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Scalable synthesis of 3-*O* functionalized deoxyribonolactones from biorenewable levoglucosenone

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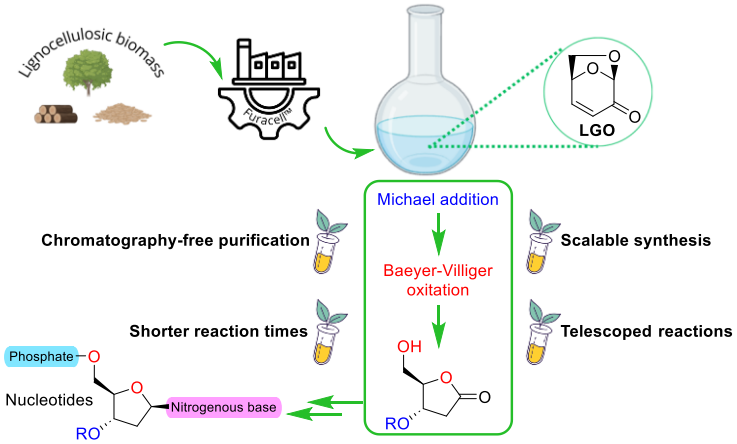
Abstract

A scalable and chromatography-free synthesis of 3-*O* functionalized deoxyribonolactones from biorenewable levoglucosenone (LGO) is presented. This study enhances the synthesis of the previously reported 2-deoxy-D-ribonolactone by employing formic acid as a safer catalyst for LGO hydration. Then, excess LGO is removed via organic extraction, enabling direct oxidation in the aqueous layer, achieving large-scale production (~25 g) without chromatography. Additionally, the synthesis of methoxy and benzyloxy derivatives follows the same principles, maintaining high efficiency and scalability. By adhering to green chemistry principles, this work contributes to the sustainable use of bio-derived LGO as a valuable building block for the chemical and pharmaceutical industries.



Keywords: Levoglucosenone, green chemistry, deoxyribonolactones, scalable synthesis

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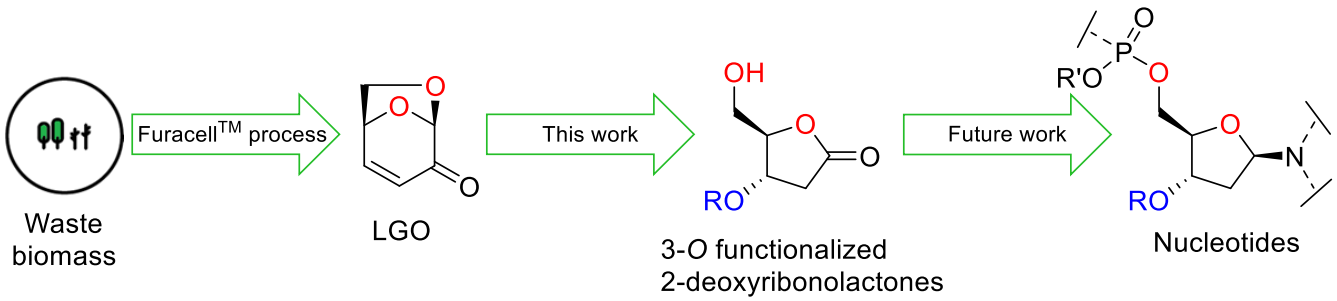
Introduction

The environmental pressure, fueled by emissions from a growing economy and population, presents a significant challenge to our world. The chemical industry bears a substantial responsibility, acting as both a contributor to these emissions and a possible actor for change. In this light, the transition from traditional, fossil-based feedstocks to renewables is essential and forms one of the 12 principles of Green Chemistry.[1]

In contrast with traditional feedstocks such as petroleum-based chemicals, natural based renewable feedstocks often possess inherent chirality and a high degree of functionalization, making them potential excellent candidates for the synthesis of pharmaceutical building blocks.[2,3] One such renewable feedstock is levoglucosenone (LGO), a functionalized chiral building block obtained from non-food biomass through a patented pyrolysis process. While carbohydrate feedstocks are typically excessively functionalized with hydroxyl groups, in contrast to hydrocarbons that lack oxygen and functional groups altogether,[4] LGO strikes a balance between these by possessing chirality and limited functionality.

LGO has already found widespread application as a chiral synthon,[5–7] owing to these desirable properties and the high stereochemical control offered by the 1,6-anhydro bridge, typically forcing reactions to occur on the less hindered *exo*-face of the molecule.[7] The reactivity of LGO towards *O*-nucleophiles, *i.e.* oxa-Michael addition, has been explored to give a variety of β *O*-functionalized adducts.[8–10] Moreover, the Baeyer-Villiger oxidation (BVO) of these products leading to functionalized lactones has also been described.[11] These lactones are important chiral building blocks for the synthesis of (new) nucleoside based drugs, for example, ribonolactone is used in the synthesis of remdesivir.[12] However, there has been a lack of focus on the scalability of synthesis routes producing these lactones from LGO, with purification typically occurring via chromatography. In this work we report on the scalable synthesis of a range of 3-*O* functionalized lactones, using green chemistry principles, focusing on chromatography-free purification and telescoping of reaction sequences, to produce these useful building blocks (Scheme 1).



Scheme 1. General overview.

