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Sulfuric acid and Amberlyst-H⁺ catalyzed condensation reactions of renewable keto acids with paraformaldehyde: synthesis of a new dispiro bis-lactone ring system 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione†

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The sulfuric acid and Amberlyst-H⁺ catalyzed condensation reactions of renewable feedstock levulinic acid with paraformaldehyde under neat conditions at 80 °C gives 2,9,11,14-tetraoxadispiro[4.1.5.3]pentadecane-3,6-dione in 91–93% yield, in which the structure was confirmed by single crystal X-ray crystallography. A similar condensation reaction between 4-ketopimelic acid and paraformaldehyde at 80 °C gives 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione. This new dispiro bis-lactone was found to composed of a 1.6 : 1 mixture of isomers with planes of symmetry bisecting the tetrahydro-2*H*-pyran-4-one rings through the carbonyl groups.

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Introduction

The recent interest in feedstock chemicals and fuels based on renewable resources has led to explorations into a variety of biomass derived materials such as lactic acid,¹ triglycerides,² 1,3-propanediol,³ furfural, 2,5-furandicarboxylic acid or its derivatives,^{4–6} and lignin derived vanillin.^{7,8} 4-Oxopentanoic acid or levulinic acid (LA) is also another potential monomer for the preparation of renewable generation polymeric materials and a feedstock compound for fuel precursors. This key renewable chemical can be produced from a number of carbohydrates and most notably from abundant cellulosic biomass *via* a series of reactions involving depolymerization of the cellulosic fragment, dehydration to 5-hydroxymethylfurfural and rehydration.^{9–11} In addition, LA was listed as one of the top 12 most promising value added chemicals from biomass by the Biomass Program of the US Department of Energy in 2004¹² and also continues to rank highly in more recent reviews of major bio refinery target products.¹³ Although the current global LA

production is around 2600 tons per year, it is expected to grow in the coming years, particularly due to the introduction of the Biofine process, which has been projected to lower the production costs to as low as US\$ 0.09–0.22 per kg.¹⁴ This versatile C-5 keto-acid can be used in the synthesis of a range of useful chemicals such as 2-methyl tetrahydrofuran, γ -valerolactone, acrylic acid, 1,4-pentanediol, β -acetylacrylic acid, α -angelica lactone, δ -amino levulinic acid, *etc.*^{14,15} and some of these compounds have been used for the preparation of polymers and fuel precursors.^{16–18} Additionally, our recent studies have revealed a new route for the preparation of a renewable C-7 polymer building block by aldol condensation between LA and glyoxylic acid as well. During this work we reported the facile preparation of the bis-lactone, 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione by sulfuric acid catalyzed condensation of LA with glyoxylic acid at 80 °C, under solvent free conditions, and the resulting unsaturated lactone could be catalytically reduced to a well-known polymer building block.¹⁹

The aldol condensation reactions between LA and formaldehyde were first reported in 1955, then during the period of 1955–1960, Olsen and co-workers published on their attempts to characterize various incomplete aldol condensation products resulting from sulphuric acid catalyzed condensation of formaldehyde with LA.^{20–23} Since these early experiments were carried out in glacial acetic acid medium with limited amount of formaldehyde, complex mixtures of products were formed with different degrees of condensation, together with their acetate derivatives as well. Then in 1964 Crabb and Cookson mentioned a LA – formaldehyde condensation product in a spectroscopy study, where they used the ¹H NMR coupling

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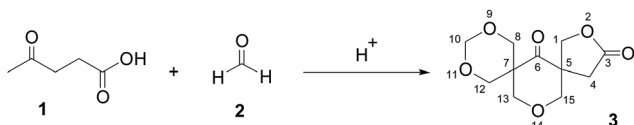


Fig. 1 Acid catalyzed condensation of levulinic acid (1) with paraformaldehyde (2) producing 2,9,11,14-tetraoxadispiro[4.1.5.3]penta-decane-3,6-dione (3).

