in 2 steps) as chiral promoter.[24]



Scheme 2. First generation of chiral auxiliaries derived from levoglucosenone.

The inductive capacity of alcohols **2**–**6** were evaluated in Diels–Alder reactions between the corresponding acrylic esters (simply prepared by treatment of the chiral alcohol with acryloyl chloride and base) and cyclopentadiene. As depicted in Scheme 3, modest *endo*/*exo* and π-facial selectivities were observed under thermal conditions, accounting for the *s-cis*/*s-trans* conformational flexibility of the dienophile. On the other hand, the use of Lewis acids (in particular Et_2AlCl and $EtAlCl_2$) afforded significant increases in both *endo*/*exo* and diastereoselectivity ratios. These results were interpreted on the basis of a preferred *s-cis* conformation of the acrylate upon chelate formation (vide infra). Final disconnection by basic hydrolysis allowed the isolation of the desired norbornene carboxylic acid and the concomitant recovery of the chiral auxiliaries in high yields.[21–24]

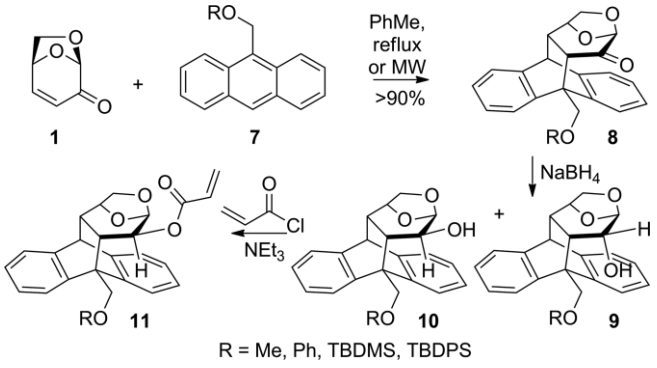


R*OH =	2	3	4	5	6	2	3	4	5	6
endo/exo	74/26	82/18	82/18	75/25	88/12	98/2	96/4	96/4	96/4	96/4
endo R/S	74/26	49/51	48/52	47/53	47/53	10/90	75/25	13/87	63/37	15/85
	Thermal Conditions					*Lewis Acids Conditions*				

Scheme 3. Evaluation of the inductive capacity of levoglucosenone-derived chiral auxiliaries in asymmetric Diels–Alder reactions.

The knowledge gathered in this first stage guided the design of a second generation of chiral inductors. Since **2** was the most promising structural motif, we hypothesized that the introduction of substituents at the benzylic position of **2** would provide new elements of steric control by imposing additional restrictions to the approach of the reagents through that side of the molecule. Our strategy to achieve this structural modification relied on the use of 9-substituted anthracene derivatives **7** (easily obtained from commercially available 9-anthracene methanol) as diene in the Diels–Alder reaction with levoglucosenone.[25–28] However, unlike was observed for anthracene, the cycloaddition reactions between **1** and **7** could not be promoted by $FeCl_3$ nor with any other Lewis acid. In fact, refluxing toluene for several days (7–10) were the only experimental conditions that afforded the desired products in good yields. To solve this drawback, we developed a microwave-promoted experimental protocol to obtain the adducts **8** in high yields and much shorter reaction times (4–5 h).[29] Further reduction of the carbonyl group of **8** gave the epimeric alcohols **9** and **10**, but only one of them could react with acryloyl chloride to yield the corresponding chiral acrylate (Scheme 4). The high steric hindrance of the other alcohol precluded its reaction. In order to increase the overall yield of the process, the unreactive alcohols **10** were oxidized to regenerate the starting ketone.[25–28]

The chiral acrylates **11** were evaluated in Diels–Alder reactions using five representative dienes, at different reaction conditions. The asymmetric induction varied with the nature of the diene and substituent at the benzylic position. In these cases, thermally or microwave-assisted reactions afforded modest *endo*/*exo* ratios and diastereoselectivities (up to 78:22 and 88:12, respectively). On the other hand, significant increase in selectivity was achieved when using Lewis acids at low temperatures (up to > 99:1), Figure 2. It was observed that R = Me and



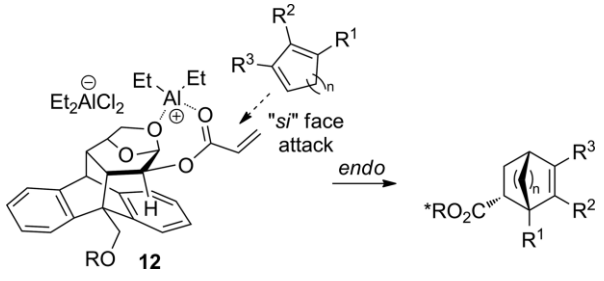
Scheme 4. Second generation of chiral auxiliaries derived from levoglucosenone.

Ph afforded the highest diastereoselectivities (up to 98 % d.e.). The hydrolysis of the cycloadducts gave the desired free carboxylic acids in high enantiomeric purity along with the corresponding chiral auxiliaries, that were recovered in quantitatively fashion to be reused.[25–28]

11a (R=Me)	98% d.e.	92% d.e.	90% d.e.	94% d.e.	72% d.e.
11b (R=Ph)	94% d.e.	88% d.e.	92% d.e.	94% d.e.	66% d.e.
11c (R=TBDMS)	82% d.e.	68% d.e.	78% d.e.	86% d.e.	52% d.e.
11d (R=TBDPS)	92% d.e.	86% d.e.	66% d.e.	84% d.e.	38% d.e.

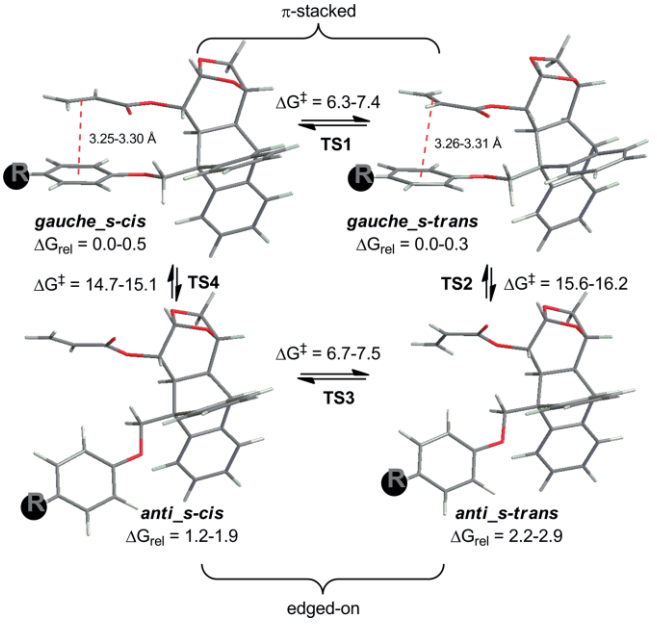
Figure 2. Best π-facial selectivities observed in the Lewis acid promoted Diels–Alder reactions between acrylates **11a–d** and five representative dienes.

The high diastereoselectivity observed when using Lewis acids was explained on the basis of the formation of a chelated complex like **12** (Scheme 5) that should be locked in the *s-cis* conformation. The addition of the diene from the more accessible face of such complex should afford the adduct *R*, as was experimentally observed. Detailed NMR spectroscopic studies of the intermediate complexes supported this hypothesis.[25,26]



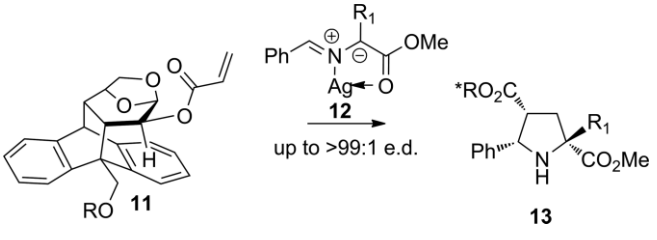
Scheme 5. Proposed mechanism for the Lewis acid promoted Diels–Alder reactions of levoglucosenone-derived chiral acrylates.

In the case of R = Ph, an interesting π-stacking interaction between the aromatic moiety at the benzylic position with the acrylate was found. Exhaustive NMR spectroscopic experiments and DFT calculations were carried out to account for the effect of such interaction in governing the diastereoselectivity of the asymmetric process.[26] The strength of the interaction when varying the electronic nature of the aromatic ring (by introducing electron withdrawing or releasing substituents at the *para*-position) was also explored, providing experimental and computational evidence to understand the effect of π-stacking interactions in the conformational dynamics of the interacting systems. In particular, we found that the equilibrium is governed by a fast *s-cis*/*s-trans* and a slow π-stacked/face-to-edged exchange conversions (Scheme 6), that in turn depends on the strength of the π–π interaction, higher for electron deficient aromatic rings.[11b]



Scheme 6. Gibbs free energy profile (in kcal/mol) computed for the conformational equilibrium of three chiral acrylates derived from levoglucosenone bearing different phenoxymethyl groups at the benzylic position, computed at the M06-2X/6-31+G(d) level of theory.

The high levels of selectivity achieved with the second generation of chiral auxiliaries derived from levoglucosenone in Diels–Alder reactions, prompted us to explore the scope of these inductors in other asymmetric transformations. For that reason, we next studied the 1,3-dipolar cycloaddition reactions between acrylates **11** and azomethine ylides, easily prepared in situ from iminoesters derived from the condensation of aldehydes and aminoesters. A combination of three representative chiral auxiliaries and azomethyne ylides derived from glycine, alanine and phenylalanine were studied at different reaction conditions (Scheme 7). The regio- and *endo* selectivities were



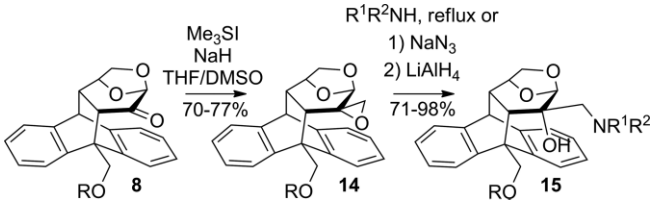
Scheme 7. Chiral auxiliaries derived from levoglucosenone in asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides.

high (> 99.9 %) and the yields and π-facial selectivities ranged from good to excellent (up to > 99:1).[30]

3.2. Chiral Ligands

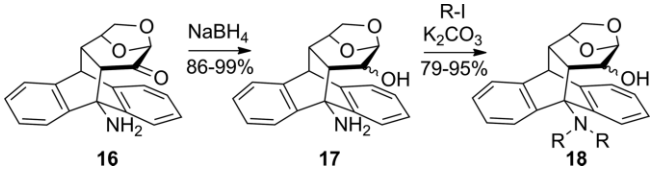
The use of chiral metal catalysts modified by chiral ligands is among the leading strategies to carry out organic reactions in excellent levels of enantiocontrol. Several chiral ligands have been developed in the last decades, and amino alcohols have attained a privileged position in the field.[31] For that reason, we also explored levoglucosenone as a chiral scaffold in the development of new amino alcohols as promising ligands in asymmetric transformations.

