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Total syntheses and production pathways of levoglucosenone, a highly valuable chiral chemical platform for the chemical industry

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Abstract

Levoglucosenone (LGO) – which possesses two chiral centers, a ketal and one α,β -unsaturated ketone moieties – is a high-value renewable chiral building block that can be used for the production of a wide range of bio-based fine chemicals and polymers, as well as green solvents. This mini-review illustrates the different main strategies that have been developed to produce LGO from different starting materials, such as lignocellulosic biomass, pure cellulose, sugars, and non-sugar compounds.

Abbreviations

BVO: Baeyer-Villiger oxidation

CHMO: Cyclohexanone monooxygenase

DMF: Dimethylformamide

EMIM: 1-ethyl-3-methylimidazolium

GVL: γ -valerolactone

HMF: Hydroxymethylfurfural

HBO: (S)- γ -hydroxymethyl- α,β -butenolide

2H-HBO: (S)- γ -hydroxymethyl- γ -butyrolactone

HPLC: High-performance liquid chromatography

IL: Ionic liquid

LGO: Levoglucosenone

NP: Nanopowder

Ni-P-MCM-41: Nickel and phosphorus co-modified mesoporous silicate-41

THF: Tetrahydrofuran

Introduction

Switching from fossil fuel-based chemistry to biomass-derived chemistry is at the heart of the biorefinery concept and is probably the biggest challenge that our civilization must overcome to not only anticipate fossil fuels shortage but also to tackle climate change and provide our society with renewable and safer chemicals to both humans and the environment [1].

The production of building blocks (also known as chemical platforms and synthons) is critical in the chemistry industry as they are elementary bricks from which chemists can build up an almost infinite range of molecules, polymers, and materials. These building blocks are all the more valuable when they possess asymmetric centers that allow access to chiral molecules without the need to implement stereoselective processes.

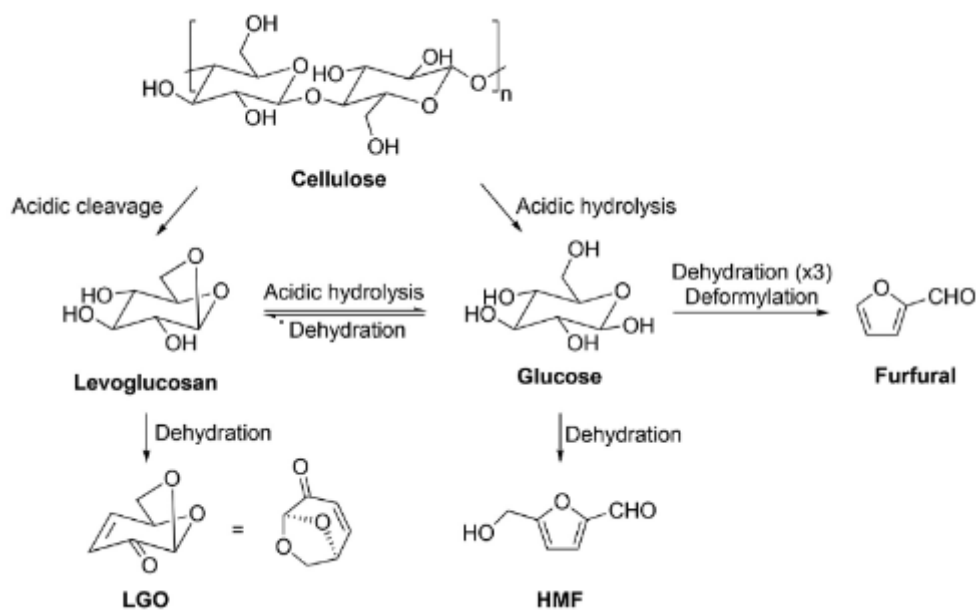
With their higher degree of oxidation and chemical functions, lignocellulosic biomass components are by far more complex and reactive than fossil hydrocarbons [2]. Although the complexity of lignocellulose components is a major obstacle for lignocellulosic biomass deconstruction, it offers a significant advantage over fossil hydrocarbons, as a source of building blocks, since they are already highly functionalized and, in the case of cellulose, possess various chiral centers (chiral pool). This chemical diversity and this asymmetry are two valuable features that are quite difficult to achieve from fossil hydrocarbons without low E-factor [3] multistep synthetic routes.

Despite its chirality, cellulose is mainly hydrolyzed into (i) fermentable glucose to access high-volume/low-value bioethanol and other organic acids (e.g., succinic acid) [4,5] or (ii) achiral compounds, such as levulinic acid or furfural [6]. Interestingly, more selective processes allow the transformation of cellulose into levoglucosenone (LGO), a chiral α,β -unsaturated bicyclic ketone with an internal ketal moiety (Scheme 1) [7].