constants to identify 1,3-dioxalane and 1,3-dioxan rings, reporting only the proton coupling constants of the 1,3-dioxan ring protons in the condensation product.²⁴ Therefore, as far as we are aware there are no reports on proper identification and complete characterization of the LA – formaldehyde condensation product in the literature. Consequently, we have undertaken to reinvestigate this reaction with a vast potential in upgrading the important renewable feedstock LA. In this publication we report our studies on condensation of LA with paraformaldehyde (PF) using a series of diverse Brønsted acid catalysts including solid acid catalysts as shown in Fig. 1, and structural studies on the condensation product. The heterogeneous Amberlyst-H⁺ catalyst was found to be equally effective as sulfuric acid in this reaction. We have studied the recyclability of this catalyst as well, since the solid acid catalysts are more attractive in scaled up processes due to facile separation and possible reusability.²⁵ In addition, we have studied the extension of this simple carbon number upgrading technique scalable to industrial production to another related renewable feedstock 4-ketopimelic acid (4-KPA) also, as shown in Fig. 2.

Experimental

Materials and instrumentation

Levulinic acid (>99%), furfural (>99%), paraformaldehyde (>99%), acetic anhydride, sulfuric acid (>99%) and Amberlyst-15 hydrogen form (catalog number 216380) were purchased from Aldrich Chemical Co. The Amberlyst-15 hydrogen form was used as it is without modification or purification. ¹H NMR spectra were recorded in CDCl₃ on a Varian Mercury plus spectrometer operating at 400 MHz and chemical shifts are given in ppm downfield from TMS ($\delta = 0.00$). ¹³C NMR spectra in CDCl₃ were recorded on the same spectrometer operating at 100 MHz; chemical shifts were measured relative to CDCl₃ and converted to $\delta(\text{TMS})$ using $\delta(\text{CDCl}_3) = 77.00$, FT-IR spectra were recorded on a Thermo Nicolet IR 200 spectrometer using KBr pellets. High resolution mass spectra were recorded using a MDS Sciex API QStar Pulsar – hybrid quadrupole/time-of-flight instrument with electro spray ionization.

General procedure for the synthesis of 2,9,11,14-tetraoxadispiro[4.1.5.3]penta-decane-3,6-dione (3)

A mixture of levulinic acid (116 mg, 1.0 mmol), paraformaldehyde (210 mg, 7.0 mmol) and Brønsted acid catalyst (10–20 mol%) was prepared in a small round bottom flask and the closed flask was heated in an oil bath at 80 °C for 6–48 h. The resulting mixture was first treated with 10 mL of ice cold water, filtered and the residue was recrystallized with aqueous ethanol to give 2,9,11,14-tetraoxadispiro[4.1.5.3]penta-decane-3,6-dione (3) as white crystals. The percent yields of 3 formed in a series of experiments are shown in Table 1. Mp 159–161 °C, Lit. mp 162–163 °C.²⁰

HRMS: calcd for C₁₁H₁₄O₆ [M + Na]⁺, 265.06881; found, 265.06605.

FT-IR: 732, 926, 986, 1039, 1135, 1169, 1197, 1369, 1699, 1794, 2857 cm⁻¹.

¹H NMR (CDCl₃) δ 2.32 (1H, d, $J = 18.0$ Hz), 3.00 (1H, d, $J = 18.0$ Hz), 3.75 (1H, d, $J = 11.6$ Hz), 3.80 (1H, d, $J = 11.6$ Hz), 3.92 (1H, d, $J = 2.2, 12.0$ Hz), 3.98 (1H, d, $J = 11.6$ Hz), 4.00 (1H, d, $J = 2.2, 11.6$ Hz), 4.02 (1H, d, $J = 11.6$ Hz), 4.03 (1H, d, $J = 11.6$ Hz), 4.21 (1H, d, $J = 9.6$ Hz), 4.29 (1H, d, $J = 9.6$ Hz), 4.35 (1H, d, $J = 12.0$ Hz), 4.60 (1H, d, $J = 6.4$ Hz), 4.97 (1H, d, $J = 6.4$ Hz).