The strategy toward the preparation of the chiral 1,2-amino alcohols was envisaged using the Diels–Alder adducts **8**, easily obtained from levoglucosenone and anthracene or 9-substituted anthracenes. The key step was the transformation of the ketone functionality into an oxirane ring, that was accomplished using a Corey–Chaykovsky reaction.[32] As depicted in Scheme 8, the desired spiro-epoxides were obtained in very good yields and perfect levels of diastereoselectivity. The only isolated isomers were identified as those resulting from the attack of the ylide from the β-face of the molecule, indicating that the steric hindrance of the annulated anthracenyl moiety is higher than that exerted by the 1,6-anhydro bridge. Finally, ring-opening reactions with a variety of amines (or sodium azide followed by $LiAlH_4$ reduction) afforded the corresponding secondary/tertiary and primary amines, respectively, in high yields.[33]



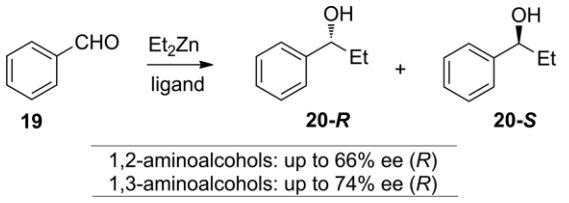
Scheme 8. Synthesis of 1,2-amino alcohols derived from levoglucosenone.

For the synthesis of 1,3-amino alcohols a conceptually different strategy was thought. A Diels–Alder reaction between levoglucosenone and 9-aminoanthracene under $FeCl_3$ catalysis, afforded adduct **16** in 91 % yield. Reduction of the carbonyl group gave access to the two epimeric amino alcohols **17**, that were further functionalized at the nitrogen group by different alkylating strategies[34] (Scheme 9).



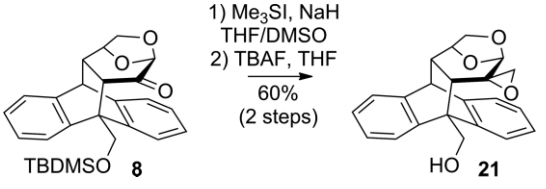
Scheme 9. Synthesis of 1,3-amino alcohols derived from levoglucosenone.

The suitability of the synthesized 1,2- and 1,3-amino alcohols derived from levoglucosenone as chiral ligands in asymmetric synthesis was assessed in the addition of Et_2Zn to benzaldehyde (Scheme 10). The level of induction obtained ranged from modest to very good, making this system a promising model to be further exploited in other asymmetric reactions.[33,34]



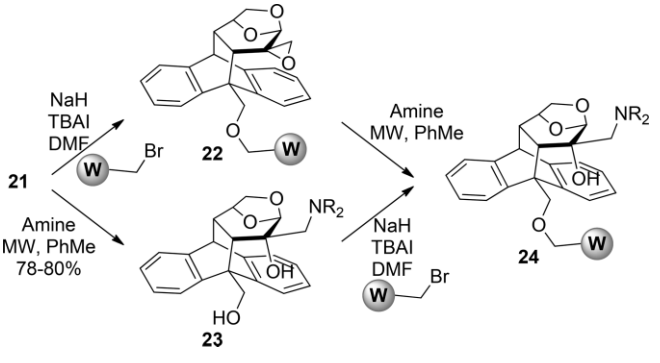
Scheme 10. Evaluation of the inductive capacity of chiral amino alcohols derived from levoglucosenone in the addition of Et_2Zn to benzaldehyde.

On the basis of those promising results, we next decided to explore the performance of the 1,2-amino alcohols after immobilization on a solid support. This would allow additional benefits compared to their soluble counterparts, as the ligand could be recovered by simple filtration, hence avoiding chromatographic purifications and simplifying the recycling of the valuable chiral materials.[35] The strategy developed to achieve our goals relied on the synthesis of compound **21** using similar reactions described above (Scheme 11).[36]



Scheme 11. Synthesis of **21**, key intermediate for the development of solid-supported amino alcohols derived from levoglucosenone.

In this case, the pendant primary alcohol at the benzylic position of the spiro-epoxide afforded the necessary functionality to anchor to the solid support, as shown in Scheme 12. Two alternative synthetic methodologies were explored for the preparation of Wang resin-bounded 1,2-amino alcohols, depending if the amine-based ring opening of the epoxide took place before or after the binding of the chiral residue to the solid support. Evaluation of the inductive capacity of the solid-supported ligands in the addition of Et_2Zn to benzaldehyde afforded similar results to those previously noted in solution.[36]

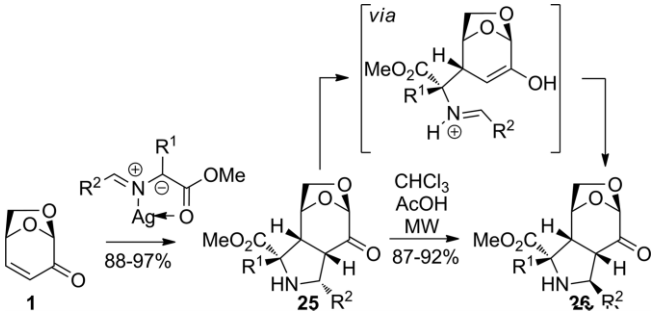


Scheme 12. Synthesis of polymer-supported 1,2-amino alcohols derived from levoglucosenone.

3.3. Chiral Organocatalysts

In further development of our interest of converting levoglucosenone into new and efficient tools for asymmetric synthesis, and having already explored the field of chiral auxiliaries and ligands, we next directed our attention towards organocatalysis. In the last decades, asymmetric organocatalysis has become one of the most exciting and deeply studied alternatives for the synthesis of enantiomerically pure compounds. The use of inexpensive, metal-free, nontoxic, and often cheap organic compounds as catalysts, along with the functional group tolerance, mild reaction conditions, and high enantioselectivities in a wide scope of asymmetric reactions, represent some of the most important features.[37] Among several molecular scaffolds that proved its value in organocatalysis, the pyrrolidines and related five-membered nitrogen containing groups have excelled for their broad application and high levels of enantioselectivity achieved.

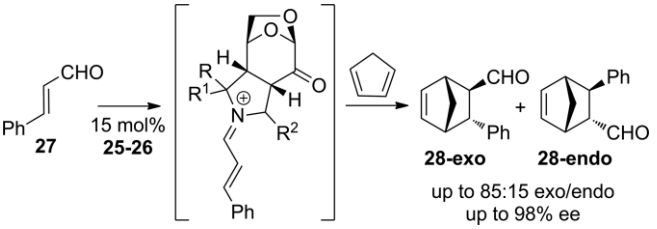
Our strategy for the synthesis of chiral pyrrolidines derived from levoglucosenone was based on the 1,3-dipolar cycloaddition of azomethine ylides. After optimizing the reaction conditions, the corresponding pyrrolidines **25** were obtained in excellent yields, with high regio- and stereoselectivities (Scheme 13). Moreover, we discovered and explored an acid-catalyzed microwave-assisted isomerization event at the benzylic position of the *endo* adducts, affording polysubstituted pyrrolidines **26** with relative configurations difficult to obtain by other synthetic procedures.[38]



Scheme 13. Synthesis of chiral pyrrolidines derived from levoglucosenone.

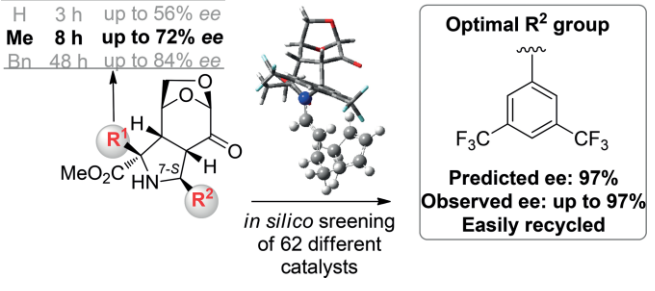
From kinetic measurements, NMR spectroscopic studies and DFT calculations we determined that such epimerization occurs through a retro-Mannich//Mannich cascade.[39] The synthesized pyrrolidines were next evaluated as chiral organocatalysts in the Diels–Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene, Scheme 14. All compounds proved to be active catalysts, achieving good to excellent yields in 5–48 h with 15 mol-% of catalyst and co-catalyst loading. An unusual *exo* selectivity was also noted (*exo*/*endo* = 85:15), outcome that was shared with only few organocatalytic systems. The enantioselectivity was also good (up to 76 % *ee*), making these compounds excellent candidates for further optimization.[38]

Such promising results encouraged us to pursue the design and development of a new generation of more efficient organocatalysts. We first undertook a complete experimental study aimed to unravel the structure-activity relationship of these types of catalysts. Following the optimized reaction conditions



Scheme 14. Evaluation of the chiral pyrrolidines derived from levoglucosenone as iminium-based organocatalysts in asymmetric Diels–Alder reactions.

shown in Scheme 13, we synthesized 21 different pyrrolidines bearing three dimensions of molecular diversity: the relative stereochemistry at C-7 and C-8, and the nature of the R^1 and R^2 groups at those positions. Despite all the compounds displayed important catalytic activity, increasing up to 160-fold the reaction rate of the Diels–Alder reaction under study, the pyrrolidines with 7(*S*) configuration were shown to be much more reactive than those with the opposite configuration at C-7.[40] In addition, considering a balance between reactivity and selectivity, the catalysts derived from alanine (R^1 = Me) were chosen for further optimization (Scheme 15). From NMR spectroscopic experiments and DFT calculations we could demonstrate that a reactive iminium intermediate with *E*-geometry was formed by condensation of (*E*)-cinnamaldehyde and the catalyst (Scheme 14). In fact, the sense of asymmetric induction experimentally found was consistent with the approach of the diene from the less hindered face of such iminium ion (*Re* face). The enantioselectivity predicted from DFT calculations at the B3LYP/6-31G* level of theory of all competing transition states (TS) nicely reflected the experimental values (78 % *ee* vs. 72 % *ee*, respectively).[40] This offered a paramount opportunity to find the optimal R^2 group at C-7 from an *in silico* screening, though a considerable reduction in the overall computational cost was required to make the system tractable. Hence, the hybrid ONIOM method was evaluated,[41] in which only the core region involving bond-forming and bond-breaking events are treated at high quantum levels (in this case, B3LYP/6-31G*), whereas the rest of the system is modelled with a less demanding method (in this case, AM1). After validating the ONIOM model with eight known and representative organocatalysts (showing a high correlation between experimental and calculated *ee* values), we next predicted the induction capacity of 62 different catalysts bearing a wide variety of groups at R^2. After the calculations were done, we selected three representative catalysts



Scheme 15. Rational design of a highly efficient organocatalyst derived from levoglucosenone in asymmetric Diels–Alder reactions.

for further synthesis and evaluation: the top-scored one, a medium-scored one and the low-scored one. These amines were prepared following our previously optimized procedure in high yields, and were evaluated in the Diels–Alder reaction between cinnamaldehyde and cyclopentadiene. Interestingly, the experimentally found enantioselectivities were in perfect agreement with the theoretical predictions.[40]

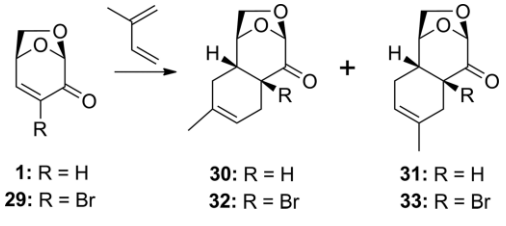
In addition, we proved that the optimal organocatalyst, the 3,5-di(trifluoromethyl)phenyl derivative (Scheme 15) could be recovered in quantitative fashion after workup an column chromatography, and reused more than five times with no apparent loss in the catalytic capacity.[4] °Current research is being made with the evaluation of these promising catalysts derived from levoglucosenone in other synthetically useful chemical transformations, and will be published in due course.