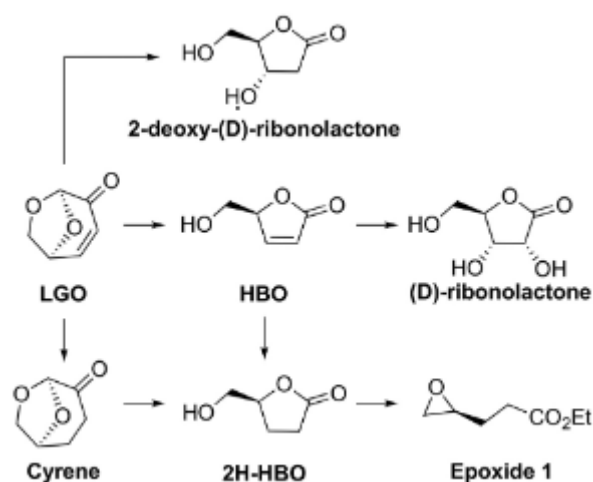
This molecule has been investigated for more than 50 years now as a valuable building block for the production of fine chemicals [8,9], a more recently the green solvent CyreneTM (Scheme 2) [10,11a,11b], a molecule that proved to be a sustainable alternative to toxic polar solvents, e.g., NMP, in many applications [12], such as liquid/liquid and liquid/solid extractions [13a,13b], multilayer graphene production [14], metal-organic frameworks (MOF) synthesis [15], amidification [16a,16b], enzymatic reduction of α -ketoesters [17], biomimetic radical coupling [18], polymerization [19a,19b], or membrane synthesis [20]. Besides CyreneTM, a great deal of work has been dedicated to the development of LGO-derived high-value chiral building blocks. For instance, three sustainable processes: lipase-mediated Baeyer-Villiger oxidation (BVO) [21a,21b], organic solvent- and catalyst-free BVO [22a,22b], and cyclohexene-monooxygenase (CHMO)-mediated BVO [23a,23b] to transform LGO and/or CyreneTM into 4(*S*)-*g*-hydroxymethyl- α,β -butenolide (HBO) [24] and (*S*)-*g*-hydroxymethyl-*g*-butyrolactone (2H-HBO), respectively, have been developed, patented, and validated at the kilo-scale (Scheme 2). From HBO, three other valuable building blocks, chiral epoxide 1 [25a,25b], (*D*)-ribonolactone [26], and 2-deoxy-(*D*)-ribonolactone [27] were also successfully synthesized (Scheme 2). LGO was also used for the synthesis of new monomers for unprecedented polymers (e.g., polyolefins [19a,19b,28a,28b], polyesters [29a,29b,29c], polyacrylates [30,31], as well as photo-crosslinkable polycarbonates [32]). Finally, LGO has been used as starting material for many chiral auxiliaries/ligands and bioactive compounds [33], including flavors (e.g., dairy lactone) [34a,34b], pheromones (e.g., japonilure [35,36]), anti-fungi [37], and anticancer drugs [38].

All aforementioned examples undoubtedly demonstrate the great potential of LGO as a chiral synthon for the synthesis of commodity (e.g., monomers and solvents) and high-value molecules (e.g., chiral synthons, drugs, and flavors). However, to unlock this potential, one needs to produce LGO at the thousand-ton scale and at a relative low price to synthesize competitive sustainable

alternatives to the current commercially available petro-based molecules. This mini-review thus aims to provide a quick overview on the different production pathways to LGO that have been reported in the literature (i.e., both scientific articles and patents) and to evaluate their scalability as well as their industrialization potential.



Scheme 1. Production of LGO, levoglucosan, furfural, and HMF from the acidic degradation of cellulose/glucose.



Scheme 2. Transforming LGO into high-value chiral building blocks and Cyrene™.

Synthetic approach from monosaccharide and derivatives, as well as non-sugar compounds

Although the majority of the reported production pathways to LGO rely on the partial dehydration of the glucose units of lignocellulosic biomass, five synthetic approaches starting from monosaccharides and derivatives, and even a non-sugar compound, have been reported in the literature.

Starting from D-galactose, Shibagaki et al. [39a,39b] devised a high-yielding eight-step pathway to LGO with a catalytic reductive decarboxylation as the key step. After having screened several

catalyst/solvent combinations, they achieved a highly selective decarboxylation by using hydrous zirconium oxide calcined at 300 °C and acetic anhydride. Despite this very good 88% decarboxylation yield (ca. 48% overall yield), this approach suffers from the use of toxic solvents (i.e., DMF) and reagents (i.e., manganese dioxide and phenol), making it unsuitable for a sustainable thousand-ton scale synthesis.

Another interesting strategy consisted in reacting glucose in the presence of used chromium-tanned leather as a heterogeneous catalyst to dehydrate it into a mixture of HMF and LGO [40]. This study by Bobbink et al. demonstrated that this quite uncommon catalyst not only compared favorably to many classical metal catalysts but also provided significant quantities of LGO (up to 12.8% determined by HPLC) at low chromium content, making it a very promising renewable alternative while valorizing the leather industry residues. Unfortunately, the authors did not investigate the purification of LGO from the crude complex mixture. It is thus impossible to determine any pure LGO yield nor evaluate the potential scalability and industrial relevance of this approach.

The next two pathways that have been explored relied on the use of levoglucosan, an intermediate formed during carbohydrates dehydration. The first pathway by Yang et al. consisted of the pyrolysis of levoglucosan loaded on activated carbon that plays the role of a solid dehydrating agent and the condensation of the resulting volatile LGO in yield up to 49% and with a claimed purity high enough to avoid any further purification step [41]. To the best of our knowledge, this process has not been industrialized despite the interesting yield and the absence of purification. Some explanations could be envisaged: levoglucosan is too expensive, and/or its loading on activated carbon is too energy-consuming (removal of water through vacuum).

The second pathway involved the use of propylsulfonic acid-functionalized silica catalysts as Brønsted catalysts in tetrahydrofuran (THF) and provided LGO yield up to 59% (determined by HPLC) at complete levoglucosan conversion. This study by Oyola-Rivera et al. demonstrated that the immobilization on such hydrophilic material prevented the solvation of the acid proton by the water produced and thus promoted LGO production [42]. Similarly, to the above glucose-based pathways, one cannot determine pure LGO yield as no purification was described in the study.