Results and Discussion

The synthesis of 3-*O* functionalized 2-deoxyribonolactones from LGO (**1**) consists of two transformations: the Michael addition of an alcohol or water to **1**, followed by Baeyer-Villiger oxidation (BVO) (Scheme 2). In general, the addition of an alcohol to **1** will occur on the less hindered, *exo*-face of the molecule.[7] These additions typically have to be catalyzed, either by an acid or a base. Notably, in the case of acid catalysis the acetal **4** is the side product, and in the case of basic catalysis the LGO-Cyrene dimer **5** is produced as a side product.[9] In

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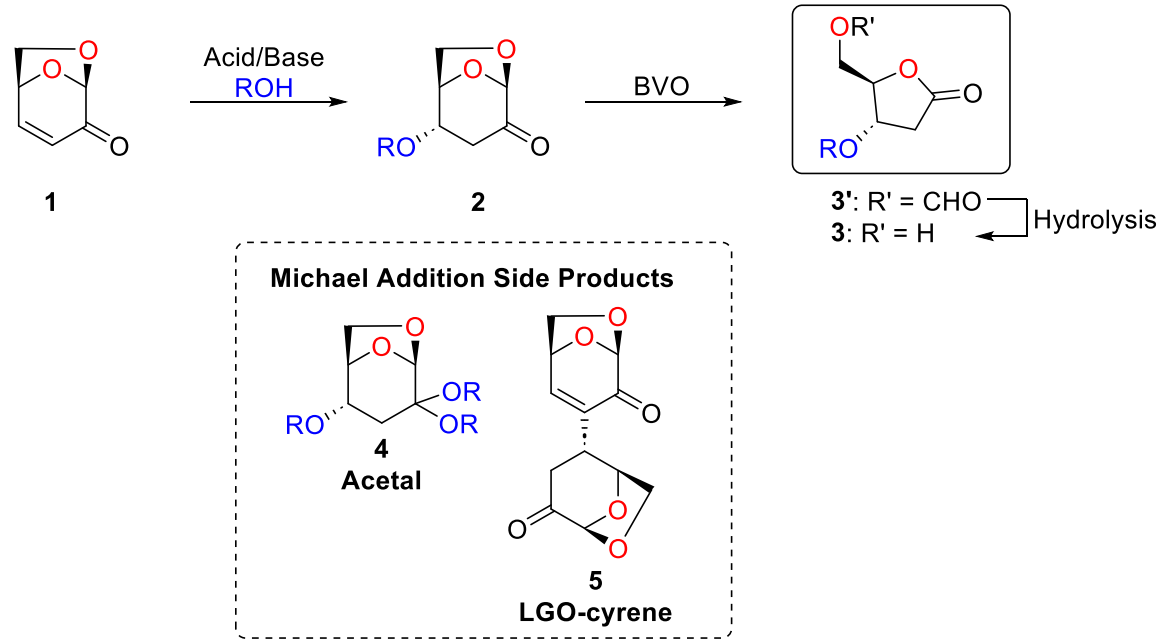
this work, we focused on the addition of water onto **1**. This reaction has been reported in literature using catalysts such as NEt_3,[10] AcOH[8] and K_3PO_4.[13] The subsequent BVO of this product, producing the lactone **3** has also been described with the BVO occurring in two separate steps, requiring two chromatographic separation. Yields of 64-65% from **1** were reported.[13,14] A recently filed patent[15] describes a one-pot process for this transformation, involving hydration in water for 2 to 6 days without a catalyst, followed by direct oxidation using hydrogen peroxide at temperatures of 50-90 °C and subsequent hydrolysis in HCl/CH_3CN. This method yields the product **3** with a 86% yield. However, it is important to note that column chromatography remains necessary in this process, which we aim to avoid.



Scheme 2. General methodology for the synthesis 3-*O* functionalized 2-deoxyribonolactones **(3)** from LGO **(1).**

We first evaluated K_3PO_4, which led to almost full conversion. However, side products including **5** were also produced. Utilizing 10% formic acid in water gave a clean reaction, with ~90% conversion towards the product (Scheme 3). Moreover, the unreacted LGO (**1**) could easily be removed from the reaction mixture with organic solvents, after which the BVO could directly be performed on the water layer with peracetic acid. From a safety perspective, it is essential that any remaining peroxides are quenched after this reaction, therefore sodium sulfite is added. However, as the product is extremely water-soluble, extraction is not feasible. The addition of acetone to the reaction mixture causes the resulting salts to precipitate, enabling convenient recovery of the products through filtration and evaporation of the solvent, without aqueous work-up. Finally, a hydrolysis step was performed using MeOH/HCl to cleave any formate ester, which is the direct product of the BVO. After evaporation of the solvent, product **3a** was obtained as a brown oil, in 83 % yield from **1** over the two steps, with a purity sufficient for further transformations (Supporting information, Figure S9. ^{1}H NMR spectrum of **3a**), without any chromatography or other purification being needed. For example, the alcohol groups were benzoyl protected to give the dibenzoylated lactone **6**, in 78% after crystallization as a white crystalline product (Scheme 4, Eq. 1). In this way a crystalline product was obtained in three steps from LGO (hydration-BVO-esterification), in 65% overall yield, without any chromatography.