4. Enantiospecific Synthesis

Levoglucosenone has also been recognized as a versatile and potentially useful building block for the construction of complex molecular structures. Several authors have reviewed the applications of levoglucosenone as starting material for different types of final products.[8]

4.1. Synthesis of Natural Products and Chiral Intermediates

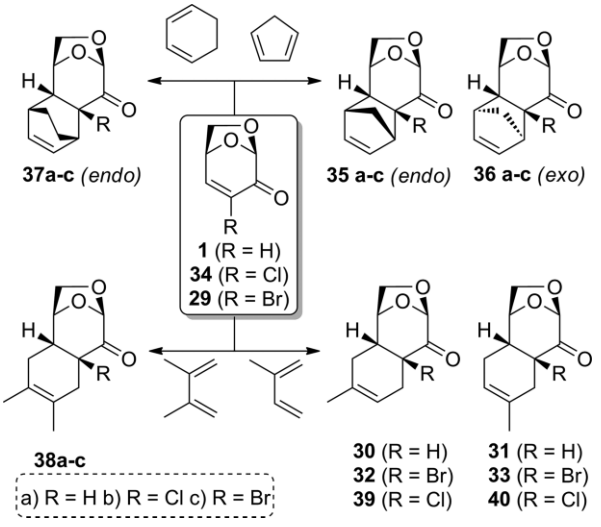
As it was already stated, the Diels–Alder reaction is one of the most powerful methods to synthesize, six-membered carbocyclic systems in a regio and stereocontrolled manner with several stereogenic centers in one step. Our group has been interested in this type of transformations for some time since it is an excellent synthetic tool in the construction of complex molecular skeletons.[42] One of the main features of this chemical transformation is the regioselective product formation when using unsymmetrical dienes and dienophiles. In simple cases the outcome can be generally predicted by the *ortho*/*para* rule. In this regard, we came across a regiochemical uncertainty found in the literature that recalled our attention when comparing the results of the Diels–Alder reaction between levoglucosenone and isoprene which were reported to afford the *meta* isomer[43] **31** (Scheme 16) and the ones published by Isobe et al.[44] with 3-bromolevoglucosenone (**29**) and the same diene that yielded the *para* adduct **32**. These reports prompted us to reinvestigate the reaction outcome using DFT calculations and experimental evidences. The new results allowed us to demonstrate that both reactions displayed the same *para* regioselectivity.[45]



Scheme 16. Regioselectivity in Diels–Alder reaction with isoprene.

At this point, we realized that it was also necessary to conduct an experimental and computational study to assess the effect of chlorine and bromine substitution in Diels–Alder reactions involving chiral α-halo enones as dienophiles.[46]

The Diels–Alder reaction using α-halo substituted enones as dienophiles is a synthetically useful method for the synthesis of *cis*-fused bicyclic ketones, bearing angular halogenation α to the carbonyl function. It should be expected that the introduction of an additional electron-withdrawing group to the carbon–carbon double bond of the enone moiety should enhance the dienophilic character, therefore increasing the reactivity in normal electron demanding Diels–Alder reactions. However, no systematic study had been pursued in order to assess the exact role of a halogen substitution in the rate and selectivity of Diels–Alder reactions involving α-halo enones (Scheme 17).



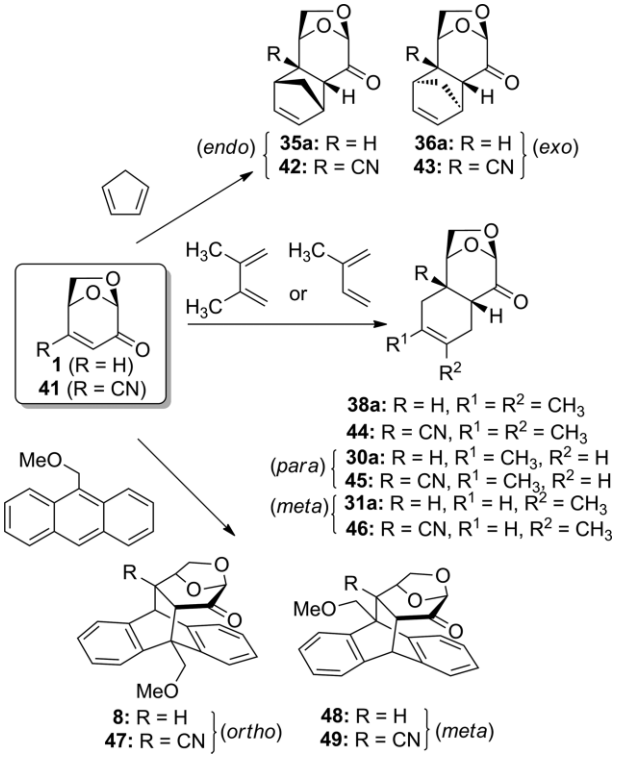
Scheme 17. Effect of halogen substitution at C-3 on the regioselectivity.

The study revealed an important rate enhancement only in the case of acyclic dienes, while the use of cyclic dienes resulted in prolonged reaction times and lower yields. DFT calculations not only effectively reproduced the reactivity and selectivity trends, but also proved that these reactions are governed by delicately balanced geometric and electronic features at the transition states.

In the context of our ongoing interest to synthesize chiral amines from levoglucosenone as novel ligands and catalysts, we have foreseen the introduction of a cyano group at the C-4 position of levoglucosenone. This structural modification would offer the possibility to create *cis* fused bicyclic ketones bearing angular cyano group β to the carbonyl, that could subsequently be easily transformed into other useful derivatives, such as 1,4-amino alcohols. We speculated that the presence of an *exo*-cyclic electron withdrawing group (EWG) should increase the reactivity of the dienophile, but would also lead to some ambiguity about which group (i.e. the ketone or the cyano) will have the dominant influence on regio- and stereoselectivity in Diels–Alder reactions with different dienes.

For these reasons, we undertook a comparative computational and experimental study of Diels–Alder reactions between levoglucosenone and 4-cyano-levoglucosenone (Scheme 18) with four different dienes: cyclopentadiene, 2-methyl-1,3-

butadiene, 2,3-dimethyl-1,3-butadiene and 9-anthracene methanolmethyl ether that could lead to regioisomeric adducts.[47] The collected experimental and computational data allowed to understand the effect of a β-cyano substitution in the dienophilic performance of the corresponding enone and predict the reactivity enhancement. However, when dealing with dienes and dienophiles with no clear electronically activated position the regiochemical preference was affected by the ease of pyramidalization of the interacting atoms.

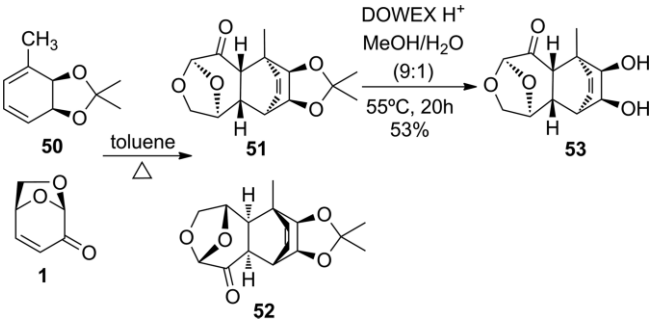


Scheme 18. Effect of a second EWG at C-4 on the regioselectivity.

In recent years there has been an increasing interest to build structural diversity, often targeting complex chiral molecules that resemble natural products in the search for new bioactive structures. These natural product like compounds usually comprise molecules with several rings and well defined stereogenic centers. At this point, the Diels–Alder reaction between two optically pure entities like levoglucosenone and the acetonide (**50**) prepared from (1*S*,2*R*)-3-methylcyclohexa-3,5-diene-1,2-diol cyclohexadiene diol which, in turn, was obtained by microbial oxidation of an aromatic precursor, could fulfil the conceptual requirements for the generation of structural complexity and diversity in an expeditious manner. Surprisingly the Diels–Alder reaction, which could potentially afford up to 8 stereoisomers, yielded mainly one product plus a minor quantity of a second isomer[48] (Scheme 19).

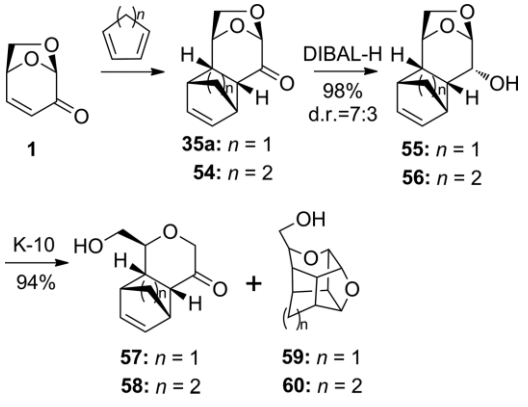
In this case, NMR spectroscopic analysis was not enough to solve the complex structure and it was necessary to resort to an X-ray diffraction analysis to confirm it. Once again, quantum chemical calculations helped to shed light on the stereochemical outcome of the cycloaddition.

Among other different types of molecular architecture designed to achieve molecular complexity, the dioxa-caged com-



Scheme 19. Natural products like compounds.