While the carbohydrate-based LGO production pathways take advantage of the chiral pool, a multi-step pathway to LGO was reported from achiral 2-vinylfuran through an enantioselective Sharpless dihydroxylation by Tanagushi et al. [43] Although this strategy provided LGO in 93% e.e., and in a relatively good overall yield (39% over 6 steps), it requires the use of toxic reagents (i.e., osmium oxide and manganese oxide), hazardous peracid, as well as toxic solvent (i.e., benzene). Without calling into question its elegance and its efficiency in terms of yield and/or stereoselectivity, this pathway is unfortunately not suitable for a sustainable large-scale production of LGO.

Synthetic approach from cellulose

Organic acid-mediated pathways

As previously described, the selectivity of the degradation of carbohydrate into LGO requires the removal of the produced water or its consumption in situ to prevent further dehydration toward HMF. Different strategies can be implemented, e.g., the use of dehydrating agents (such as the aforementioned functionalized silicates) or that of a polar solvent to limit the contact between LGO and water. The latter strategy was studied by Cao et al. for the dehydration of cellulose into LGO in the presence of an acid catalysis, i.e., sulfuric acid, and two polar aprotic solvents, i.e., *g*-valerolactone (GVL) and THF [44a,44b]. An in-depth analysis of the impact of several parameters (e.g., solvent, acid concentration, reaction time, and temperature) was conducted, and it was shown that LGO can be produced in yield up to 95% from 1%w cellulose in THF at 210 °C with 7.5 mM

sulfuric acid. Inventors also demonstrated that, as the reaction proceeds, the dehydration of intermediates causes the water concentration in the reaction mixture to rise to no more than about 2%w water. They also found out that a controlled addition of water to the reaction medium allowed to gradually replace LGO by HMF. In view of this excellent yield, one could have thought that this process would be industrialized. Nevertheless, it seems that it is not the case. Two reasons may explain it: the toxicity of THF and/or the low concentration of cellulose that necessitate the use of big reactors and large volume of solvent.

Similarly, Cao et al. explored the use of dioxane and several acids [45]. Their study demonstrated that a LGO yield up to 38% could be achieved by treating 1%w cellulose in dioxane with 15 mM p-toluenesulfonic acid or methanesulfonic acid. Not only this process has the same drawbacks as the previous one (i.e., low cellulose concentration, large reactor and large volume of solvent, and toxicity of the solvent), but the average yields call for costly extra purification steps to separate LGO from the other dehydration products (e.g., HMF and furfural). To overcome this, it was shown that the addition of phosphorus pentoxide, acting as a drying agent, at 1%w significantly decreased the content in dehydration by-products without affecting too much the LGO yield, thus simplifying the purification process. Despite this improvement, there is little chance that this process gets industrialized with regard to the low cellulose concentration and the use of toxic dioxane.

In an attempt to tackle the issue related to low cellulose concentration in acid-catalyzed LGO production in solvents, Xu et al. investigated the pyrolysis of acid-impregnated cellulose [46]. It was shown that replacing pure cellulose by 0.1%w phosphoric acid- or sulfuric acid-impregnated cellulose, in fast pyrolysis at 350 °C, increased significantly the LGO yield to 18.3%w, 36 times higher than with untreated cellulose (0.5%w). This improvement does not, however, simplify the purification of LGO as levoglucosan is also produced at a similar yield.

Like in the case of levoglucosan, Ye et al. explored the catalytic fast pyrolysis of cellulose in the presence of phosphoric acid-activated carbon to selectively produce LGO [47]. Here again, the activated carbon proved more efficient than classical acids. The highest LGO yield (14.7%) was obtained under a catalyst-to-cellulose ratio of 1/3 at 300°C. It is noteworthy to mention that, although the yield is relatively low, the selectivity based on the liquid products (that contains LGO, other dehydration products, such as HMF, levoglucosan, as well as water) reached 76.3%. Compared to the same approach on levoglucosan, this process does not suffer from the cost of the starting material (cellulose). However, the energy consumption of the catalyst production may hinder its scale-up.

Metal catalyst-mediated pathways

The pyrolysis of cellulose in the presence of metal catalysts has been also widely investigated. For instance, Li et al. performed the pyrolysis of cellulose in the presence of Ni and P co-modified mesoporous silicate-41 (Ni-P-MCM-41) catalyst with various P-to-Ni ratios to explore its effects, as well as that of several factors, including catalyst/sample ratio and pyrolysis temperature [48]. Data demonstrated that all the Ni-P-MCM-41 catalysts, especially the one with a P-to-Ni ratio of 5, exhibited excellent catalytic capability and selectivity for LGO production, providing LGO yields up to 21.37%w. Although authors claimed that the Ni-PMCM-41 catalyst proved more efficient than previously reported catalysts, including activated carbon, not one comparative study has been conducted to support it.

Following a similar strategy, Casoni et al. investigated the pyrolysis of microcrystalline cellulose in contact with Mobil™ Composition of Matter (MCM)-41 and Fe-, Al-, and Cu-substituted samples at 400°C in a fixed-bed glass reactor and showed that, among all the catalysts tested, Al-MCM-41

provided the highest LGO conversion (53%w) [49]. Nevertheless, a second regeneration of the catalyst diminished the specific surface area and the surface acidity, resulting in a notable decrease in LGO yield. Such a limited recyclability of the catalysts is a critical obstacle in terms of cost.