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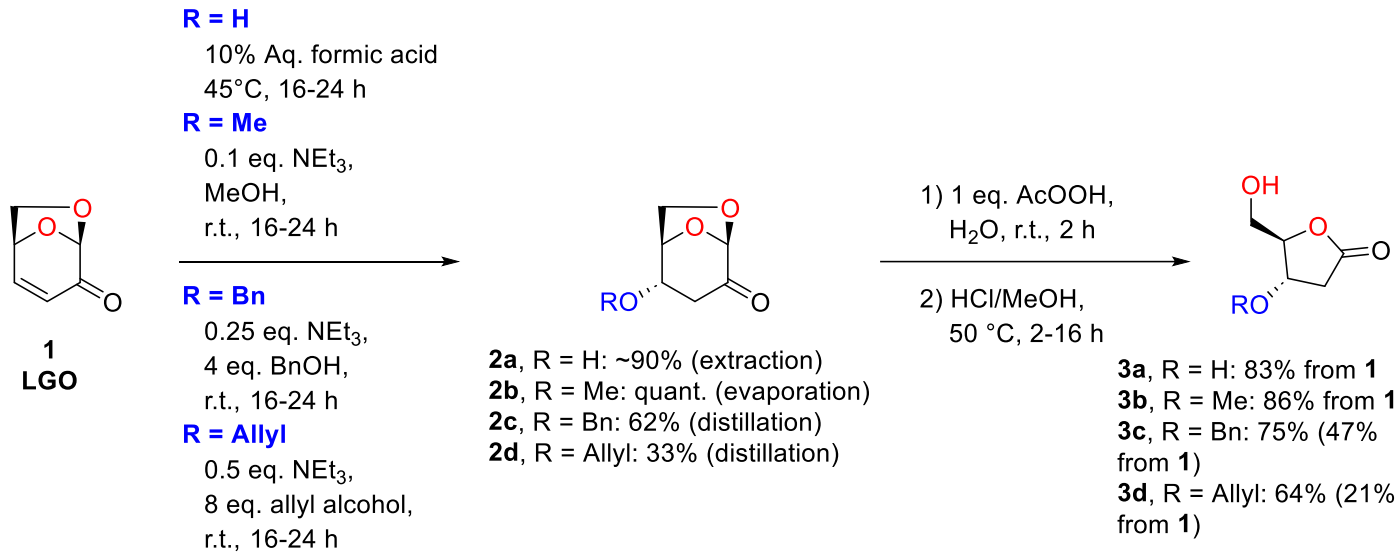

Scheme 3. Synthesis of 3-*O* functionalized lactones.

Next, we focused on the methoxy substituted lactone **3b** (Scheme 3). This compound has been reported by a long sequence starting from mannose or mannitol.[16] Another author reported this compound originating from LGO (**1**), by direct BVO of **1** with MeOH as the solvent, producing this compound as a side product in very low yields (4%).[17] The MeOH addition product of **1** has been described, by stirring it in MeOH, with NEt_3 as a catalyst.[18] This same procedure was used, giving the product with 88% yield after purification over silica. Tetramethylguanidine (TMG) was also evaluated, but gave too many side reactions. When this reaction was performed in MeOH/HCl, the dimethyl acetal of the methanol adduct (**4**) was obtained, as was previously described.[8] Notably we could reduce the amount of catalyst to only 0.5 mL (0.1 eq.) and omitting the filtration over silica gel, as the product was obtained in pure form after evaporation of the solvent and base, giving MeO-LGO derivative (**2b**) in quantitative yield. The Baeyer-Villiger reaction of this product proceeded smoothly with peracetic acid, followed by cleavage in MeOH/HCl, giving the product **3b** in 86% yield without any further purification.

The synthesis of the benzyloxy derivative **3c** proved more challenging (Scheme 3). The addition of benzyl alcohol (BnOH) into **1** has been described in literature with NEt_3[18] and KOBn.[19] The reaction was performed according to Kawai *et al.*,[18] which gave the product in 51% isolated yield after column chromatography. This reaction was made more practical by lowering the amounts of benzyl alcohol and NEt_3 (Table 1). HCl was also evaluated as a catalyst, but this did not give more promising results. Finally, instead of using column chromatography, the product **2c** could be purified by distillation under high vacuum (150 °C at 2-3 mbar). This was then subjected to the BVO and formate cleavage as performed before. In this case, the product **3c** could be extracted from the aqueous reaction mixture with EtOAc, as it is much more apolar than the lactones **3a** and **3b**. Finally, crystallization from Et_2O allowed the isolation of the product **3c** as a crystalline solid in 75% yield. Further transformation of the product **3c**, in which the alcohol group was benzoyl-protected, led to the formation of benzoylated lactone **7** in 91% yield after purification, obtained as an oil (Scheme 4, Eq. 2). In this way, the product was synthesized in three steps from LGO (benzyl alcohol addition–BVO–esterification) with an overall yield of 42%, requiring only a single chromatography step.

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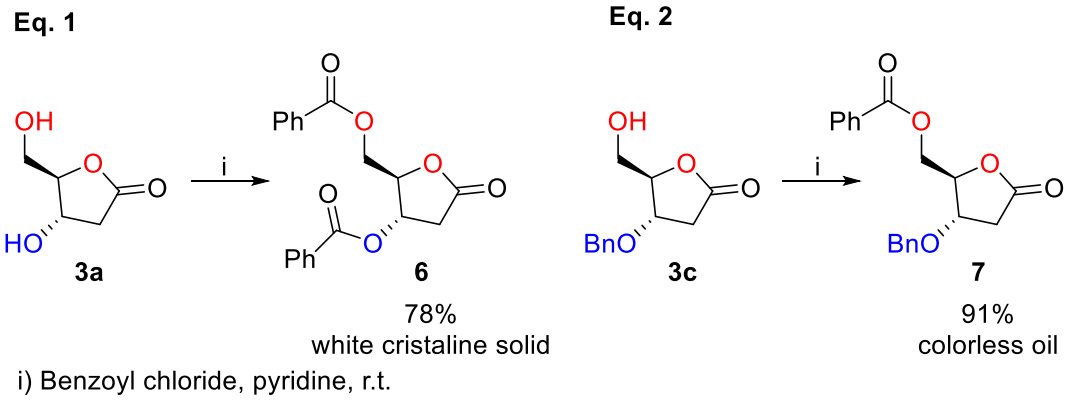
Table 1. Optimization of the benzyl alcohol addition into **1**