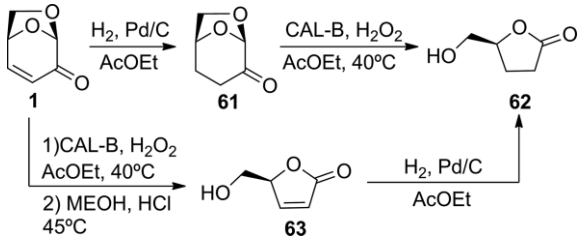
pounds showed highly promising applications. The access to enantiomerically pure caged products still remains a challenging endeavor an attractive challenge. For this reason, we developed a short and efficient methodology for the synthesis of novel chiral dioxa-caged compounds derived from the cycloaddition adduct from levoglucosenone and simple cyclic dienes. The reaction sequence involves a cascade 3-step cationic cyclization, which was performed in high yields and selectivities under mild condition with Montmorillonite K-10 as catalyst[49] (Scheme 20) The usefulness of this acidic aluminosilicate catalyst in related semi-pinacol rearrangements to obtain pyran-3-ones was also studied. Differences in the reaction pathways were found for the epimeric alcohols and DFT calculations were used to explain this stereoelectronic effects.



Scheme 20. Synthesis of dioxa-caged compounds.

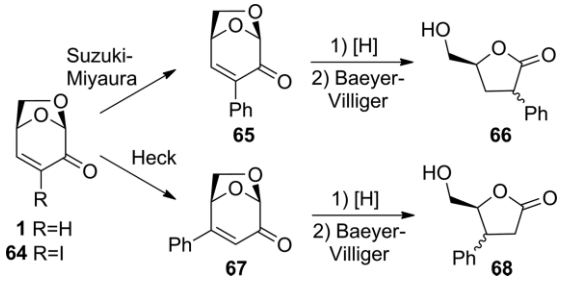
With a diverse approach, Paris et al.[50] used metal-containing zeolites as heterogeneous catalyst in a Baeyer–Villiger oxidation of levoglucosenone with hydrogen peroxide to generate optically pure γ-butyrolactones. Koseki et al.[51] had originally reported this synthetic transformation more than two decades ago but it is still of great interest and Flourat et al.[52] used a chemo-enzymatic approach for a similar oxidative conversion through a lipase-mediated Baeyer Villiger reaction. They employed *Candida Antarctica B* lipase as biocatalyst in the presence of hydrogen peroxide and acyl donor to obtain a mixture of the (*S*)-γ-hydroxymethyl-α,β-butenolide and the corresponding formate lactone (Scheme 21).

Greatrex and co-workers[53] have studied the used of modern methods of metal-catalyzed cross-coupling reaction to derivatize levoglucosenone in order to develop new transformations



Scheme 21. Synthesis of γ-butyrolactones.

that could turn this biorenewable resource into a novel building block. They used Suzuki–Miyaura, Heck and palladium-catalyzed hydroarylation reactions to afford C-3 and C-4 aryl-substituted levoglucosenone derivatives and their further conversion into chiral 5-hydroxymethyl-γ-butyrolactones by means of a Baeyer–Villiger oxidation step (Scheme 22).



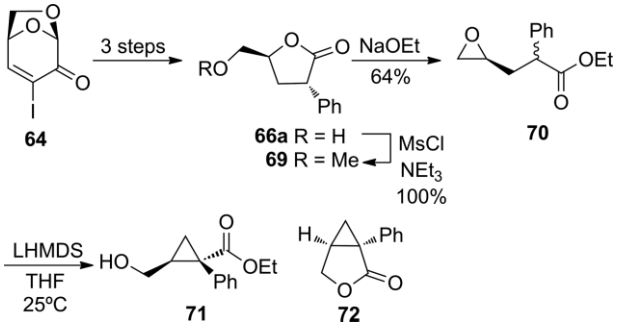
Scheme 22. Synthesis of substituted γ-butyrolactones.

Their attempts to introduce benzyl groups on the 3-iodide derivatives of levoglucosenone by a Suzuki–Miyaura reaction failed; however, they overcame the obstacle by a direct aldol reaction with dihydrolevoglucosenone. In this way, (*3R,5S*)-3-benzyl-5-(hydroxymethyl)-4,5-dihydrofuran-2*(3H)*-one, a precursor used for the synthesis of protease inhibitor Indinavir[54] was achieved in a straightforward manner.

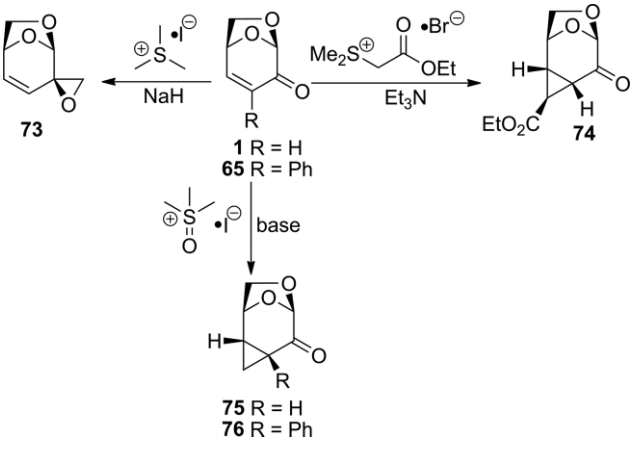
Subsequently, they used this derivatization procedure for the synthesis of chiral multi-functionalized cyclopropane rings, a moiety that is commonly encountered in synthetic bioactive materials, due to their rigid bond angles which restrict conformation freedom and promote selective interactions with biological targets. They first reported[55] the cyclopropane formation through the hydrogenation of the C-3 functionalized levoglucosenone derivative followed by Baeyer–Villiger oxidation to afford the 5-hydroxymethyl-γ-butyrolactone, epoxide formation and finally the intramolecular oxirane ring opening with concomitant cyclopropane ring closing (Scheme 23).

Lately Greatrex's group reported[56] the different chemical reactivity observed when using the stabilized or unstabilized sulfur ylides. For example the unstabilized dimethylsulfonium methylide yields epoxides by 1,2-addition to the ketone group present in levoglucosenone while stabilized ylides like dimethylsufoxonium methylide affords the cyclopropane ring through a 1,4-adddition to the α,β-unsaturated system (Scheme 24).

Isolevoglucosenone **81** is an isomer of levoglucosenone with a transposed unsaturated carbonyl system and also an interesting building block. Different strategies[57] have been reported regarding the conversion of levoglucosenone **1** into isolevo-

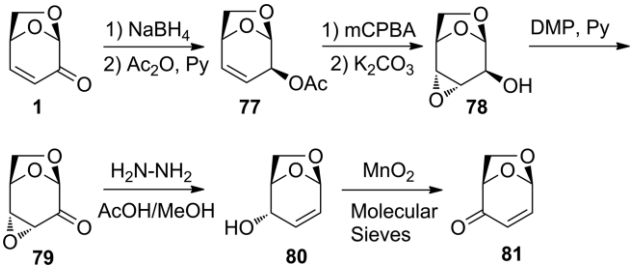


Scheme 23. Synthesis of chiral cyclopropane precursors.



Scheme 24. Direct cyclopropanation of levoglucosenone.

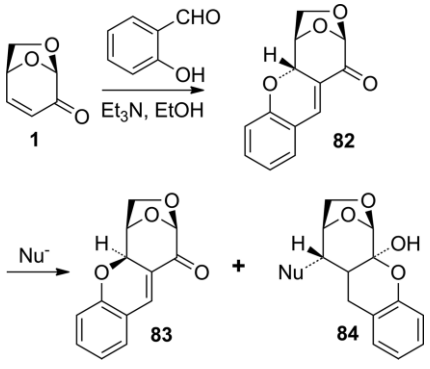
glucosenone **81**, the most recent approach involves a Wharton rearrangement of an epoxy-ketone.[57f] Direct epoxidation of the α,β-unsaturated carbonyl system proved to be unsuccessful but the oxirane ring could be efficiently prepared from the allylic alcohol. The epoxidation diastereoselectivity was substantially increased when the corresponding allylic acetate **77** was the starting material. Acetate hydrolysis and reoxidation of the alcohol **78** with Dess–Martin periodinane yielded the needed intermediate **79** which was subjected to the reaction with hydrazine to afford the rearranged product **80** and subsequently oxidized to yield **81** (Scheme 25).



Scheme 25. Conversion of levoglucosenone into isolevoglucosenone.

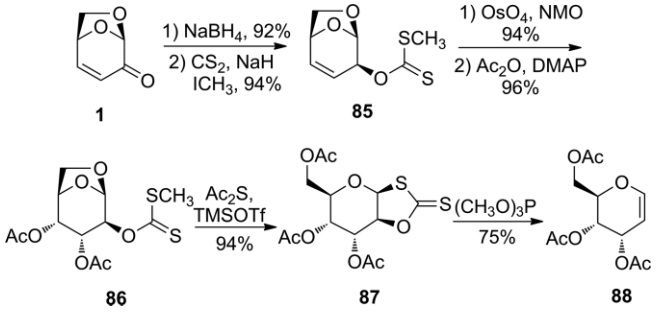
Brel et al.[59] synthesized different C-2 derivatives of dihydrolevoglucosenone by nucleophilic additions of vinyl and alkynyl fragments to the carbonyl group. Further transformation of the ethenyl or ethynyl substituents by [3+2] dipolar cycloaddition processes afforded different heterocyclic rings.

Samet et al.[58] reported a stereoselective oxa-Michael-aldol tandem reaction that levoglucosenone undergo with 2-hydroxybenzaldehydes to yield oxepino [4,5-*b*]chromen-1-ones **82** which can subsequently suffer a nucleophilic attack to undergo a chromene ring opening to afford different rearranged products **83** and **84** (Scheme 26).



Scheme 26. Oxa-Michael-aldol tandem reaction.

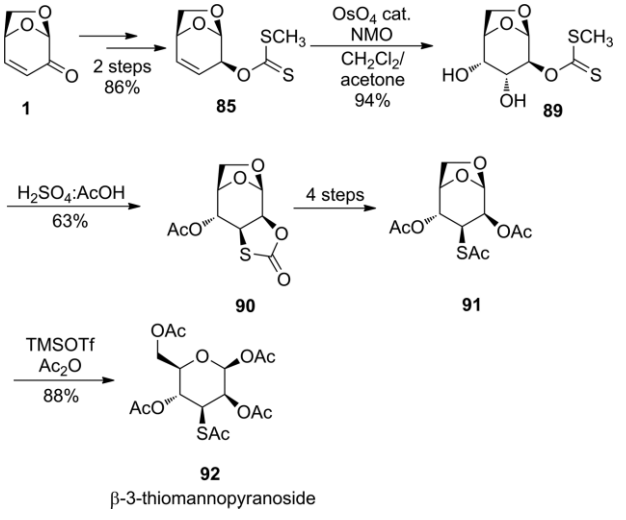
Glycals are versatile synthetic intermediates in carbohydrate synthesis owing to the chemical behavior of their enol ether functionality. The glycal method is a well-established procedure to obtain a wide array of glycoconjugated derivatives. However, not all the glycal configurations are easily available. D-glycals, such as D-gulal and D-allal are among those rare sugar derivatives. Different methods have been reported for the synthesis of D-allal,[60] but to the best of our knowledge none of them have allowed this building block to become commercially available. Hence, the development of a straightforward synthesis for this product is still a challenging goal. Based on the premises of simplicity and effectiveness, our group devised the synthesis of tri-*O*-acetyl-D-allal[61] **88** from levoglucosenone in six steps and 58 % overall yield, Scheme 27. More recently, in order to improve the *greenness* of the synthetic sequence a radical initiated fragmentation process was used to substitute the Corey–Winter protocol. Preliminary experiments showed promising results when using lauryl peroxide as radical initiator.