The efficiency of nanopowder (NP) titanium oxide, aluminum oxide, and aluminum titanate (AlTi) were also tested for the fixed-bed pyrolysis of cellulose by Chen et al. [50] It was shown that the best LGO yield (22%) was achieved by using the mix oxide NP AlTi at 350°C, when yields up to only 5.7% were obtained with coarse AlTi. This outcome might be partly ascribed to the enhanced dehydration of cellulose chains in contact with the catalyst but also the higher quantity of exposed acidic centers in nanoparticles. This catalyst has been used up to four cycles and a decrease in bio-oil production from 6.0% (run 1) to 4.1% (run 4) was observed. Unfortunately, no information was provided on the specific impact of the recycling on the LGO yield.

Qian et al. synthesized and explored the effect of magnetic solid acid $\text{Fe}_3\text{O}_4/\text{CeSO}_3\text{H}_6$ in catalytic fast pyrolysis of cellulose [51]. In their study, the best LGO yield (20%w) was obtained with a 1:1 catalyst-to-cellulose ratio at 300°C. A great benefit of such catalyst is its straightforward removal from the reactor with a magnet. However, although it can be recycled, its efficiency decreases gradually at every reaction cycle.

Ionic liquid-mediated pathways

Another interesting strategy that has been reported in the literature is the use of ionic liquid (IL). The latter not only acts as a catalyst, but it also avoids organic solvents while - theoretically - facilitating the recovery of LGO.

Kudo et al. examined the catalytic activity of various types of ILs in the pyrolysis of cellulose for the production of LGO. The procedure consists of simply mixing cellulose with the ILs and subjecting the resulting mixture for the pyrolysis at 300°C to produce volatile products, including LGO, that were then separated from the ILs layer [52a,52b]. Among the 13 ILs tested, ILs bearing sulfonate ions provided the best LGO yields, [EMIM]CH₃CSO₃ giving the highest (29.7%w). It was also shown that these ILs are thermostable and can be readily recovered and reused. However, one needs to compromise between LGO yield and IL recovery: if highest LGO yield is sought, [EMIM]CH₃CSO₃ will be chosen, and the IL recovery will be 81.6%, whereas [BMMIM]CF₃SO₃ will result in a quantitative IL recovery (99.6%) but in a lower LGO yield (21.4%w). It is noteworthy to mention that the reported yields are HPLC yield; moreover, the study did not address the purification of LGO from the crude mixture that contains not only furfural, HFM, 1,6-anhydro-β-D-glucopyranose, 1,4:3,6-dianhydro-α-D-glucopyranose but also levoglucosan. It is thus difficult to evaluate what the final pure LGO yield would be.

Capitalizing on IL-mediated pyrolysis, Kudo et al. went one step further and designed a method for the continuous production of LGO where the volatiles, generated by the fast pyrolysis of cellulose at 380°C, are reformed at 275°C in the presence of several catalysts consisting of an IL e having a moderate hydrogen-bond basicity e supported over porous char [53]. The highest LGO yield (31.6% on a cellulose carbon basis, i.e., 24.6%w) was obtained with the [BMMIM]OTf-based IL. Furthermore, the authors demonstrated that this reaction system can be also applied to the production of Cyrene™ by adding hydrogen and a hydrogenation catalyst in the catalytic bed. Nevertheless, one still needs to improve hydrogenation selectivity to optimize this process.

Non-conventional pathways

A couple of non-conventional pyrolysis processes have been designed to avoid the use external heating, which is quite often the most energy-consuming step in LGO production.

Doroshenko et al. reported a greener approach based on a microwave (MW)-assisted pyrolysis in the presence of readily available clays [54]. In this study, they found out that a synergetic effect between different types of catalysts - bentonite and Al-pillared bentonite - allowed to finely tune both the water content and the quantity in acid centers. Under these conditions, LGO was obtained in 12.3%w with 63% purity. Despite its efficiency, such a process is difficult to industrialize on a thousand-ton scale due to the absence of industrial-scale MW reactors.

Another non-conventional transformation of cellulose into LGO consisted in the use of plasma electrolysis as a low-energy alternative to classical pyrolysis [55]. Using aprotic polar solvent and high-voltage alternative current electricity as the plasma source, A et al. achieved complete liquefaction of cellulose, and the highest LGO yield (43%) was obtained after 15 min of conversion in γ -valerolactone using a voltage of 6 kV and frequency of 6 kHz. An in-depth study of the energy consumption of this novel plasma-mediated production of LGO in solvent and that of the conventional external heating in-solvent process demonstrated that plasma electrolysis provides greater LGO yields using significantly less energy. More precisely, compared to conventional heating, the plasma electrolysis of cellulose in γ -valerolactone resulted in an increase in LGO yield by 154% while consuming 72% less energy. Moreover, the authors also shown that, contrary to the acid-mediated dehydration of cellulose into LGO, plasma generates hydrogen radicals that promote a more efficient cellulose depolymerization and dehydration. Like in the case of MWs, the use of plasma for the conversion of biomass is not yet deployed on an industrial scale.

Direct biomass-degradation approach

While many LGO production processes have been designed from cellulose, producing LGO directly from lignocellulosic biomass is the most straightforward approach as it does not require any costly and energy- and/or chemical-consuming pre-fractionation of the biomass to isolate cellulose. Please note that, in this section, only processes conducted at the gram scale (or higher) will be described.