Entry	Catalyst	Eq. BnOH	Yields (Product 3c/ Dimer 5/ LGO 1)
1	0.5 eq. NEt_3	10	82/9/9
			51% of **3c** after column
2	0.1 eq. NEt_3	10	73/4/23
3	0.25 eq. NEt_3	10	82/9/9
4	1.5 eq. 5N HCl	10	70/ 22*/8
5	0.25 eq. NEt_3	8	81/5/14
			59% of **3c** after distillation
6	0.25 eq. NEt_3	4	78/11/11
			62% of **3c** after distillation

*Acetal as side product, not the dimer

The synthesis of the allyl derivative **3d** was also performed (Scheme 3). The synthesis of this compound was recently described by the Allais group.[11] Using NEt_3 (0.5 eq.) as a catalyst and allyl alcohol as the solvent, a moderate conversion to the adduct **2d** was obtained. Purification of this compound via column chromatography was not possible due to its instability, due to retro-Michael addition. Distillation was possible (80 °C at 2-3 mbar), however some LGO still remains in the distilled product. Finally, the allyl adducts required chromatography after the BVO to obtain the pure product **3d**.



Scheme 4. Further transformations of the products **3a** and **3c**.

Conclusions

In this work, scalable synthesis routes were successfully optimized for four essential lactone building blocks, using LGO (**1**), a renewable platform molecule, as the starting material. Notably, for the hydroxy and methoxy adducts, no additional purification steps were required to achieve technical-grade products, highlighting the efficiency and practicality of the developed processes. The benzyloxy adduct was purified through a combination of distillation and crystallization, ensuring high purity and avoiding the use of chromatographic purification. These advancements contribute to the broader adoption of LGO as a sustainable feedstock for the synthesis of pharmaceutically relevant compounds. By demonstrating efficient and scalable routes to key lactone

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derivatives, this work reinforces the potential of LGO to drive innovation in green chemistry and supports the transition towards a more sustainable chemical industry.

Experimental Section

General: Unless stated otherwise all reagents and solvents were purchased from commercial sources and used without further purification. IR spectra of the materials and compounds were measured in neat form using a Shimadzu IRAffinity1S WL FTIR spectrophotometer. A Bruker Avance III HD-400 spectrophotometer was used to measure ^{1}H-NMR and ^{13}C-NMR spectra in solution at 400 and 100 MHz, respectively, using a 1H/BB z-gradient probe (BBO, 5 mm). The spectra were acquired using standard sequences available in the Bruker pulse program library and further processed using TOPSPIN 4.1. MS spectra were obtained via HPLC-MS. The HPLC used was an Agilent 1200 series HPLC system fitted with an Ascentis® Express C18 column (particle size 2.7 µm, length 30 mm, internal diameter 4.6 mm). A mixture of acetonitrile/water (5 mM NH_4OAc) was used as the eluent. As detectors for the HPLC a UV-Vis detector and an Agilent 1100 series LC/MSD-type SL mass spectrometer (ESI, 4000 V) using a mass-selective single quadrupole were used. Thin layer chromatography (TLC) was used to determine suitable solvent systems for chromatography, using glass-backed 0.25-mm Merck silica gel 60 F254 TLC plates, and visualized under UV light (254 nm). The chromatography itself was done using a Büchi Reveleris® X2 flash chromatography system (normal phase) using prepacked Reveleris® silica.

(1R,2S,5R)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-4-one 2a: To a flask containing LGO (**1**) (10.00 g, 79.30 mmol, 1 eq.) was added 100 mL of a 10% formic acid/water solution. This mixture was stirred overnight at 45 °C after which the conversion could be determined using ^{1}H-NMR (DMSO-d_6), and this was typically ~90%. The water layer was then extracted three times with dichloromethane (3x100 mL) to remove the unreacted LGO. This water layer was evaporated, followed by dissolving the crude in acetone (100 mL), $MgSO_4$ was added, this was filtered and evaporated to give **2a** as a yellow oil (10.80 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.14 (1H, ddt, *J* 16.9, 2.3 and 1.2 Hz, H_3); 2.92 (1H, dd, *J* 16.9, 5.9 Hz, H_3); 3.76 (1H, dd, *J* 7.8 and 5.6 Hz, H_6); 3.97 (1H, dd, *J* 7.8 and 1.2 Hz, H_6); 4.10-4.12 (1H, m, H_4); 4.57-4.59 (1H, m, H_5); 5.05 (1H, s, H_1); 5.38 (1H, br s, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 40.5 (C_3); 64.6 (C_6); 68.9 (C_4); 77.2 (C_5); 100.4 (C_1); 200.7 (C_2). IR (ATR, cm^{-1}): vOH = 3451; vCO = 1734; vmax = 1113, 1094, 1007, 961, 905, 866, 455, 428. MS (ESI): *m/z* (%) 185 ([M+18 (H_2O) + 23]$^+$, 100). Spectral data matched literature.[13]