Scheme 27. Synthesis of tri-*O*-acetyl-D-allal.

On the other hand, thiosugars are an important class of carbohydrates derivatives due to their biological and physicochemical properties. Natural thiosugars have been used as biological targets and agents against bacteria, fungi, etc. In synthetic applications, these compounds have a remarkable use in glycosylation reactions. While anomeric thiosugars are common substrates, 3-thio and 4-thiosugars are interesting synthetic targets, and efforts have been devoted toward their construction.

In this case, we also used the allylic xanthate **85** as precursor for an efficient and straightforward synthesis of a novel 3-thiomannoside derivative (1,2,4,6-tetra-*O*-acetyl-3-*S*-acetyl-3-thio-β-D-mannopyranoside) (Scheme 28).[62] A *cis*-dihydroxylation of **85** under catalytic conditions afforded the diol **89**, further xanthate–thiocarbonate interconversion under acid mediated reaction was the key step for the new C–S bond formation in intermediate **90**. The free thiol spontaneously oxidized to the disulfide affording the dimeric structure. Reduction of the disulfide linkage and in situ acetylation allowed to achieve the ring-opening of the 1,6-anhydro bridge. The 3-thiomannopyranoside **92** was obtained enantiospecifically in eight synthetic steps in 14 % overall yield. This sulfur-containing monosaccharide offers significant opportunities for use as a surrogate of mannose for the construction of relevant glycomimetic molecules.



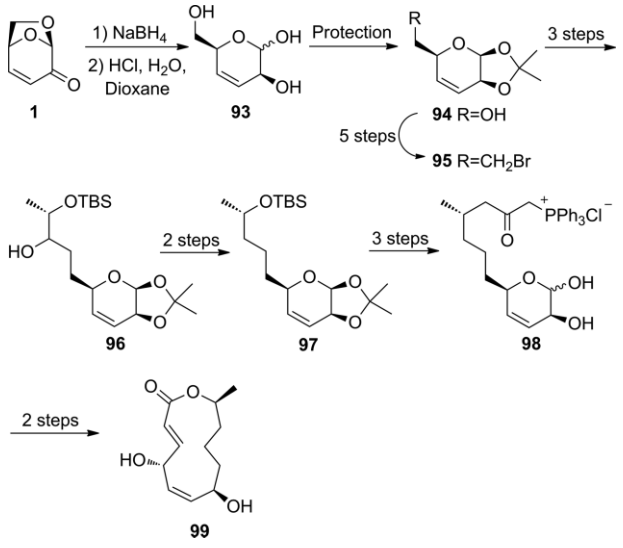
Scheme 28. Synthesis of 1,2,4,6-tetra-*O*-acetyl-3-*S*-acetyl-3-thio-β-D-mannopyranoside.

Schobert and co-worker[63] have developed an innovative approach for the construction of (+)-chloriolide **99**, a 12 membered macrolide, they used levoglucosenone as chiral scaffold and took advantage of the *Z* geometry of the double bond and C-5 stereochemistry plus the efficient reduction of the bicyclic ketone to obtain the hydroxyl group at C-2 with the needed stereochemistry (Scheme 29).

Valeev et al. reported different partial attempts toward the synthesis of Eleutherobin (**100**) and some analogs, also employing levoglucosenone as a key starting material (Figure 3).

Eleutherobin is a polycyclic natural product that belongs to the family of Eleuthesides. It was isolated in 1994 from soft corals and was the second compound after Taxol capable to stabilizing microtubules.[64] Its complex molecular architecture and interesting biological properties encouraged the scientific community to be interest on their chemical synthesis.[65]

A cycloaddition reaction of levoglucosenone with piperylene afforded cycloadduct **101** which was the starting point for the construction of substituted analogs of Eleutherobin's ring A[66–68] (Scheme 30).



Scheme 29. Synthesis of (+)-chloriolide.

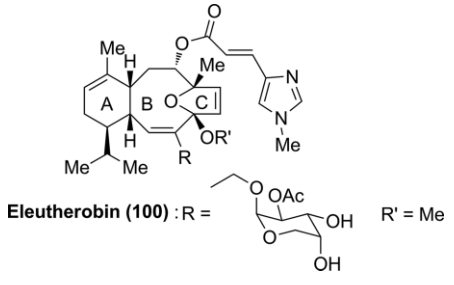
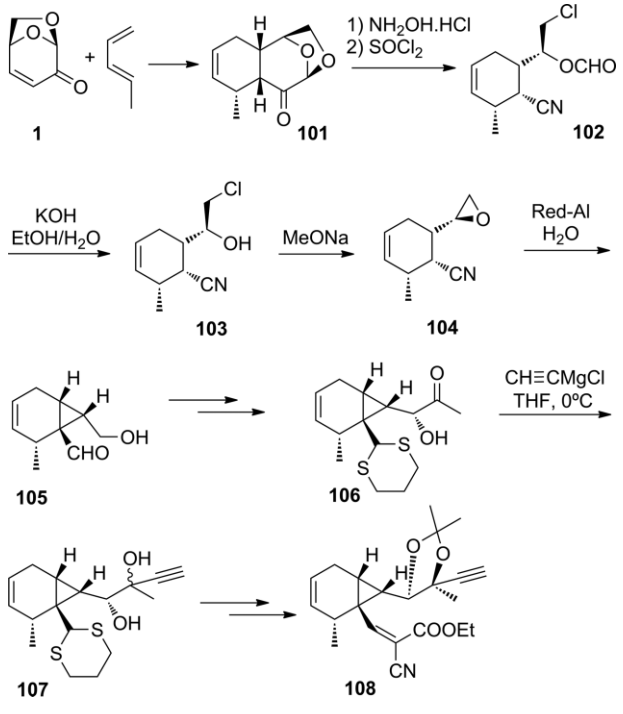
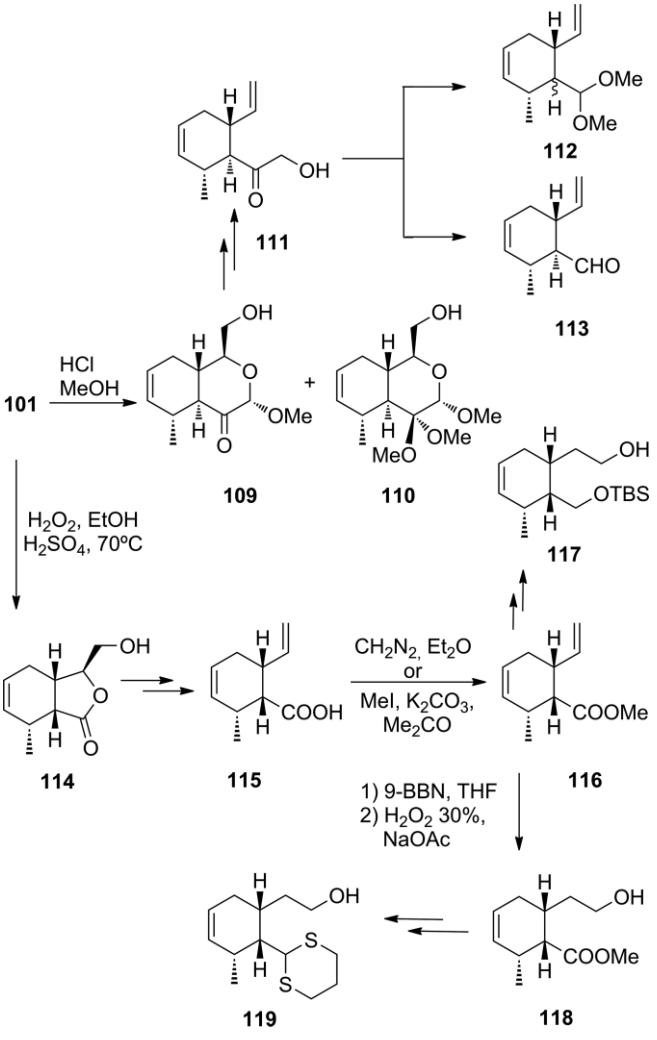


Figure 3. Eleutherobin.



Scheme 30. Attempts towards the synthesis of Eleutherobin's ring A.

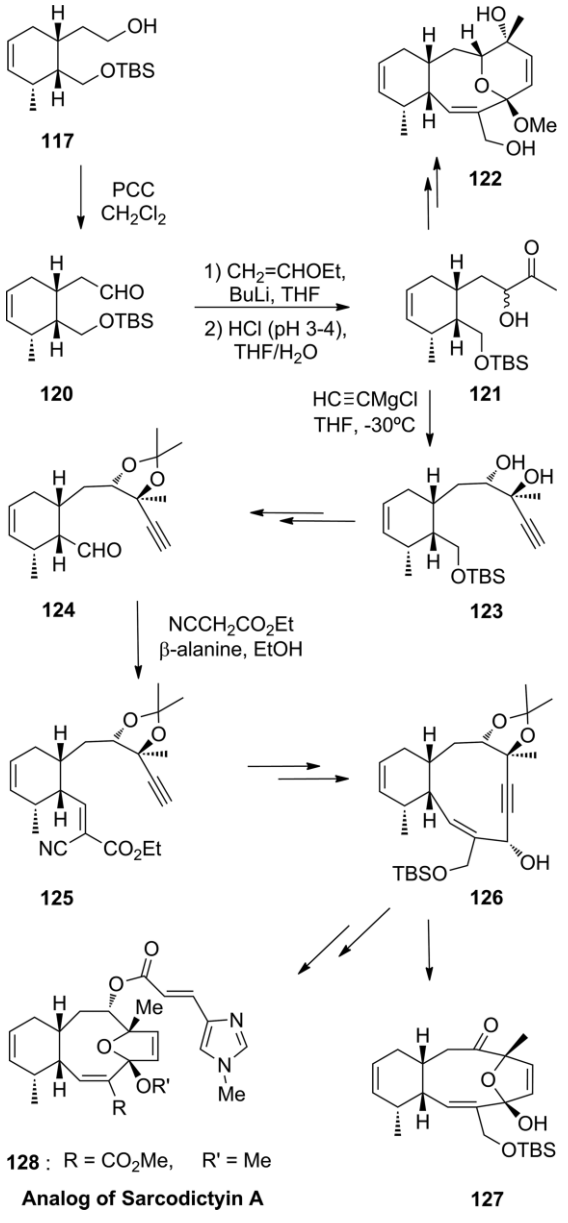
The functionalized cyclopropane derivative **105** was a key intermediate in their synthetic strategy but further attempts to obtained structurally related cyclopropane derivatives were unsuccessful.[69] Another trial described by the group[70] started with compound **101** which was transformed in two different precursors for the preparation of ring A in Eleutheside analogs Scheme 31.