¹³C NMR (CDCl₃) δ 33.7 (C-4), 49.9 (C-5), 53.3 (C-7), 68.2 (C-8/12), 68.7 (C-8/12), 70.9 (C-13/15), 72.1 (C-13/15), 74.4 (C-1), 94.0 (C-10), 173.4 (C-3), 204.5 (C-6).

Recyclability study of the solid acid catalyst Amberlyst-15 H⁺ in the synthesis of 3

A mixture of levulinic acid (116 mg, 1.0 mmol), paraformaldehyde (210 mg, 7.0 mmol) and Amberlyst-15 H⁺ (20 mol%) was prepared in a small round bottom flask and the closed flask was heated in an oil bath at 80 °C for 24 h. The resulting mixture was treated with 10 mL of ethanol, centrifuged at 1700g for 6 min to recover the solid catalyst. The catalyst was further washed with a second 10 mL portion of ethanol, then combined ethanol layer was evaporated and the residue was recrystallized from aqueous ethanol to give 3 as white crystals. The recovered Amberlyst-15 H⁺ catalyst was dried at 50 °C, for 15 h, and was reused for the synthesis of 3 using the same procedure. The % yields of reusing the same catalyst sample in five catalytic cycles are shown in Fig. 3.

Synthesis of 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione (5)

A mixture of 4-ketopimelic acid (174 mg, 1.0 mmol), paraformaldehyde (150 mg, 5.0 mmol) and conc. H₂SO₄ (20 mol%)

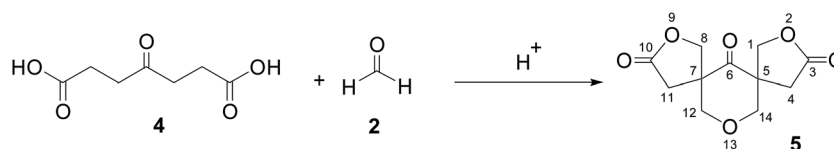


Fig. 2 Acid catalyzed condensation of 4-ketopimelic acid (4) with paraformaldehyde (2) producing of 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione (5).



Table 1 Reactant mole ratios, catalysts, reaction conditions and isolated % yields in the acid catalyzed condensation of levulinic acid (LA, 1) with paraformaldehyde (PF, 2) producing 2,9,11,14-tetraoxadispiro[4.1.5.3]pentadecane-3,6-dione (3)

Entry	LA : PF (mole : mole)	Catalyst (mole%)	Reaction conditions (temperature, time)	3 yield (%)
1	1 : 6	H ₂ SO ₄ (10)	70 °C, 6 h	32
2	1 : 7	H ₂ SO ₄ (10)	80 °C, 12 h	55
3	1 : 7	H ₂ SO ₄ (10)	80 °C, 24 h	62
4	1 : 7	H ₂ SO ₄ (20)	80 °C, 24 h	93
5	1 : 10	H ₂ SO ₄ (20)	80 °C, 48 h	86
6	1 : 7	H ₃ PO ₄ (20)	80 °C, 24 h	40
7	1 : 7	<i>p</i> -TsOH (20)	80 °C, 24 h	88
8	1 : 7	[(HSO ₃) ³ C ₃ C ₁ im][Cl] (20)	80 °C, 24 h	76
9	1 : 7	Amberlyst-15 H ⁺ form (20)	80 °C, 24 h	91
10	1 : 6	Amberlyst-15 H ⁺ form (20)	80 °C, 24 h	80
11	1 : 6	Amberlyst-15 H ⁺ form (10)	80 °C, 24 h	53
12	1 : 7	Amberlyst-15 H ⁺ form (20)	80 °C, 12 h	55
13	1 : 7	SiO ₂ -SO ₃ H, (20)	80 °C, 24 h	42

was prepared in a small round bottom flask and the closed flask was heated in an oil bath at 80 °C for 24 h. The resulting mixture was first treated with 10 mL of ice cold water, filtered, and the residue was recrystallized with aqueous ethanol to give 22,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione (5) as white crystals. 211 mg, 88% yield, mp 186–188 °C.

HRMS: calcd for C₁₁H₁₂O₆ [M + Na]⁺, 263.05316; found, 263.05039.