Telescoped synthesis of (4S,5R)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3H)-one 3a: To a flask containing **1** (25.22 g, 200 mmol, 1 eq.), 250 mL of a 10% formic acid/water solution was added. This mixture was stirred overnight at 45 °C, after which the conversion could be determined using ^{1}H NMR (DMSO-d_6), typically ~90%. The water layer was then extracted three times with dichloromethane (3x200 mL) to remove unreacted **1**. The water layer was transferred to a flask, cooled in a cold-water bath (~10-20 °C). To this flask, AcOOH (38 wt%, 31.6 mL, 13.7 g, 180 mmol, 1 eq.) was added via an addition funnel over 15 minutes. The reaction completion was monitored by ^{1}H NMR (DMSO-d_6), and after two hours, the reaction was quenched with the addition of Na_2SO_3 (22.69 g, 180 mmol, 1 eq.). This mixture was stirred for at least 5 minutes, and the quenching of all peroxides was confirmed using a peroxide test strip. Acetone (1 L) was then added slowly, and the precipitated salts were filtered off. The intermediary product was obtained by evaporating the solvent. To this, 100 mL of MeOH and 7.5 mL of concentrated (37%) HCl were added, and the mixture was stirred at 50 °C until completion (^{1}H NMR, DMSO-d_6), typically taking around 2-4 hours or overnight. The mixture was filtered, evaporated, redissolved in acetone, filtered, evaporated, and dried under high vacuum to obtain the product **3a** as a brown

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oil (21.80 g, 83% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.22 (1 H, dd, *J* 7.7 and 2.3 Hz, H_2'); 2.81 (1H, dd, *J* 17.7 and 6.4 Hz, H_2); 3.52 (1H, dd, *J* 12.8 and 3.8 Hz, H_5); 3.55 (1H, dd, *J* 3.7 and 0.8 Hz, H_5); 4.23-4.28 (2H, m, H_3 and H_4). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 38.0 (C_2); 60.8 (C_5); 67.6 (C_3); 88.2 (C_4); 176.2 (C_1). IR (ATR, cm^{-1}): ν_{OH} = 3385; $\nu_{C=O}$ = 1747; ν_{max} = 1167, 1082, 1051, 1020, 986, 934, 905, 613. MS (ESI): *m/z* (%) 133 ([M+1]$^+$, 40); 150 ([M+18]$^+$, 80); 155 ([M+23]$^+$, 100); 287 ([2M+23]$^+$, 60).

(1*R*,2*S*,5*R*)-2-methoxy-6,8-dioxabicyclo[3.2.1]octan-4-one 2b: 1 (25.22 g, 200 mmol, 1 eq.) was dissolved in 250 mL MeOH. NEt_3 (2.79 mL, 2.02 g, 20 mmol, 0.1 eq.) was added and the reaction was stirred overnight, after which the solvent and the catalyst are evaporated, furnishing the product **2b** quantitatively as a yellow oil (31.63 g, quant.). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.29 (1H, ~dq, *J* 17.1 and 1.2 Hz, H_3); 2.94 (1H, ~dd, *J* 17.1 and 6.0 Hz, H_3); 3.29 (3H, s, OCH_3); 3.78-3.82 (2H, m, H_6 and H_4); 4.01 (1H, dd, *J* 7.9 and 1.2 Hz, H_6); 4.86-4.89 (1H, m, H_5); 5.08 (1H, s, H_1). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 37.4 (C_3); 55.7 (OCH_3); 64.6 (C_6); 73.4 (C_5); 78.1 (C_4); 100.4 (C_1); 200.1 (C_2). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1738; ν_{max} = 2980, 1907, 1115, 1086, 1028, 1005, 984, 895, 483. MS (ESI): *m/z* (%) 199 ([M+18+23]$^+$, 100); 375 ([2M+23]$^+$, 100).

Telescoped synthesis of (4*S*,5*R*)-5-(hydroxymethyl)-4-methoxydihydrofuran-2(3*H*)-one 3b: 2b (31.63 g, 200 mmol, 1 eq.) without purification was dissolved in 100 mL water and cooled in a cold water bath (~10-20 °C). Peracetic acid (38%, 35.1 mL, 15.21 g, 200 mmol, 1 eq.) was slowly added. The reaction completion was monitored by ^{1}H-NMR (DMSO-d_6), and after two hours, the reaction was quenched with the addition of Na_2SO_3 (25.21 g, 200 mmol, 1 eq.). This mixture was stirred for at least 5 minutes, and the quenching of all peroxides was confirmed using a peroxide test strip. Acetone (1 L) was then added slowly, and the precipitated salts were filtered off. The intermediary product was obtained by evaporating the solvent. To this, 100 mL of MeOH and 7.5 mL of concentrated (37%) HCl were added, and the mixture was stirred at 50 °C until completion (^{1}H-NMR, DMSO-d_6), typically taking around 2-4 hours or overnight. The mixture was evaporated, redissolved in acetone, filtered, evaporated, and dried under high vacuum to obtain the product **3b** as a brown oil (25.159 g, 86% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.42 (1H, dd, *J* 18.1 and 1.5 Hz, H_2); 2.84 (1H, dd, *J* 18.1 and 6.6 Hz, H_3); 3.25 (3H, s, OCH_3); 3.57 (1H, dd, *J* 3.7 and 0.8 Hz, H_5); 4.01 (1H, dt, *J* 6.5 and 1.4 Hz, H_3); 4.54 (1H, td, *J* 3.7 and 1.1 Hz, H_4). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 30.7 (C_2); 55.8 (OCH_3); 61.0 (C_5); 77.7 (C_3); 84.9(C_4); 175.9 (C_1). IR (ATR, cm^{-1}): ν_{OH} = 3347; $\nu_{C=O}$ = 1753; ν_{max} = 1368, 1175, 1084, 1049, 1015, 608, 575, 545. MS (ESI): *m/z* (%) 147 ([M+1]$^+$, 100); 164 ([M+18]$^+$, 80); 169 ([M+23]$^+$, 50).