Scheme 31. Others attempts towards the synthesis of Eleutherobin's ring A.

Intermediate **107** was subsequently used for the synthesis of the ten-membered carbocycle skeleton present in the Eleutheside family of natural products[71] (Scheme 32) as well as the macrocycle ring system present in the Eunicellane[72] and Sarcodictyin[73] families of diterpenoids (**128**), two other kinds of marine natural products with potent cytotoxic effects.

Several synthetic approaches of this group were focused in the structural modification of ring A, ring C and to obtain lactone structures related with Eleutheside. In the first case, they applied a Diels–Alder reaction between levoglucosenone and more functionalized dienes in order to obtain different menthane derivatives and oxa-cage derivatives.[74] For ring C, they developed a 1,2-addition reaction to yield a chiral carbon chain that represent the C-3-C-8 Eleutheside`s fragment[75] and in the last example, applying Diels–Alder and Michael addition with different cycloalkanones, they obtain medium and large-size lactones also related with Eleutheside.[76]



Scheme 32. Approaches towards the synthesis of Eleutherobin's ring C.

Several synthetic approaches of this group were focused in the structural modification of ring A, ring C and to obtain lactone structures related with Eleuthesides. In the first case, they applied a Diels–Alder reaction between levoglucosenone and more functionalized dienes in order to obtain different menthane derivatives and oxa-cage derivatives.[74] For ring C, they developed a 1,2-addition reaction to yield a chiral carbon chain that represents Eleutheside's C-3–C-8 fragment,[75] and in the last example, applying Diels–Alder and Michael addition with different cycloalkanones, they obtained medium- and large-size lactones also related with Eleuthesides.[76]

Other skeletons associated with natural products that Valeev's group prepared starting from levoglucosenone includes the iridoids family, γ-butyrolactones such as whisky and cognac lactones, and estrone analogs. Iridoids are a type of monoterpenoids in the general form of cyclopentanopyran, found in a wide variety of plants and some animals. In plants, they act primarily as a defense against herbivores or against infection by microorganisms.[77]

The *trans*- and *cis*-5-butyltetrahydro-4-methylfuran-2-ones have been identified as aroma components of aged alcoholic beverages such as whisky, cognac or other spirits from oak barrels in which they are kept for maturing. These lactones are named according to commonly drink in which they are found. In view of the importance of these substances as flavors and the need for stereoselective routes to 4,5-disubstituted tetrahydrofuran-2-ones their structures have become popular for testing new synthetic methodology.[78] In order to obtain this type of structures, authors applied Diels–Alder reaction with levoglucosenone (**129**, **130**, **131**, **132**),[79,80] annulation of α-bromoisolevoglucosenone (**133**),[81] Dieckmann condensation over levoglucosenone derivative (**134**, **135**)[82] and functionalization of adducts of levoglucosenone by Baeyer–Villiger oxidations (**136**–**140**)[83] (Figure 4).

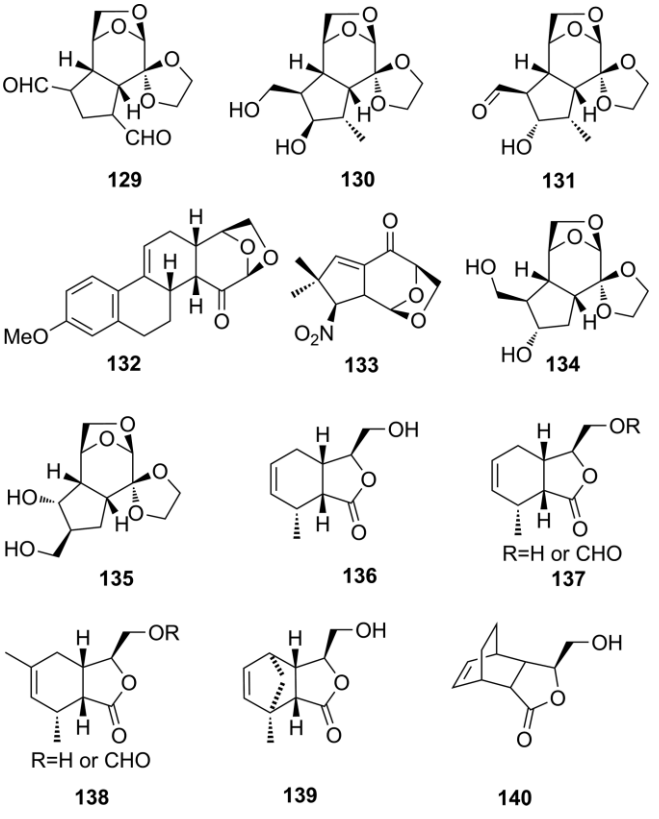


Figure 4. Molecular structures related to natural products.

4.2. Levoglucosenone as Building Block for De Novo Drug Design

In a recent publication Witczak et al. used the concept of "sugar code" to refer to the interaction of carbohydrates with cellular components and coined the idea of "Functional Carbohydrate-Pharmacophore" (FCP) as a novel strategy to study the biological response from functionalized sugar derivatives.

Based on literature precedents, thio-sugars may have therapeutic potential and can decrease cancer cell viability.[84] In

their study the authors[85] synthesized three (1–4)-*S*-thiodisaccharides that had been previously reported (**141**–**143**) and a novel thio-derivative **144** (Figure 5), all of them derived from levoglucosenone and were tested to ascertain their cytotoxicity and apoptosis induction ability on four different cancer cells lines. They found that the thiodisaccharides **141** was the most potent one, and taken together, the four compounds were potential anti-tumor agents with low toxicity.

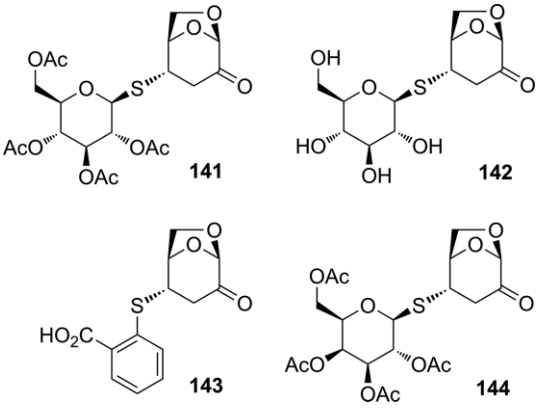


Figure 5. Witczak's thioderivatives.

Contemporary to this work, we designed a similar strategy and screened novel thio-derivatives (**145**–**149**) from levoglucosenone as well as 3-bromolevoglucosenone (**29**)[86] (Figure 6). The tests were conducted against two commonly used human hepatocarcinoma cell lines, Huh-7 and HepG2,[87] and revealed that levoglucosenone and 3-bromolevoglucosenone were active but also were those derivatives bearing an aromatic ring at C-4. Surprisingly, based on the IC_{50} value, compounds **29** and **147** were more active than Sorafenib, and the first one was even comparable in activity with Cisplatin, two of the drugs clinically used to treat HCC.

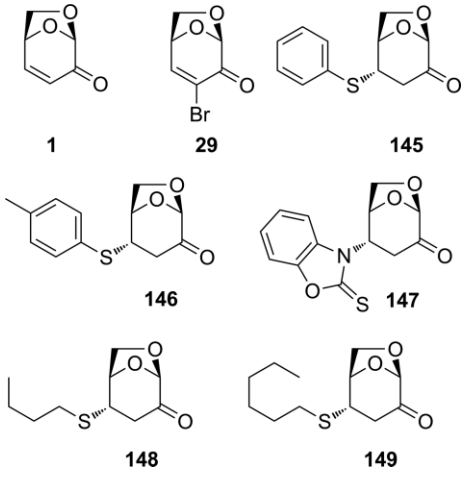


Figure 6. Compounds tested against hepatocarcinoma.

With another perspective we applied an autographic assay in a bioguided fractionation to analyze the biological effect of bio-oils produced by pyrolysis of soybean hulls. Levoglucosenone resulted to be the main constituent of the bio-oils and showed a remarkable antimicrobial activity against Salmonella *typhimurium*.[88] Further derivatization of this molecular scaffold (**6**, **29**, **61**, **78**, **150**, **151**) (Figure 7) allowed to assess the structure/activity relationship for the observed antibacterial effect.

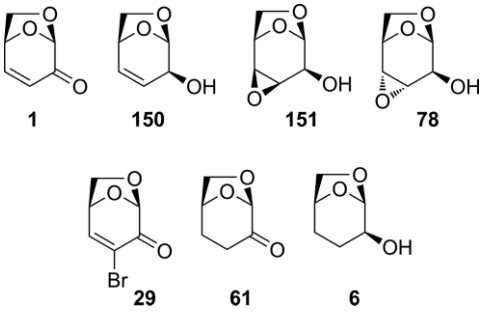


Figure 7. Compounds tested against Salmonella *typhimurium*.

The biological results suggest that the carbonyl group play an important role for the antibacterial activity. The loss of this functional group causes a significant decrease in the observed effect, only the 3-bromolevoglucosenone can improve the bioactivity.

5. Conclusions and Perspectives

Levoglucosenone is a promising and versatile organic molecule which offers a wide variety of applications in organic synthesis, including the development of new tools of asymmetric synthesis, enantiospecific synthesis of complex natural and unnatural products, and medicinal chemistry. In addition, this valuable enone can be easily obtained enantiomerically pure from the pyrolysis of biomass-derived materials, field that is currently receiving tremendous attention for green and sustainable issues.

Considering the actual need of replacing chemical feedstock derived from oil with more renewable alternatives, the suitability offered by levoglucosenone will surely motivate new and exciting studies in years to come.