FT-IR: 731, 926, 960, 1023, 1149, 1196, 1232, 1377, 1422, 1710, 1792, 2855 cm⁻¹.

A mixture of conformational isomers in 1.6 : 1 ratio, ¹H NMR (CDCl₃) δ 2.32 (2H, d, *J* = 18.0 Hz), 2.52 (2H, d, *J* = 17.6 Hz), 2.97 (2H, d, *J* = 17.6 Hz), 3.23 (2H, d, *J* = 18.0 Hz), 3.78 (2H, d, *J* = 11.6 Hz), 3.88 (2H, d, *J* = 12.0 Hz), 3.97 (2H, d, *J* = 12.0 Hz), 4.10 (2H, d, *J* = 11.6 Hz), 4.22 (2H, d, *J* = 9.2 Hz), 4.27 (2H, d, *J* = 9.6 Hz), 4.41 (2H, d, *J* = 9.2 Hz), 4.50 (2H, d, *J* = 9.6 Hz). ¹³C NMR (CDCl₃) δ 33.2 (C-4,11), 33.9 (C-4,11), 53.6 (C-5,7), 53.9 (C-5,7), 70.2 (C-1,8), 70.4 (C-1,8), 74.3 (C-12,14), 74.5 (C-12,14), 172.6 (C-3,10), 201.7 (C-6).

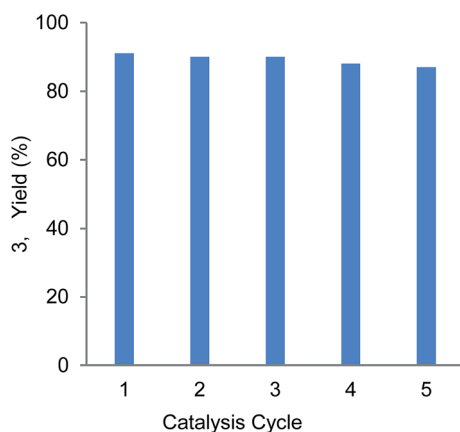


Fig. 3 Recyclability of the solid acid catalyst Amberlyst-15 H⁺ in the synthesis of 3. A mixture of levulinic acid (1.0 mmol), paraformaldehyde (7.0 mmol) and 20 mol% Amberlyst-15 H⁺ were used in all experiments, 80 °C, and 24 h.

Crystal structure determination of 2,9,11,14-tetraoxadispiro [4.1.5.3]pentadecane-3,6-dione (3)

The single crystals suitable for X-ray crystallography were grown by dissolving the sample in methanol (30 mg mL⁻¹) and allowing the undisturbed solution to evaporate slowly at room temperature for one week. Single crystal X-ray diffraction experiment for 3 was performed on a Bruker AXS SMART APEX CCD diffractometer equipped with a cryostat system [graphite monochromatic Mo K α radiation, λ = 0.71073 Å] at 215 K. Data integration and final unit cell parameters were obtained using SAINT²⁶. Absorption corrections were applied by a semi-empirical approach using SADABS,²⁷ and the crystal structure was solved by direct methods and refined using SHELXS and SHELXL program packages.²⁸ All H-atom positions were located using difference Fourier methods and refined freely. In 3 the oxycarbonyl fragment O(1)–C(2)–O(3) (ESI, Fig. 3†) of hydrofuran ring is disordered over two positions and was refined with partial occupancies of 0.88(4) and 0.12(4). The minor position was refined in isotropic approximation. The C-bound hydrogen atoms were found from difference Fourier map and refined freely. Compound 3 with formula C₁₁H₁₄O₆, *M*_r = 242.22; crystallizes in the monoclinic crystal system, sp. gr. *P*2₁/*n*. Unit cell dimensions: *a* = 10.326(3) Å, *b* = 5.8596(15) Å, *c* = 17.227(4) Å, β = 97.085(4)°; *V* = 1034.4(5) Å³, *Z* = 4; *D*(calcd) = 1.555 Mg m⁻³, μ = 0.128 mm⁻¹, *F*(000) = 512.