De Bruyn et al. demonstrated that pyrolyzing a lignin-rich biorefinery waste stream (crude waste softwood hydrolysis lignin) under MW heating resulted in the conversion of unconverted saccharides into LGO in an 8%w yield with high selectivity [56a,56b]. Not only this process allows the production of LGO, but it also provides a purer lignin that can be further valorized in many high-value applications. Although very elegant, it is still difficult to deploy this MW-assisted pyrolysis technology at the industrial scale.

Aiming to valorize the sawdust produced in the pulp and paper industry, Circa Group developed an extruder-based continuous fast catalytic pyrolysis of this ligno-cellulosic waste in presence of an acid and a polar solvent [57]. Although their patent does not disclose the optimal conditions nor the LGO yield, the most efficient acids are among orthophosphoric acid, sulfuric acid, methanesulfonic acid, trifluoromethanesulfonic acid, hydrohalic acids, nitric acid, and formic acid at 0.1 to 10%w, while 190-500°C and tetramethylene sulfone seem to be the best temperature range and solvent, respectively. It is worth mentioning that, besides LGO, this process also provides a biochar that can be valorized as well. To date and to the best of our knowledge, this is the only process that has been scaled at the demonstration scale worldwide. Currently producing at the 50 T/year scale at the Boyer Norske Skog paper plant (Tasmania), Circa Group has received a H2020 BBI Flagship grant (Resolute project) to produce LGO at the 1000 T/year scale at the Carling platform (Saint-Avold, Grand Est, France).

Conclusion

LGO is undoubtedly a high-value building blocks and, as such, has been a target of choice for many scientists. Although elegant to the eyes of synthetic chemists, the (stereoselective) total syntheses that have been developed to prepare LGO from monosugars and non-sugar compounds will never leave the laboratory. LGO coming from the selective dehydration of sugars (mainly glucose), cellulose, and acid-catalyzed pyrolysis has been the substrate and the technology of choice, respectively, for the production of LGO. Nevertheless, in an attempt to improve selectivity, yields, productivity, and energy efficiency, different substrates (e.g., mono- sugars, lignocellulosic biomass, and unconverted sugars-rich lignin waste streams), catalysts (e.g., organic acids, metal catalysts, and ILs), heating methods (e.g., external heating, microwave, and plasma), solvents (e.g., organic solvents and ILs), as well as continuous processes, have been investigated. Although many of these pyrolytic processes provided LGO in amount large enough to be considered as selective, most of them will never be commercialized, either due to their cost, or the un- availability of the technology at the industrial scale. As of today, the one and only technology that has been demonstrated at the multi-ton scale is the continuous acid-mediated fast catalytic pyrolysis of sawdust designed by Circa Group. This ton-scale access to LGO opens the way to its full exploitation toward high-value applications (e.g., green solvents, chiral building blocks, drugs, flavors/fragrances, pheromones, monomers, and polymers) more than 50 years after the first report of LGO in the literature. It was time!

Disclosure statement

Given their role as Guest Editor, Florent Allais had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Alina M. Balu.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

*of special interest

**of outstanding interest

1. **De Jong E, et al.: Biorefinery concepts in comparison to petrochemical refineries. In Book: industrial biorefineries and white biotechnology chapter: biorefinery concepts in comparison to petrochemical refineries publisher. Edited by Ashok Pandey, Rainer Höfer, Christian Larroche, Mohammad Taherzadeh, Madhavan Nampoothiri, Eds, Elsevier; 2015. <https://doi.org/10.1016/B978-0-444-63453-5.00001-X>.
This chapter provides an overview of the biorefinery concept and how it differs from fossil fuels-based refinery.
2. Beckham GT, et al.: Opportunities and challenges in biological lignin valorization. *Curr Opin Biotechnol* 2016, 42:40. <https://doi.org/10.1016/j.copbio.2016.02.030>.
3. Sheldon RA: The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chem* 2017, 19:18. <https://doi.org/10.1039/C6GC02157C>.
4. Kumar R, et al.: Sustainable production and purification of succinic acid: a review of membrane-integrated green approach. *Production* 2020, 277, 123954. <https://doi.org/10.1016/j.jclepro.2020.123954>.

5. Dickinson D, et al.: Sustainable bio-succinic acid production: superstructure optimization, techno-economic, and lifecycle assessment. *Energy Environ Sci* 2021, 14:3542. <https://doi.org/10.1039/D0EE03545A>.
6. Zhang Z, et al.: Mini-review on the synthesis of furfural and levulinic acid from lignocellulosic biomass. *Processes* 2021, 9:1234. <https://doi.org/10.3390/pr9071234>.
7. Halpern Y, et al.: Levoglucosenone (1,6-anhydro-3,4-dideoxy-d-3-b-D-pyranosen-2-one). Major product of the acid-catalyzed pyrolysis of cellulose and related carbohydrates. *J Org Chem* 1973, 38:204. <https://doi.org/10.1021/jo00942a005>.
8. Comba MB, et al.: Levoglucosenone and its new applications: valorization of cellulose residues. *Eur J Org Chem* 2018, 5:590. <https://doi.org/10.1002/ejoc.201701227>.
9. **Camp JE, Greatrex BW: Levoglucosenone: bio-based platform for drug discovery. *Front Chem* 2022, 10, 902239. <https://doi.org/10.3389/fchem.2022.902239>.

In this review, the authors demonstrate the great potential of LGO for the production of high value chiral drugs.