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Keywords: Levoglucosenone · Asymmetric synthesis · Sustainable chemistry · Biomass · Cellulose

[1] F. W. Lichtenthaler, *Acc. Chem. Res.* **2002**, *35*, 728–737.
[2] a) S. Van de Vyver, J. Geboers, P. A. Jacobs, B. F. Sels, *ChemCatChem* **2011**, *3*, 82–94; b) S. Kromus, B. Kamm, M. Kamm, P. Fowler, M. Narodoslawsky in *Biorefineries – Industrial Processes and Products* (Eds.: B. Kamm, P. R. Gruber, M. Kamm), Wiley-VCH, Weinheim, **2008**, pp. 253–294.
[3] C. J. Liu, H. M. Wang, A. M. Karim, J. M. Sun, Y. Wang, *Chem. Soc. Rev.* **2014**, *43*, 7594–7623.
[4] M. X. Guo, W. P. Song, J. Buhain, *Renewable Sustainable Energy Rev.* **2015**, *42*, 712–725.

[5] a) H. M. Wang, J. Male, Y. Wang, *ACS Catal.* **2013**, *3*, 1047–1070; b) S. Adhikari, V. Srinivasan, O. Fasina, *Energy Fuels* **2014**, *28*, 4532–4538.
[6] a) C. Di Blasi, C. Branca, A. Galgano, P. D'Agostino, *Energy Fuels* **2015**, *29*, 6476–6484; b) T. Kan, V. Strezov, T. J. Evans, *Renewable Sustainable Energy Rev.* **2016**, *57*, 1126–1140.
[7] S. Kudo, N. Goto, J. Sperry, K. Norinaga, J. Hayashi, *ACS Sustainable Chem. Eng.* **2017**, *5*, 1132–1140.
[8] a) Z. J. Witczak (Ed.), *Levoglucosenone and Levoglucosans, Chemistry and Applications*, ATL Press, Mount Prospect, USA, **1994**; b) Z. J. Witczak, K. Tatsuta (Eds.), *Carbohydrate Synthons in Natural Products Chemistry. Synthesis Functionalization, and Applications, ACS Symposium Series No. 841*, American Chemical Society, Washington, DC, **2003**; c) A. M. Sarotti, M. M. Zanardi, R. A. Spanevello, A. G. Suárez, *Curr. Org. Synth.* **2012**, *9*, 439–459.
[9] a) Y. Tsuchiya, K. Sumi, *J. Appl. Polym. Sci.* **1970**, *14*, 2003–2013; b) Y. Halpern, R. Riffer, A. Broido, *J. Org. Chem.* **1973**, *38*, 204–209.
[10] V. Corne, M. C. Botta, E. D. V. Giordano, G. F. Giri, D. F. Llompart, H. D. Biava, A. M. Sarotti, M. I. Mangione, E. G. Mata, A. G. Suárez, R. A. Spanevello, *Pure Appl. Chem.* **2013**, *85*, 1683–1692 and references cited therein.
[11] a) J. Sherwood, M. De bruyn, A. Constantinou, L. Moity, C. Rob McElroy, T. J. Farmer, T. Duncan, W. Raverty, A. J. Hunta, J. H. Clark, *Chem. Commun.* **2014**, *50*, 9650–9652; b) V. Corne, A. M. Sarotti, C. Ramirez de Arellano, R. A. Spanevello, A. G. Suárez, *Beilstein J. Org. Chem.* **2016**, *12*, 1616–1623.
[12] M. De bruyn, J. Fan, V. L. Budarin, D. J. Macquarrie, L. D. Gomez, R. Simister, T. J. Farmer, W. D. Raverty, S. J. McQueen-Mason, J. H. Clark, *Energy Environ. Sci.* **2016**, *9*, 2571–2574.
[13] a) F. Shafizadeh, R. H. Furneaux, T. T. Stevenson, *Carbohydr. Res.* **1979**, *71*, 169–191; b) J. S. Swenton, J. N. Freskos, P. Dalidowicz, M. L. Kern, *J. Org. Chem.* **1996**, *61*, 459–464.
[14] X. Meng, H. Zhang, C. Liu, R. Xiao, *Energy Fuels* **2016**, *30*, 8369–8376 and references cited therein.
[15] S. Kudo, Z. Zhou, K. Norinaga, J.-i. Hayashi, *Green Chem.* **2011**, *13*, 3306–3311.
[16] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, *Green Chem.* **2007**, *9*, 1137–1140.
[17] M. Shibagaki, K. Takahashi, H. Kuno, I. Honda, H. Matsushita, *Chem. Lett.* **1990**, *19*, 307–310.
[18] C. Z. Morin in *Levoglucosenone and Levoglucosans: Chemistry and Applications* (Ed.: Z. J. Witczak), ATL Press, Mount Prospect, USA, **1994**, pp. 17–21.
[19] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto in *Comprehensive Asymmetric Catalysis, Vols. I–III*, Springer, New York, **1999**; b) G. Q. Lin, Y. M. Li, A. S. C. Chan in *Principles and Applications of Asymmetric Synthesis*, John Wiley & Sons, New York, **2001**.
[20] a) J. M. DeSimone, *Science* **2002**, *297*, 799–803; b) P. T. Anastas, T. C. Williamson in *Green Chemistry Frontiers in Benign Chemical Syntheses and Processes*, Oxford Science Publications, New York, **1998**; c) M. Butters, D. Catterick, A. Craig, A. Curzons, D. Dale, A. Gillmore, S. P. Green, I. Marziano, J. P. Sherlock, W. White, *Chem. Rev.* **2006**, *106*, 3002–3027.
[21] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, *Tetrahedron Lett.* **2004**, *45*, 8203–8206.
[22] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, *Tetrahedron Lett.* **2005**, *46*, 6987–6990.
[23] A. M. Sarotti, R. A. Spanevello, C. Duhayon, J.-P. Tuchagues, A. G. Suárez, *Tetrahedron* **2007**, *63*, 241–251.
[24] M. M. Zanardi, A. G. Suárez, *Tetrahedron Lett.* **2009**, *50*, 999–1002.
[25] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, *Org. Lett.* **2006**, *8*, 1487–1490.
[26] A. M. Sarotti, I. Fernández, R. A. Spanevello, M. A. Sierra, A. G. Suárez, *Org. Lett.* **2008**, *10*, 3389–3392.
[27] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, *Tetrahedron* **2009**, *65*, 3502–3508.
[28] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, *ARKIVOC* **2011**, *vii*, 31–37.
[29] A. M. Sarotti, M. M. Joullie, R. A. Spanevello, A. G. Suárez, *Org. Lett.* **2006**, *8*, 5561–5564.
[30] D. F. Llompart, A. M. Sarotti, V. Corne, A. G. Suárez, R. A. Spanevello, G. A. Echeverría, O. E. Piro, E. E. Castellano, *Tetrahedron Lett.* **2014**, *55*, 2394–2397.
[31] a) E. Juaristi, C. Anaya de Parrodi, *Synlett* **2006**, 2699–2715; b) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–837.
[32] a) Y. Peng, J. Yang, W. Li, *Tetrahedron* **2006**, *62*, 1209–1215; b) E. Corey, M. J. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353.
[33] M. M. Zanardi, M. C. Botta, A. G. Suárez, *Tetrahedron Lett.* **2014**, *55*, 5832–5835.
[34] M. M. Zanardi, A. G. Suárez, *Tetrahedron Lett.* **2015**, *56*, 3762–3765.
[35] a) A. Vidal-Ferran, N. Bampos, A. Moyano, M. A. Pericàs, A. Riera, J. K. Sanders, *J. Org. Chem.* **1998**, *63*, 6309–6318; b) P. Gaertner, A. Kundu in *Chiral Auxiliaries on Solid Support In The Power of Functional Resins in Organic Synthesis* (Eds.: J. Tulla-Puche, F. Albericio), Wiley-VCH: Weinheim, **2008**, p. 329.
[36] M. C. Botta, H. D. Biava, R. A. Spanevello, E. G. Mata, A. G. Suárez, *Tetrahedron Lett.* **2016**, *57*, 2186–2189.
[37] a) P. I. Dalko in *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley–VCH, Weinheim, **2007**; b) H. Pellissier in *Recent Developments in Asymmetric Organocatalysis*, The Royal Society of Chemistry, Cambridge, UK, **2010**; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; d) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; e) A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; f) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; g) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; *Angew. Chem.* **2004**, *116*, 5248; h) A. Milo, A. J. Neel, F. D. Toste, M. S. Sigman, *Science* **2015**, *347*, 737–743.
[38] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, G. A. Echeverría, O. E. Piro, *Org. Lett.* **2012**, *14*, 2556–2559.
[39] G. G. Gerosa, N. Grimblat, R. A. Spanevello, A. G. Suárez, A. M. Sarotti, *Org. Biomol. Chem.* **2017**, *15*, 426–434.
[40] G. G. Gerosa, R. A. Spanevello, A. G. Suárez, A. M. Sarotti, *J. Org. Chem.* **2015**, *80*, 7626–7634.
[41] a) S. Dapprich, I. Komaromi, K. S. Byun, K. Morokuma, M. J. Frisch, *THEOCHEM* **1999**, *461–462*, 1–21; b) I. B. Bersuker in *Computational Chemistry: Reviews of Current Trends, Vol. 6*, World Scientific, Singapore, **2001**, pp. 69–135.
[42] a) M. I. Mangione, A. M. Sarotti, A. G. Suárez, R. A. Spanevello, *Carbohydr. Res.* **2011**, *346*, 460–464; b) S. C. Pellegrinet, R. A. Spanevello, *Org. Lett.* **2000**, *2*, 1073–1976; c) S. C. Pellegrinet, R. A. Spanevello, M. T. Baumgartner, A. B. Pierini, *Tetrahedron* **2000**, *56*, 5311–5316; d) S. C. Pellegrinet, M. T. Baumgartner, A. B. Pierini, R. A. Spanevello, *Molecules* **2000**, *5*, 451–452; e) S. C. Pellegrinet, M. T. Baumgartner, R. A. Spanevello, *Molecules* **2000**, *5*, 411–412; f) S. C. Pellegrinet, R. A. Spanevello, *Tetrahedron Lett.* **1997**, *38*, 8623–8626; g) S. C. Pellegrinet, R. A. Spanevello, *Tetrahedron: Asymmetry* **1997**, *8*, 1983–1986.
[43] M. S. Miftakhov, I. N. Gaisina, F. A. Valeev, *Russ. Chem. Bull.* **1996**, *45*, 1942–1944.
[44] T. Nishikawa, M. Asai, N. Ohyabu, N. Yamamoto, Y. Fukuda, M. Isobe, *Tetrahedron* **2001**, *57*, 3875–3883.
[45] A. M. Sarotti, A. G. Suárez, R. A. Spanevello, *Tetrahedron Lett.* **2011**, *52*, 3116–3119.
[46] A. M. Sarotti, R. A. Spanevello, A. G. Suárez, *Tetrahedron Lett.* **2011**, *52*, 4145–4148.
[47] G. F. Giri, A. M. Sarotti, R. A. Spanevello, *Carbohydr. Res.* **2015**, *415*, 54–59.
[48] G. Carrau, N. Veiga, L. Suescun, G. F. Giri, A. G. Suárez, R. Spanevello, D. González, *Tetrahedron Lett.* **2016**, *57*, 4791–4794.
[49] M. A. Zurita, A. Avila, R. A. Spanevello, A. G. Suárez, A. M. Sarotti, *Carbohydr. Res.* **2015**, *402*, 67–70.
[50] C. Paris, M. Moliner, A. Corma, *Green Chem.* **2013**, *15*, 2101–2109.
[51] a) K. Koseki, T. Ebata, H. Kawakami, H. Masushita, Y. Naoi, K. Itoh, *Heterocycles* **1990**, *31*, 423–426; b) K. Koseki, T. Ebata, H. Kawakami, European Patent 0418925B1 (**1991**).
[52] a) A. L. Flourat, A. A. M. Peru, A. R. S. Teixeira, F. Brunissen, F. Allais, *Green Chem.* **2015**, *17*, 404–412; b) A. R. S. Teixeira, A. L. Flourat, A. A. M. Peru, F. Brunissen, F. Allais, *Front. Chem.* **2016**, *4*, 16.
[53] K. P. Stockton, C. J. Merritt, C. J. Sumby, B. W. Greatrex, *Eur. J. Org. Chem.* **2015**, 6999–7008.
[54] E. T. Ledingham, K. P. Stockton, B. W. Greatrex, *Aust. J. Chem.* https://doi.org/10.1071/CH17227.
[55] a) K. P. Stockton, B. W. Greatrex, *Org. Biomol. Chem.* **2016**, *14*, 7520–7528; b) A. A. M. Peru, A. L. Flourat, C. Gunawan, W. Raverty, M. Jevric, B. W. Greatrex, F. Allais, *Molecules* **2016**, *21*, 988–997.