Total of 15 211 reflection intensities were measured, including 3061 [*R*(int) = 0.0586] independent reflections and 2129 reflections with *I* > 2 σ (*I*). Goodness-of-fit on *F*² 1.045. Final divergence factors for reflections with *I* > 2 σ (*I*): *R*₁ = 0.0510, *wR*₂ = 0.1095. *R* indices (all data): *R*₁ = 0.0825, *wR*₂ = 0.1229.

Crystallographic data for 3 have been deposited with the Cambridge Crystallographic Data Center with deposition number CCDC 1521968.

Results and discussion

Synthesis and characterization of 2,9,11,14-tetraoxadispiro [4.1.5.3]pentadecane-3,6-dione (3)

In our experiments we have studied the condensation between LA and paraformaldehyde under neat conditions, omitting the



use of glacial acetic acid as a solvent to avoid the formation of acetate products as seen in previous studies.^{20–23} In addition, we have used at least six equivalents of formaldehyde as 5 equivalents are required for complete hydroxymethylation and another equivalent for 1,3-dioxane ring closure. However the early attempts with exactly six equivalents gave much lower yields and experiments using seven equivalents of para formaldehyde produced the highest yields. Theoretically only six equivalents of formaldehyde are sufficient to give **3**, although the optimized conditions revealed the usage of seven equivalents. Therefore, we have checked the crude reaction product of the seven equivalent experiment by ¹H NMR for any by products, and no side products were detected. However, some unreacted paraformaldehyde was observed on the relatively low temperature upper section of the reaction flask due to sublimation. Therefore, the extra equivalent was necessary to compensate for the sublimation during the reaction, since reactions were carried out without a solvent.

The yields of product **3** from a series of experiments testing various Brønsted acid catalysts under different conditions, levulinic acid–formaldehyde mole ratios are shown in Table 1. In the initial experiment LA : PF 1 : 6 ratio was tested as it is the stoichiometric ratio to produce the tricyclic condensation product. However, with 10 mol% sulfuric acid catalyst was used at 70 °C, for 6 h, producing only a 32% yield as shown in entry 1 of Table 1. The increase in molar ratio to LA : PF 1 : 7 and increasing the reaction time up to 24 h and catalyst loading to 20 mol% improved the yield of **3** to 93% as shown in entries 2–4 in the Table 1. Further increases in the amount of PF to LA : PF 1 : 10 and reaction time to 48 h caused a slight decrease in the yield. Therefore, optimum reaction conditions were found to be heating a mixture of LA and PF in 1 : 7 mole ratio for 24 h at 80 °C, with 20 mol% conc. H₂SO₄ as the catalyst, as shown in Table 1.

We have tested additional strong acid catalysts as well; phosphoric, *p*-toluenesulfonic acids and the acidic ionic liquid: 1-(3-propylsulfonic)-3-methylimidazolium chloride [(HSO₃)³C₃C₁-im][Cl];^{29,30} nevertheless these acids produced only lower yields of **3** (entries 6–8). The solid acid catalysts are easier to recover for reuse and can be considered as environmentally benign catalysts, therefore two solid acid catalysts Amberlyst-15 (4.7 mmol H⁺ per g) and sulfonated silica: SiO₂–SO₃H (0.726 mmol H⁺ per g)³¹ were also tested under similar conditions. Amberlyst-15 gave a 91% yield, comparable to conc. H₂SO₄, whereas SiO₂–SO₃H gave a low 42% yield (entries 9 and 13).

The controlled experiments using LA: PF ratio 1 : 6 with Amberlyst-15 H⁺ catalyst loadings at 20 and 10% gave lower yields, 80 and 53% (entries 10 and 11). Furthermore, a shorter reaction time of 12 h, with LA : PF ratio 1 : 7 also produced a lower yield of 55% as shown in entry 12.