10. Sherwood J, et al.: Dihydrolevoglucosenone (Cyrene) as a bio-based alternative for dipolar aprotic solvents. *Chem Commun* 2014, 50:9650. <https://doi.org/10.1039/C4CC04133J>.
11. ** (a) Mouterde LMM, et al.: Enzymatic reduction of levoglucosenone by an alkene reductase (OYE 2.6): a sustainable metal- and dihydrogen-free access to the bio-based solvent Cyrene®. *Green Chem* 2018, 20:5528. <https://doi.org/10.1039/C8GC03146K>. (b) Stewart JD, et al.: US2018025184. 2018. March, 29th.

This article and the corresponding patent describe the biocatalyzed production of Cyrene™ as a hydrogen- and metal catalyst-free alternative to palladium-catalyzed hydrogenation.

12. **Camp JE: Bio-available solvent Cyrene: synthesis, derivatization, and applications. *ChemSusChem* 2018, 11:3048. <https://doi.org/10.1002/cssc.201801420>.

In this review, the authors demonstrate the great potential of Cyrene™ for the production of high value chiral drugs, green solvents ...

13. (a) Duval A, Avérous L: Dihydrolevoglucosenone (Cyrene™) as a versatile biobased solvent for lignin fractionation, processing, and chemistry. *Green Chem* 2022, 24:338. <https://doi.org/10.1039/D1GC03395F>. (b) Brouwer T, Schuur B: Dihydrolevoglucosenone (Cyrene), a biobased solvent for liquid–liquid extraction applications. *ACS Sustainable Chem Eng* 2020, 8, 14807. <https://doi.org/10.1021/acssuschemeng.0c04159>.
14. Pan K, et al.: Sustainable production of highly conductive multilayer graphene ink for wireless connectivity and IoT applications. *Nat Commun* 2018, 9:5197. <https://doi.org/10.1038/s41467-018-07632-w>.
15. Zhan J, et al.: Dihydrolevoglucosenone (Cyrene) as a green alternative to N,N-dimethylformamide (DMF) in MOF synthesis. *ACS Sustainable Chem Eng* 2016, 4:7186. [10.1021/acssuschemeng.6b02115](https://doi.org/10.1021/acssuschemeng.6b02115).
16. (a) Wilson KL, et al.: Cyrene as a bio-based solvent for HATU mediated amide coupling. *Org Biomol Chem* 2018, 16:2851. <https://doi.org/10.1039/C8OB00653A>. (b) Bousfield TW, et al.: Synthesis of amides from acid chlorides and amines in the bio-based solvent Cyrene™. *Green Chem* 2019, 21:3675. <https://doi.org/10.1039/C9GC01180C>.
17. de Gonzalo G: Biocatalysed reductions of α-ketoesters employing Cyrene™ as cosolvent. *Biocatal Biotransform* 2021. <https://doi.org/10.1080/10242422.2021.1887150>. ahead of print 1-6.
18. Mention MM, et al.: Biomimetic regioselective and high-yielding Cu(i)-catalyzed dimerization of sinapate esters in green solvent Cyrene™: towards sustainable antioxidant and anti-UV ingredients. *Green Chem* 2020, 22:2077. <https://doi.org/10.1039/D0GC00122H>.
19. (a) Fadlallah S, et al.: Chemo-enzymatic synthesis of a levoglucosenone-derived bi-functional monomer and its ring-opening metathesis polymerization in the green solvent Cyrene™. *Polym Chem* 2020, 11:7471. <https://doi.org/10.1039/D0PY01471K>. (b) Grune C, et al.: Cyrene™ as an alternative sustainable solvent for the preparation of poly(lactic-co-glycolic