(1*R*,2*S*,5*R*)-2-(benzyloxy)-6,8-dioxabicyclo[3.2.1]octan-4-one 2c:

Procedure I, with column chromatography: **1** (1.26 g, 10 mmol, 1 eq.) was added to a flask containing 10 mL benzyl alcohol and NEt_3 (0.7 mL, 0.5 eq. 5 mmol) was added. The reaction was stirred overnight. The majority of the benzyl alcohol was distilled (oil bath ~150 °C, vacuum at 40-50 mbar) and the residue was purified by column chromatography (SiO_2), eluting stepwise using 25-50-100% Et_2O in hexanes, collecting three fractions. The first is residual benzyl alcohol, the second is the product **2c**, which was collected as a colorless oil (1.195 g, 51%) and finally, a third fraction: the LGO-cyrene dimer **4** as a white solid (0.506 g, 20%).

Procedure II, with Vacuum distillation, upscaled: **1** (25.22 g, 200 mmol, 1 eq.) and benzyl alcohol (80 mL, 800 mmol, 4 eq.) were added to a flask. The product was distilled under high vacuum (2-3 mbar). Benzyl alcohol came over with the temperature of the oil bath around 80 °C, the temperature was then raised and a mixed fraction containing some leftover benzyl alcohol, LGO, and a small amount of the product was collected. Finally the product boiled over, with a boiling point of 150 °C at 2-3 mbar, with the oil bath around 200 °C. In this way the compound **2c** was collected as a thick yellow oil (29.11 g, 62%). Boiling point: 150 °C at 2-3 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.37 (1H, ddt, *J* 17.2, 2.4 and 1.2 Hz, $H_{3'}$); 2.98 (1H, dd, *J* 17.1 and 6.0 Hz, H_3); 3.81 (1H, dd, *J* 7.9 and 5.7 Hz, H_6); 4.01-4.04 (2H, m, H_6 and H_4); 4.56 (1H, d_{AB}, *J* 12.1 Hz, C<u>H</u>(H)Ph); 4.59 (1H, d_{AB}, *J* 12.1 Hz, C<u>H</u>(H)Ph); 4.93-4.94 (1H, m, H_5); 5.11 (1H, s, H_1); 7.27-7.38 (5H, m, 5xCH_{arom}). ^{13}C NMR (100.6 MHz, DMSO-d_6):

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δ_C 37.7 (C_3); 64.7 (C_6); 69.5 (OCH_2Ph); 74.0 (C_5); 76.2 (C_4); 100.4 (C_1); 127.49 (CH_{arom}); 127.51 (2 x CH_{arom}); 128.3 (2 x CH_{arom}); 138.1 ($C_{arom,quat}$); 200.2 (C_2). IR (ATR, cm^{-1})= $\nu_{C=O}$= 1737; ν_{max}= 1116, 1070, 1024, 962, 903, 737, 697.

Telescoped synthesis of (4*S*,5*R*)-4-(benzyloxy)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one 3c: 2c (26.487 g, 113.1 mmol, 1 eq.) was dissolved in 50 mL water, to which 50 mL MeOH was added to obtain good solubility. Peracetic acid (35 wt%, 21.75 mL, 8.60 g, 113.1 mmol, 1 eq.) was added dropwise to a cooled (~10-20 °C) solution. The reaction completion was monitored by ^{1}H NMR (DMSO-d_6), and after two hours, the reaction was quenched with the addition of Na_2SO_3 (14.26 g, 113.1 mmol, 1 eq.). This mixture was stirred for at least 5 minutes, and the quenching of all peroxides was confirmed using a peroxide test strip. Acetone (0.5 L) was then added slowly, and the precipitated salts were filtered off. The intermediary product was obtained by evaporating the solvent. To this, 100 mL of MeOH and 7.5 mL of concentrated (37%) HCl were added, and the mixture was stirred at 50 °C until completion (^{1}H NMR, DMSO-d_6), typically taking around 2-4 hours or overnight. Water and EtOAc were added, the layers were separated and the water layer was extracted two more times with EtOAc. The combined organic layers were dried, evaporated and crystallized from Et_2O (~100 mL) to give the product **3c** as a white crystalline solid (18.93 g, 75%). M.p: 66.7-68.3 °C (from Et_2O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.51 (1H, dd, *J* 18.0 and 1.7 Hz, $H_{2'}$); 2.88 (1H, dd, *J* 18.1 and 6.6 Hz, H_2); 3.58 (2H, ddd, *J* 5.3, 3.8 and 1.6 Hz, H_5); 4.23 (1H, dt, *J* 6.6 and 1.5 Hz, H_3); 4.53 (2H, s, CH_2Ph); 4.55 (1H, td, *J* 3.7 and 1.4 Hz, H_4); 5.15 (1H, t, *J* 5.4 Hz, OH); 7.27-7.38 (5H, m, 5 x CH_{arom}). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 35.3 (C_2); 61.0 (C_5); 69.8 (CH_2Ph); 75.7 (C_3); 85.2 (C_4); 127.6 (CH_{arom}); 127.7 (2 x CH_{arom}); 128.3 (2 x CH_{arom}); 137.8 ($C_{arom,quat}$); 175.7 (C_1). IR (ATR, cm^{-1}): ν_{OH} = 3381; $\nu_{C=O}$ =1759; ν_{max} = 1200, 1090, 1067, 1018, 746, 696, 606, 480. MS (ESI): *m/z* (%) 223 ($[M+1]^+$, 60); 240 ($[M+18]^+$, 100); 467 ($[2M+23]^+$, 20).