We have studied the recyclability of the Amberlyst-15 H⁺ catalyst by reusing the recovered catalyst for four more cycles. The % yields of **3**, in five catalytic cycles are shown in Fig. 3. This experiment shows that Amberlyst-15 H⁺ solid acid catalyst can be reused up to five cycles without appreciable loss in catalytic activity. The LA, PF condensation product was identified as 2,9,11,14-tetraoxadispiro[4.1.5.3]pentadecane-3,6-dione (**3**) by spectroscopic methods and X-ray crystallography. High

resolution mass spectrum of the product indicated the molecular formula of **3** as C₁₁H₁₄O₆. The FT-IR spectrum of **3** shows strong absorptions at 1699 and 1794 cm⁻¹ for ketone and γ -lactone carbonyl groups. The ¹H NMR of **3** showed 14 separate peaks for the 14 protons in the compound (ESI, Fig. 1†). The high field pair of doublets at 2.32 (1H, d, *J* = 18.0 Hz), and 3.00 (1H, d, *J* = 18.0 Hz) ppm can be assigned to two C-4 methylene protons. The ¹H–¹H COSY spectrum of **3** showed a cross-peak for 2.32, 3.00 ppm doublets further confirming their coupling. The two doublets at 4.60 and 4.97 ppm with a coupling constant of 6.4 Hz was assigned to C-10 methylene dioxy group protons in the 1,3-dioxolane ring. The ¹³C NMR spectrum of **3** showed 11 peaks for the 11 carbons in the compound. The low field carbon absorptions at 173.4 and 204.5 ppm can be assigned to γ -lactone and ketone carbonyl groups of the tricyclic product.

Compound **3** crystallized in a centrosymmetric space group belonging to monoclinic crystal system. All bond lengths and bond angles in molecule **3** are consistent with the corresponding reference values (ESI, Tables 1 and 2†).³² Single crystal X-ray structure of **3** shows chair conformations of tetrahydro-2H-pyran-4-one and 1,3-dioxane ring as shown in Fig. 4. Hydrofuran ring adopts an envelope conformation with C(5) atom deviating at 0.418 Å from the C(2)–O(3)–C(4)–C(6) mean plane. Molecules **3** in crystal are linked to each other through van der Waals interactions (ESI, Fig. 4†).

Synthesis and characterization of 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione (**5**)

The aldol condensation reaction of 4-ketopimelic acid (4-KPA) and PF was studied as an extension of the acid catalyzed LA–PF reaction and as an effort to upgrade this renewable feedstock as well. The 4-ketopimelic acid or 4-oxoheptanedioic acid is another important biomass derived compound, related to levulinic acid. This keto-diacid was prepared by Perkin reaction of furfural with acetic anhydride and hydrolysis of the resulting β -furanylacrylic acid as shown in Fig. 5, following our previously reported method in 57% overall yield.³³ Although 4-KPA is known for more than 70 years, this symmetrical diacid has been used in the synthesis only in a few occasions.³⁴ Missio *et al.* have used 4-KPA as the key starting compound for the enantioselective synthesis of (–)- γ -jasmolactone,³⁵ and in a few occasions the diacid has been used directly as a monomer in polymer synthesis.^{36–41}

Based on the experience from LA–PF study, we have used five equivalents of PF in the 4-KPA–PF experiments, leaving one extra equivalent than the required four equivalents for complete hydroxymethylation of both α -carbons at the keto group. The optimum reaction conditions were found to be heating a mixture of 4-KPA and PF in 1 : 5 mole ratio for 24 h at 80 °C, with 20 mol% conc. H₂SO₄ as the catalyst. The product was isolated after washing the acid with water and was identified as a compound with a new spiro bis-lactone ring system; 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione by spectroscopic methods. The attempts to produce crystals suitable for single crystal X-ray crystallography were not successful with this condensation product. High resolution mass spectrum of the product indicated the molecular formula of **5** as C₁₁H₁₂O₆. The