- acid) nanoparticles. *J Pharmacol Sci* 2021, 110:959.
<https://doi.org/10.1016/j.xphs.2020.11.031>.
20. Milescu RA, et al.: Polymer chemistry applications of Cyrene and its derivative cygnet 0.0 as safer replacements for polar aprotic solvents. *ChemSusChem* 2021, 14:3367.
<https://doi.org/10.1002/cssc.202101125>.
21. * (a) Flourat AL, et al.: Chemo-enzymatic synthesis of key intermediates (S)-g-hydroxymethyl- α,β -butenolide and (S)- γ -hydroxymethyl- γ -butyrolactone via lipase-mediated Baeyer–Villiger oxidation of levoglucosenone. *Green Chem* 2015, 17:404.
<https://doi.org/10.1039/C4GC01231C>. (b) Allais F, et al.: US201515307712. 2017. June, 1st. This article and the corresponding patent describe the biocatalyzed production of HBO and 2H HBO as a sustainable alternative to peracid-based Baeyer-Villiger oxidation.
22. ** (a) Bonneau G, et al.: Organic solvent- and catalyst-free Baeyer–Villiger oxidation of levoglucosenone and dihydrolevoglucosenone (Cyrene®): a sustainable route to (S)- γ -hydroxymethyl- α,β -butenolide and (S)- γ -hydroxymethyl- γ -butyrolactone. *Green Chem* 2018, 20:2455. <https://doi.org/10.1039/C8GC00553B>. (b) Allais F, et al.: US201716315143. 2019. July, 11th. This article and the corresponding patent describe the H₂O₂-mediated production of HBO and 2H-HBO as an organic solvent- and (bio)catalyst-free alternative to peracid-mediated Baeyer-Villiger oxidation.
23. * (a) Mouterde LMM, et al.: Identification and expression of a CHMO from the *Pseudomonas aeruginosa* strain Pa1242: application to the bioconversion of Cyrene™ into a key precursor (S)- γ -hydroxymethyl-butylolactone. *Green Chem* 2021, 23:2694.
<https://doi.org/10.1039/D0GC04321D>. (b) Allais F, et al.: US2021388403. 2021. December, 16th. This article and the corresponding patent describe the CHMO-mediated biocatalyzed production of 2H-HBO as a sustainable alternative to H₂O₂-mediated Baeyer-Villiger oxidation.
24. ** Flourat AL, et al.: (S)- γ -Hydroxymethyl- α,β -butenolide, valuable chiral synthon: syntheses, reactivity, and applications. *Org Process Res Dev* 2020, 24:615.
<https://doi.org/10.1021/acs.oprd.9b00468>. This review demonstrates the great potential of HBO as a chiral synthon in fine chemistry.
25. (a) Peru AAM, et al.: Chemo-enzymatic synthesis of chiral epoxides ethyl and methyl (S)-3-(Oxiran-2-yl)propanoates from renewable levoglucosenone: an access to enantiopure (S)-Dairy lactone. *Molecules* 2016, 21:988. <https://doi.org/10.3390/molecules21080988>. (b) Allais F, et al.: US10183923. 2019. January, 22th.
26. Moreaux M, et al.: High-yielding diastereoselective syn-dihydroxylation of protected HBO: an access to D-(+)-Ribono-1,4-lactone and 5-O-protected analogues. *Eur J Org Chem* 2019, 7:1600.
<https://doi.org/10.1002/ejoc.201801780>.
27. Diot-Néant F, et al.: Green synthesis of 2-deoxy-D-ribo-lactone from cellulose-derived levoglucosenone (LGO): a promising monomer for novel bio-based polyesters. *Eur Polym J* 2021, 159, 110745. <https://doi.org/10.1016/j.eurpolymj.2021.110745>.
28. (a) Debsharma T, et al.: Ring-Opening metathesis polymerization of biomass-derived levoglucosenol. *Angew Chem, Int Ed* 2019, 58:6718. <https://doi.org/10.1002/anie.201814501>. (b) Debsharma T, et al.: Cellulose-derived functional polyacetalby cationic ring-opening polymerization of levoglucosenylmethyl ether. *Angew Chem, Int Ed* 2019, 58, 18492.
<https://doi.org/10.1002/anie.201908458>.
29. (a) Kayishaer A, et al.: Unprecedented biodegradable cellulose-derived polyesters with pendant citronellol moieties: from monomer synthesis to enzymatic degradation. *Molecules* 2021, 26, 7672. <https://doi.org/10.3390/molecules26247672>. (b) Fadlallah S et al: Sustainable hyper-branched functional materials via green polymerization of readily accessible levoglucosenone-derived monomers. *Macromol Rapid Commun* 2021, 42, 2100284.
<https://doi.org/10.1002/marc.202100284>. (c) Diot-Néant F, et al.: Sustainable synthesis and polycondensation of levoglucosenone-cyrene-based bicyclic diol monomer: access to renewable

polyesters. *ChemSusChem* 2020, 13, 2482. <https://doi.org/10.1002/cssc.202000680>.

30. Ray P, et al.: Synthesis of bioacrylic polymers from dihydro-5-hydroxyl furan-2-one (2H-HBO) by free and controlled radical polymerization. *ACS Omega* 2018, 3, 2040. <https://doi.org/10.1021/acsomega.7b01929>.

31. Diot-Néant F, et al.: Chemo-enzymatic synthesis and free radical polymerization of renewable acrylate monomers from cellulose-based lactones. *ACS Sustainable Chem Eng* 2018, 6, 17284. <https://doi.org/10.1021/acssuschemeng.8b04707>.

32. Fadlallah S, et al.: Fully renewable photocrosslinkable polycarbonates from cellulose-derived monomers. *Green Chem* 2022, 24:2871. <https://doi.org/10.1039/d1gc04755h>.

33. Liu X, et al.: Levoglucosenone and its pseudoenantiomer isolevoglucosenone as scaffolds for drug discovery and development. *ACS Omega* 2020, 5, 13926. <https://doi.org/10.1021/acsomega.0c01331>.

34. (a) Peru AAM, et al.: Chemo-enzymatic synthesis of chiral epoxides ethyl and methyl (S)-3-(Oxiran-2-yl)propanoates from renewable levoglucosenone: an access to enantiopure (S)-Dairy lactone. *Molecules* 2016, 21:988. <https://doi.org/10.3390/molecules21080988>. (b) Allais F, et al.: US10183923. 2019. January, 22th.

35. Xu H, et al.: Catalytic asymmetric synthesis of Japonilure and its enantiomer. *Tetrahedron: Asymmetry* 2014, 25:1372. <https://doi.org/10.1016/j.tetasy.2014.09.008>.

36. [Unpublished results]

37. Sharipov BT, et al.: Synthesis and fungicidal activity of methylsulfanylmethyl ether derivatives of levoglucosenone. *Chem Heterocycl Compd (N Y, NY, U S)* 2019, 55:31. <https://doi.org/10.1007/s10593-019-02415-7>.

38. Tsai YH, et al.: Design, synthesis and evaluation of novel levoglucosenone derivatives as promising anticancer agents. *Bioorg Med Chem Lett* 2020, 30, 127247. <https://doi.org/10.1016/j.bmcl.2020.127247>.

39. (a) Shibagaki M, et al.: Synthesis of levoglucosenone. *Chem Lett* 1990, 307. <https://doi.org/10.1246/cl.1990.307>. (b) Shibagaki M, et al.: EP0416577. 1990. May, 9th.