[56] E. T. Ledingham, C. J. Merritt, C. J. Sumby, M. K. Taylor, B. W. Greatrex, *Synthesis* **2017**, *49*, 2652–2662.
[57] a) P. Köll, T. Schultek, R. W. Rennecke, *Chem. Ber.* **1976**, *109*, 337–344; b) R. H. Furneaux, G. J. Gainsford, F. Shafizadeh, T. T. Stevenson, *Carbohydr. Res.* **1986**, *146*, 113–128; c) D. Horton, J. P. Roski, P. Norris, *J. Org. Chem.* **1996**, *61*, 3783–3793; d) Z. J. Witczak, H. Chen, P. Kaplon, *Tetrahedron: Asymmetry* **2000**, *11*, 519–532; e) Z. J. Witczak, P. Kaplon, M. Kolodziej, *J. Carbohydr. Chem.* **2002**, *21*, 143–148; f) X. Ma, N. Anderson, L. V. White, S. Bae, W. Raverty, A. C. Willis, M. G. Banwell, *Aust. J. Chem.* **2015**, *68*, 593–599.
[58] A. V. Samet, D. N. Lutov, S. I. Firganf, Y. V. Nelyubina, V. V. Semenov, *Russ. Chem. Bull. Int. Ed.* **2013**, *62*, 2196–2201.
[59] V. K. Brel, A. V. Samet, L. D. Konyushkin, A. I. Stash, V. K. Belsky, V. V. Semenov, *Mendeleev Commun.* **2015**, *25*, 44–46.
[60] a) M. Kugelman, A. K. Mallams, H. F. Vernay, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1113–1126; b) R. D. Guthrie, R. W. Irvine, *Carbohydr. Res.* **1979**, *72*, 285–288; c) M. D. Wittman, R. L. Halcomb, S. J. Danishefsky, J. Golik, D. Vyas, *J. Org. Chem.* **1990**, *55*, 1979–1981; d) R. L. Halcomb, S. J. Danishefsky, M. D. Wittman. U. S. Patent 5,104,982 (**1992**); e) O. Boutureira, M. A. Rodríguez, M. I. Matheu, *Org. Lett.* **2006**, *8*, 673–676; f) T. Fujiwara, M. Hayashi, *J. Org. Chem.* **2008**, *73*, 9161–9163.
[61] E. D. V. Giordano, A. Frinchaboy, A. G. Suarez, R. A. Spanevello, *Org. Lett.* **2012**, *14*, 4602–4605.
[62] M. B. Comba, A. G. Suárez, A. M. Sarotti, M. I. Mangione, R. A. Spanevello, E. D. V. Giordano, *Org. Lett.* **2016**, *18*, 1748–1751.
[63] M. Ostermeier, R. Schobert, *J. Org. Chem.* **2014**, *79*, 4038–4042.
[64] T. Lindel, *Angew. Chem. Int. Ed.* **1998**, *37*, 774–776; *Angew. Chem.* **1998**, *110*, 806.
[65] K. C. Nicolaou, F. van Delft, T. Ohshima, D. Vourloumis, J. Xu, S. Hosokawa, J. Pfefferkorn, S. Kim, T. Li, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2520–2524; *Angew. Chem.* **1997**, *109*, 2630.
[66] Y. A. Kondrova, O. Y. Krasnoslobodtseva, L. V. Spirikhin, F. A. Valeev, *Russ. J. Org. Chem.* **2010**, *46*, 1151–1156.
[67] Y. A. Khalilova, O. Y. Krasnoslobodtseva, B. T. Sharipov, L. V. Spirikhin, F. A. Valeev, *Russ. J. Org. Chem.* **2012**, *48*, 513–518.
[68] B. T. Sharipov, O. Y. Krasnoslobodtseva, L. V. Spirikhin, F. A. Valeev, *Russ. J. Org. Chem.* **2010**, *46*, 129–137.
[69] Y. A. Khalilova, O. Y. Doronina, B. T. Sharipov, L. V. Spirikhin, F. A. Valeev, *Russ. J. Org. Chem.* **2013**, *49*, 1002–1010.
[70] B. T. Sharipov, A. A. Pershin, A. N. Pilipenko, Sh. M. Salikhov, F. A. Valeev, *Russ. J. Org. Chem.* **2013**, *49*, 1460–1468.
[71] a) B. T. Sharipov, A. A. Pershin, Sh. M. Salikhov, F. A. Valeev, *Russ. J. Org. Chem.* **2014**, *50*, 1258–1267; b) A. A. Pershin, B. T. Sharipov. Sh. M. Salikhov, F. A. Valeev, *Russ. J. Org. Chem.* **2015**, *51*, 1536–1544.
[72] B. T. Sharipov, A. A. Pershin, Sh. M. Salikhov, F. A. Valeev, *Russ. J. Org. Chem.* **2016**, *52*, 978–982.
[73] a) B. T. Sharipov, A. A. Pershin, Sh. M. Salikhov, F. A. Valeev, *Russ. J. Org. Chem.* **2016**, *52*, 721–726; b) B. T. Sharipov, A. A. Pershin, F. A. Valeev, *Mendeleev Commun.* **2017**, *27*, 119–121.
[74] a) A. N. Pilipenko, B. T. Sharipov, F. A. Valeev, *Russ. J. Org. Chem.* **2014**, *50*, 1504–1510; b) B. T. Sharipov, A. N. Pilipenko, F. A. Valeev, *Russ. J. Org. Chem.* **2014**, *50*, 1628–1635; c) I. M. Biktagirov, L. Kh. Faizullina, Sh. M. Salikhov, M. M. Iskakova, M. G. Safarov, F. Z. Galin, F. A. Valeev, *Russ. J. Org. Chem.* **2015**, *51*, 576–581.
[75] a) A. N. Davydova, B. T. Sharipov, F. A. Valeev, *Russ. J. Org. Chem.* **2015**, *51*, 1408–1417; b) O. Y. Doronina, Y. A. Khalilova, B. T. Sharipov, L. V. Spirikhin, F. A. Valeev, *Russ. J. Org. Chem.* **2012**, *48*, 1419–1423; c) Y. A. Khalilova, A. R. Tagirov, O. Y. Doronina, L. V. Spirikhin, Sh. M. Salikhov, F. A. Valeev, *Russ. J. Org. Chem.* **2014**, *50*, 110–116.
[76] Y. A. Khalilova, L. V. Spirikhin, Sh. M. Salikhov, F. A. Valeev, *Russ. J. Org. Chem.* **2014**, *50*, 117–127.
[77] C. A. Boros, F. R. Stermitz, *J. Nat. Prod.* **1990**, *53*, 1055–1147.
[78] C. W. Jefford, A. W. Sledeski, J. Boukouvalas, *Helv. Chim. Acta* **1989**, *72*, 1362–1370.
[79] I. M. Biktagirov, L. Kh. Faizullina, Sh. M. Salikhov, M. G. Safarov, F. A. Valeev, *Russ. J. Org. Chem.* **2015**, *51*, 1457–1463.
[80] L. Kh. Faizullina, D. M. Faizullina, Y. S. Galimova, Sh. M. Salikhov, V. A. Shamukaev, R. L. Safiullin, F. A. Valeev, *Russ. J. Org. Chem.* **2015**, *51*, 1725–1728.
[81] I. M. Biktagirov, L. Kh. Faizullina, Sh. M. Salikhov, M. G. Safarov, F. A. Valeev, *Russ. J. Org. Chem.* **2014**, *50*, 1317–1322.
[82] M. M. Iskakova, I. M. Biktagirov, L. Kh. Faizullina, Sh. M. Salikhov, M. G. Safarov, F. A. Valeev, *Russ. J. Org. Chem.* **2014**, *50*, 105–109.
[83] A. N. Davydova, A. A. Pershin, B. T. Sharipov, F. A. Valeev, *Mendeleev Commun.* **2015**, *25*, 271–272.
[84] a) I. Robina, P. Vogel, Z. J. Witczak, *Curr. Org. Chem.* **2001**, *5*, 1177–1214; b) Z. J. Witczak, P. Kaplan, P. M. Dey, *Carbohydr. Res.* **2003**, *338*, 11–18.
[85] a) Z. J. Witczak, J. Sarnik, A. Czubatka, E. Forma, T. Poplawski, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5606–5611; b) J. Sarnik, A. Czubatka-Bienkowska, A. Macieja, R. Bielski, Z. J. Witczak, T. Poplawski, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1215–1219.
[86] G. Giri, M. Danielli, R. A. Marinelli, R. A. Spanevello, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3955.3957.
[87] A. C. Krelle, A. S. Okoli, G. L. Mendz, *J. Cancer Ther.* **2013**, *4*, 606–631.
[88] G. F. Giri, G. Viarengo, R. L. E. Furlán, A. G. Suárez, E. García Véscovi, R. A. Spanevello, *Ind. Crops Prod.* **2017**, *105*, 113–123.

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