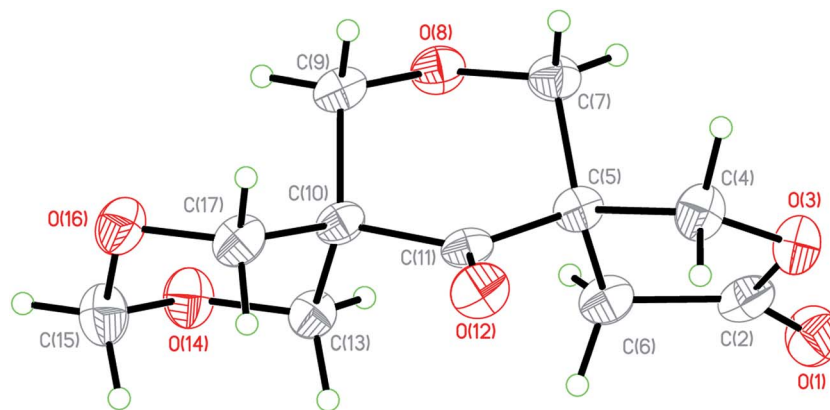


Fig. 4 Single crystal X-ray structure of 2,9,11,14-tetraoxadispiro[4.1.5.3]pentadecane-3,6-dione (**3**). Bond distances and angles are in the ESI.†

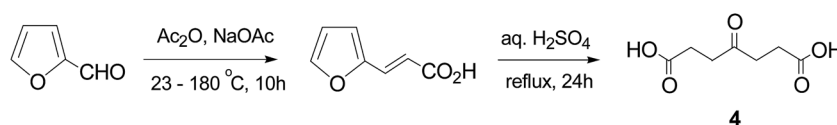


Fig. 5 Synthesis of 4-ketopimelic acid (**4**) from furfural via β -furanylacrylic acid.

FT-IR spectrum of **5** shows strong absorptions at 1710 and 1792 cm^{-1} for ketone and γ -lactone carbonyl groups. The ^1H NMR of **5** showed 12 doublet peaks in two sets indicating the adduct **5** is composed of two conformational isomers in 1.6 : 1 ratio. In addition, the simpler ^1H NMR spectra points out that both these isomers have symmetry planes that bisects the molecule through the keto carbonyl group and O-13 axis.

The high field pair of doublets at 2.32 (2H, d, $J = 18.0$ Hz) and 3.23 (2H, d, $J = 18.0$ Hz) ppm can be assigned to two C-4,11 methylene protons of the minor isomer. Whereas the doublets at 2.52 (2H, d, $J = 17.6$ Hz) and 2.97 (2H, d, $J = 17.6$ Hz) ppm can be assigned to two C-4,11 methylene protons of the major isomer. The pairs peaks at 33.2, 33.9 ppm in the carbon spectrum were assigned to C-4/11 of the two isomers; similarly, 53.7, 53.9 ppm for the C-5/7; 70.2, 70.4 ppm for C-1/8 and 74.3, 74.5 ppm were assigned to C-12/14 of the two isomers. Interestingly, only single peaks were observed for γ -lactone and keto carbonyl carbons of the two isomers at 172.6 and 201.7 ppm (complete NMR spectra are available in the ESI, Fig. 1†). The ^1H - ^1H COSY NMR spectrum of **5** also confirmed these assignments. We have tested common solvents and solvent mixtures for separation of the two isomers using thin layer chromatography and crystallization; however, all attempts to separate the isomers by chromatography as well as fractional crystallization were not successful.

Computational studies on the structures of **3**

The DFT calculations (B3LYP/6-31G* method) were performed to identify energetically most stable conformation of **3**. All attempts to model boat conformation of tetrahydro-2H-pyran-4-one ring of **3** ultimately led to the chair conformation. The most stable calculated chair conformation of **3** has the structure **3a**, which differs from the one obtained by X-ray crystallography

Table 2 Relative energies of B3LYP/6-31G* optimized structures of **3**. The optimized structures are available in the ESI, Fig. 5

Structure	Lactone carbonyl	Lactone ring	1,3-Dioxane ring	$E_{\text{rel}}^a / \text{kcal mol}^{-1}$
3a	Up	Out	Chair	0
3b	Down	Out	Chair	0.4
3c	Up	In	Chair	1.6
3d TS	Down	Out	Chair	1.3
3e	Down	In	Boat	9.3
3f	Down	Out	Boat	5.1

^a $E_{\text{tot}} + \text{ZPVE}$.