(1*R*,2*S*,5*R*)-2-(allyloxy)-6,8-dioxabicyclo[3.2.1]octan-4-one 2d: 1 (6.3 g, 50 mmol, 1 eq) was added to a flask containing allyl alcohol (23.23 g, 27 mL, 400 mmol, 8 eq.) and NEt_3 (3.5 mL, 2.53 g, 25 mmol, 0.5 eq.) was added. Allyl alcohol was evaporated around 40-50 mbar, followed by distillation under high vacuum (2-3 mbar). The product **2d** distilled around 80 °C and was collected as a yellow oil (4.518 g, 33%) that still contained ~10% LGO. Boiling point: 80 °C at 2-3 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.30 (1H, ddt, *J* 17.1, 2.4 and 1.2, $H_{3'}$); 2.95 (1H, dd, *J* 17.1 and 6.0 Hz, H_3); 3.79 (1H, dd, *J* 7.9 and 5.6 Hz, H_6); 3.95 (1H, dt, *J* 6.0 and 1.4 Hz, H_6); 4.00-4.04 (2H, m, $C\underline{H}_2CH=CH_2$); 5.09 (1H, s, H_1); 5.15 (1H, dq, *J* 10.4 and 1.5 Hz, $CH_2CH=C\underline{H}_2$); 5.26 (1H, dq, *J* 10.4 and 1.5 Hz, $CH_2CH=C\underline{H}_2$); 5.88 (1H, ddt, *J* 17.2, 10.4 and 5.2 Hz, $CH_2C\underline{H}=CH_2$). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 37.7 (C_3); 64.7 (C_6); 68.7 (C_4); 74.0 (C_5); 76.1 ($\underline{C}H_2CH=CH_2$); 100.3 (C_1); 116.6 ($CH_2CH=\underline{C}H_2$); 135.0 ($CH_2\underline{C}H=CH_2$); 200.1 (C_2).

Telescoped synthesis of (4*S*,5*R*)-4-(allyloxy)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one 3d: 2d without any purification (3.019 g, 16.4 mmol, 1 eq.) was dissolved in 10 mL water. Peracetic acid (35 wt %, 3.15 mL, 1.25 g, 16.4 mmol, 1 eq.) was added dropwise to a cooled (~10-20 °C) solution. The reaction completion was monitored by ^{1}H NMR (DMSO-d_6), and after two hours, the reaction was quenched with the addition of Na_2SO_3 (2.07 g, 16.4 mmol, 1 eq.). This mixture was stirred for at least 5 minutes, and the quenching of all peroxides was confirmed using a peroxide test strip. Acetone (50 mL) was then added slowly, and the precipitated salts were filtered off. The intermediary product was obtained by evaporating the solvent. To this, 10 mL of MeOH and 0.75 mL of concentrated (37%) HCl were added, and the mixture was stirred at 50 °C until completion (^{1}H NMR, DMSO-d_6), typically taking around 2-4 hours or overnight. The reaction mixture was filtered and evaporated. The crude was purified by column chromatography (SiO_2, 40% EtOAc in hexanes) to give the product as a colourless oil (1.81 g, 64%). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.44 (1H, dd, *J* 18.1 and 1.7, H_2); 2.86 (1H, dd, *J* 18.1 and 6.6 Hz, H_2); 3.57 (2H, d, *J* 3.7 Hz, H_5); 3.99 (2H, ~dd, *J* 5.3 and 1.4 Hz, $C\underline{H}_2CH=CH_2$); 4.17 (1H, dt, *J* 6.6 and 1.6 Hz, H_3); 4.47 (1H, td, *J* 3.7 x 1.3 Hz, H_4); 5.16 (1H, dq, *J* = 10.4 and 1.5 Hz, $CH_2CH=C\underline{H}_2$); 5.27 (1H, m, $CH_2CH=C\underline{H}_2$); 5.84-5.93 (1H, m, $CH_2C\underline{H}=CH_2$). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 35.2 (C_2); 60.9 (C_5); 68.8

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($\underline{C}H_2CH=CH_2$); 75.2 (C_3); 85.2 (C_4); 116.8 ($CH_2CH=\underline{C}H_2$); 134.7 ($CH_2\underline{C}H=CH_2$); 175.7 (C_1). **IR** (ATR, cm^{-1}): ν_{OH} = 3447; $\nu_{C=O}$ =1763; ν_{max} = 1171, 1082, 1016, 999, 982, 932, 519, 434. MS (ESI): *m/z* (%) 173 ($[M+1]^+$, 100); 190 ($[M+18]^+$, 90). Spectral data matches literature.[11]

(1*S*,1'*S*,2*R*,5*R*,5'*R*)-6,6',8,8'-tetraoxa[2,3'-bi(bicyclo[3.2.1]octan)]-2'-ene-4,4'-dione 5: White solid, m.p. 172.3-173.5 °C (from EtOAc/petroleum ether), 0.506 g, 20%. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.17 (1H, d, *J* 17.0 Hz, $H_{3'}$); 3.08 (1H, dd, *J* 17.0 and 8.6 Hz, $H_{3'}$); 3.36 (1H, d, *J* 8.5 Hz, $H_{4'}$); 3.70 (1H, d_{AB}, *J* 6.9 Hz, H_6); 3.76 (1H, dd, *J* 6.9 and 4.7 Hz, H_6); 3.90 (1H, dd, *J* 7.6 and 5.4 Hz, $H_{6'}$); 4.28 (1H, dd, *J* 7.7 Hz, $H_{6'}$); 4.52 (1H, d, *J* 4.8 Hz, $H_{5'}$); 5.11 (1H, s, $H_{1'}$); 5.28 (1H, t, *J* 4.7 Hz, H_5); 5.45 (1H, s, H_1); 7.12 (1H, dd, *J* 4.9 and 1.0 Hz, H_4). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 34.2 ($C_{3'}$); 37.6 ($C_{4'}$); 66.0 (C_6); 67.2 ($C_{6'}$); 71.9 (C_5); 74.5 ($C_{5'}$); 100.1 (C_1); 100.6 ($C_{1'}$); 135.7 (C_3); 145.6 (C_4); 188.6 (C_{C1}); 200.7 (C_1). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1730 and 1684; ν_{max} = 1099, 980, 966, 910, 899, 883, 866, 455. MS (ESI): *m/z* (%) 253 ($[M+1]^+$, 100); 275 ($[M+18]^+$, 100). Spectral data matches literature.[20]