40. * Bobbink D, et al.: Leather-promoted transformation of glucose into 5-hydroxymethylfurfural and levoglucosenone. *ChemSusChem* 2019, 7:1437. <https://doi.org/10.1002/cssc.201802830>.

This article describes the use of leather industry waste as a cheap and sustainable heterogenous catalyst for the production of HMF and LGO.

41. Yang Z, et al.: CN113372398. 2021. October, 10th.

42. Oyola-Rivera O, et al.: Catalytic dehydration of levoglucosan to levoglucosenone using Brønsted solid acid catalysts in tetrahydrofuran. *Green Chem* 2019, 21:4988. <https://doi.org/10.1039/C9GC01526D>.

43. Taniguchi T, et al.: Non-carbohydrate route to Levoglucosenone and its enantiomer employing asymmetric dihydroxylation. *Synlett* 1996, 10:971. <https://doi.org/10.1055/s1996-5652>.

44. ** (a) Cao F, et al.: Dehydration of cellulose to levoglucosenone using polar aprotic solvents. *Energy Environ Sci* 2015, 8:1808. <https://doi.org/10.1039/C5EE00353A>. (b) Huber GW, et al.: US9376451. 2016. June, 28th.

This article and the corresponding patent describe the most efficient LGO production process from cellulose in terms of yield (up to 95%).

45. Cao Q, et al.: Dehydration of saccharides to anhydro-sugars in dioxane: effect of reactants, acidic strength and water removal in situ. *Cellulose* 2020, 27:9825. <https://doi.org/10.1007/s10570-020-03490-2>.

46. Xu F, et al.: Improved production of levoglucosan and levoglucosenone from acid-impregnated cellulose via fast pyrolysis. *Cellulose* 2022, 29:1463. <https://doi.org/10.1007/s10570-021-04387-4>.

47. Ye X-n, et al.: Catalytic fast pyrolysis of cellulose and biomass to selectively produce levoglucosenone using activated carbon catalyst. ACS Sustainable Chem Eng 2017, 5, 10815. <https://doi.org/10.1021/acssuschemeng.7b02762>.

48. Li K, et al.: Catalytic fast pyrolysis of biomass with Ni-P-MCM-41 to selectively produce Levoglucosenone. J Anal Appl Pyrol 2020, 148, 104824. <https://doi.org/10.1016/j.jaap.2020.104824>.

49. ** Casoni AI, et al.: Catalytic pyrolysis of cellulose using MCM-41 type catalysts. Appl Catal Gen 2016, 514:235. <https://doi.org/10.1016/j.apcata.2016.01.017>.

This article reports on one of the most efficient mesoporous catalyst-mediated pyrolyses of cellulose into LGO in terms of yield.

50. * Fabri D, et al.: Pyrolysis of cellulose catalysed by nanopowder metal oxides: production and characterisation of a chiral hydroxylactone and its role as building block. Green Chem 2007, 9:1374. <https://doi.org/10.1039/b707943e>.

This article describes the improvements brought in cellulose pyrolysis by using nanoparticles.

51. * Qian L, et al.: Selective production of levoglucosenone by catalytic pyrolysis of cellulose mixed with magnetic solid acid. Cellulose 2021, 28:7579. <https://doi.org/10.1007/s10570021-04010-6>.

This article describes the use of magnetic solid acid as an easy way to recover the catalyst from the pyrolysis medium.

52. * (a) Kudo Z, et al.: Efficient levoglucosenone production by catalytic pyrolysis of cellulose mixed with ionic liquid. Green Chem 2011, 13:3306. <https://doi.org/10.1039/c1gc15975e>. (b) Kudo S, et al.: Sulfonate ionic liquid as a stable and active catalyst for levoglucosenone production from saccharides via catalytic pyrolysis. Catalysts 2013, 3:757. <https://doi.org/10.1039/C1GC15975E>.

These two articles are among the first ones that describe the use of ionic liquids in LGO production from saccharides.

53. ** Kudo S, et al.: Production of levoglucosenone and dihydrolevoglucosenone by catalytic reforming of volatiles from cellulose pyrolysis using supported ionic liquid phase. ACS Sustainable Chem Eng 2017, 5:1132. <https://doi.org/10.1021/acssuschemeng.6b02463>.

This article goes one step further in the ionic liquid-mediated pyrolysis of cellulose into LGO by making the process continuous.

54. Doroshenko A, et al.: Selective microwave-assisted pyrolysis of cellulose towards levoglucosenone using clay catalysts. ChemSusChem 2019, 24:5224. <https://doi.org/10.1002/cssc.201903026>.

55. * A.L., et al.: Plasma electrolysis of cellulose in polar aprotic solvents for production of levoglucosenone. Green Chem 2020, 22:7871. <https://doi.org/10.1039/d0gc02813d>.

This article describes the first work involving the use of plasma as an alternative to conventional external heating in pyrolysis of cellulose.

56. * (a) De Bruyn M, et al.: A new perspective in bio-refining: levoglucosenone and cleaner lignin from waste biorefinery hydrolysis lignin by selective conversion of residual saccharides. Energy Environ Sci 2016, 9:2571. (b) De Bruyn M, et al.: WO2016170329. 2016. October, 27th.

To the best of our knowledge, this article and the corresponding patent describe the only production process of LGO from sugars-enriched lignin stream.

57. ** Court GR, et al.: US2012111714. 2012. May, 10th.

This patent describes the only one LGO-production process validated at the multi-ton scale.