analysis. The B3LYP/6-31G* optimized **3a** structure has the lactone carbonyl group oriented up with respect to tetrahydro-2H-pyran-4-one ring keto carbonyl group, *i.e.* **3a** up,out (ESI, Fig. 5†). On the other hand, X-ray structure; **3b** down,out is higher in energy by only 0.4 kcal mol^{-1} (Table 2). The in-conformation of lactone ring in **3c** up,in has the higher relative energy than the out orientation, but the energy barrier for in/out flipping of lactone ring in transition state **3d** down,out **TS** is very low (1.3 kcal mol^{-1}) indicating a facile conformational change around C1 and C4 methylene groups. The boat conformation of 1,3-dioxane ring is energetically less favourable than chair conformation, giving the boat conformers **3e** and **3f** with the highest relative energies.

Proposed mechanism for the formation of the condensation product 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione (**5**)

We have proposed a mechanism for the formation of the new tricyclic bis-lactone 2,9,13-trioxadispiro[4.1.4.3]tetradecane-



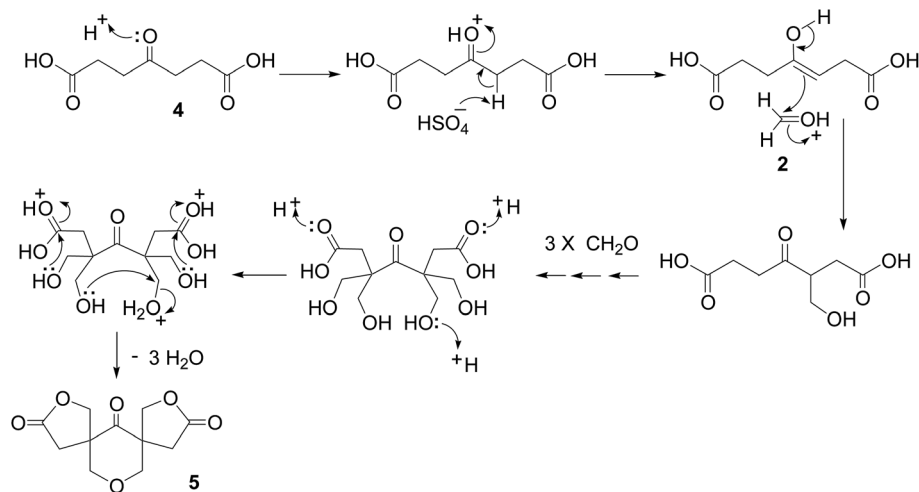


Fig. 6 Proposed mechanism for the formation of 2,9,13-trioxadispiro[4.1.4.3]tetradecane-3,6,10-trione (5) by the H_2SO_4 catalyzed condensation of 4-ketopimelic acid (4) with paraformaldehyde (2).

3,6,10-trione (5) by the acid catalyzed condensation of 4-ketopimelic acid (4) with paraformaldehyde (2) as shown in Fig. 6. The stepwise acid catalyzed aldol condensation of 4-KPA with four molecules of formaldehyde can lead to four hydroxymethylations at C-3 and C-5 of 4-KPA. Then this $\alpha,\alpha,\alpha',\alpha'$ -tetrahydroxymethyl-4-KPA intermediate undergoes two lactonizations and a ring closure to a tetrahydro-2H-pyran-4-one under acidic conditions producing the tricyclic product 5.

Conclusion

The acid catalyzed condensation reaction of renewable feedstock levulinic acid with paraformaldehyde can be used to upgrade the carbon number of levulinic acid from C-5 to C-11 in excellent yield by simple catalytic process without a solvent. The condensation product was identified as 2,9,11,14-tetraoxadispiro[4.1.5.3]pentadecane-3,6-dione. A similar condensation between another renewable feedstock 4-ketopimelic acid with paraformaldehyde gives a new dispiro bis-lactone ring system 2,9,13-trioxadispiro [4.1.4.3]tetradecane-3,6,10-trione, which was formed as a two symmetrical isomeric compounds in 1.6 : 1 ratio. Acid catalyzed aldol condensation without a solvent is an all renewable carbon based path to produce these useful lactones and currently we are studying the possible polymerizations of these compounds to produce renewable carbon based polyesters and polyamides.⁴²

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