((2*R*,3*S*)-3-(benzoyloxy)-5-oxotetrahydrofuran-2-yl)methyl benzoate 6: 3a (21.80 g, 165 mmol, 1 eq.) was dissolved in 250 mL dichloromethane, under N_2 and pyridine was added (53.3 mL, 52.21 g, 660 mmol, 4 eq.). The flask was placed in an ice bath and benzoyl chloride (47.9 mL, 57.99 g, 412.5 mmol, 2.5 eq.) was added dropwise, via an addition funnel, over 15 minutes. The reaction was allowed to come to room temperature and stirred for two hours, after which water (250 mL) was added. The phases were separated, and the water layer was extracted two more times with 250 mL dichloromethane. The combined organic layers were washed with sat. Na_2CO_3, 1N HCl and brine, after which it was dried over $MgSO_4$, filtered, evaporated and crystallized from ~300 mL EtOH to give the product as white crystals (44.00 g, 78%). M. p.: 97.6-99.8 °C (from EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.93 (1H, dd, *J* 18.8 and 2.3 Hz, $H_{2'}$); 3.30 (1H, dd, *J* 18.9 and 7.5 Hz, H_2); 4.58-4.67 (2H, m, H_5); 5.11-5.14 (1H, m, H_4); 5.66 (1H, dt, *J* 7.4 and 2.1 Hz, H_3); 7.53-7.58 (4H, m, 4 x CH_{arom}); 7.68-7.71 (2H, m, 2 x CH_{arom}); 7.97-8.03 (4H, m, 4 x CH_{arom}). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 34.4 (C_2); 63.9 (C_5); 72.7 (C_3); 81.6 (C_4); 128.8 (2 x CH_{arom}); 128.9 (2 x CH_{arom}); 128.98 ($C_{arom,quat}$); 129.03 ($C_{arom,quat}$); 129.3 (2 x CH_{arom}); 129.5 (2 x CH_{arom}); 133.67 (CH_{arom}); 133.75 (CH_{arom}); 165.1 (COPh); 165.3 (COPh); 174.1 (C_1). IR (ATR, cm^{-1}): ν_{CO} = 1765, 1724 and 1713; ν_{max} = 1265, 1163, 1117, 1098, 1057, 1047, 705. MS (ESI): *m/z* (%) 358 ($[M+18]^+$, 100).

((2*R*,3)-3-(benzyloxy)-5-oxotetrahydrofuran-2-yl)methyl benzoate 7: 3c (250 mg, 1.12 mmol, 1 eq.) was dissolved in 5 mL dichloromethane, under N_2 and pyridine was added (364 µL, 355.9 mg, 4.5 mmol, 4 eq.). The flask was placed in an ice bath and benzoyl chloride (326 µL, 395.3 mg, 2.8 mmol, 2.5 eq.) was added slowly. The reaction was allowed to come to room temperature and stirred for two hours, after which water (10 mL) was added. The phases were separated, and the water layer was extracted two more times with 10 mL dichloromethane. The combined organic layers were washed with sat. Na_2CO_3, 1N HCl and brine, after which it was dried over $MgSO_4$, filtered, evaporated and purified by column chromatography (SiO_2, 20% Acetone in hexanes) to give the product as a colourless oil (332.8 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.66 (1H, dd, J = 18.3 and 2.4 Hz, $H_{2'}$); 3.06 (1H, dd, J = 18.3, 6.8 Hz, H_2); 4.41 (1H, dt, J = 6.9, 2.3 Hz, H_3); 4.51 (2H, qd, J = 12.2, 4.6 Hz, H_5), 4.59 (2H, s, CH_2Ph), 4.93 (1H, ddd, J = 5.8, 4.0 and 2.0 Hz, H_4); 7.27-7.33 (1H, m, CH_{arom}); 7.33- 7.38 (4H, m, CH_{arom}); 7.52-7.60 (2H, m, CH_{arom}); 7.65-7.73 (1H, m, CH_{arom}); 7.91-7.97 (2H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 35.4 (C_2); 64.5 (C_5); 70.6 (CH_2Ph); 75.7 (C_3); 82.3 (C_4); 128.1 (CH_{arom}); 128.2 (2 x CH_{arom}); 128.8 (2 x CH_{arom}); 129.4 (2 x CH_{arom}); 129.6 ($C_{arom,quat}$); 129.7 (2 x CH_{arom}); 134.1 (CH_{arom}); 138.1 ($C_{arom,quat}$); 165.7 (COPh); 175.6 (C_1). IR (ATR, cm^{-1}): ν_{CO} = 1780, 1719; ν_{max}= 1267, 1069, 709. MS (ESI): *m/z* (%) 327 ($[M+1]^+$, 4); 344 ($[M+18]^+$, 100).

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Supplementary Material

The Supporting Information contains the ^{1}H and ^{13}C NMR spectra for all of the synthesized compounds.

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