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Production of levulinic acid and use as a platform chemical for derived products

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Abstract

Levulinic acid (LA) can be produced cost effectively and in high yield from renewable feedstocks in a new industrial process. The technology is being demonstrated on a 1 ton/day scale at a facility in South Glens Falls, New York. Low cost LA can be used as a platform chemical for the production of a wide range of value-added products. This research has demonstrated that LA can be converted to methyltetrahydrofuran (MTHF), a solvent and fuel extender. MTHF is produced in >80% molar yield via a single stage catalytic hydrogenation process. A new preparation of δ -aminolevulinic acid (DALA), a broad spectrum herbicide, from LA has also been developed. Each step in this new process proceeds in high (>80%) yield and affords DALA (as the hydrochloride salt) in >90% purity, giving a process that could be commercially viable. LA is also being investigated as a starting material for the production of diphenolic acid (DPA), a direct replacement for bisphenol A. © 2000 ACEEE Published by Elsevier Science B.V. All rights reserved.

Keywords: Levulinic acid; Methyltetrahydrofuran; δ -Aminolevulinic acid; Diphenolic acid; Paper sludge; Renewables to chemicals; Platform chemicals

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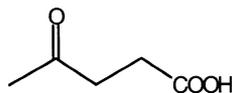
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1. Introduction

Biomass can be used as a raw material to produce large numbers of chemicals, each with the potential to be as fundamental to the chemical industry as methane or BTX. Yet, to date, many of these products have failed in the marketplace because they do not pass the most practical test of market viability: is the product available at a low enough cost to use as a chemical product or intermediate? Levulinic acid (**1**, LA, 4-oxopentanoic acid), has frequently been proposed as such a building block [1,2].



1, levulinic acid

Despite its status as an expensive and relatively small market specialty chemical (about 1 million lb/year at \$4.00–\$6.00/lb), LA and its derivatives have found use in highly diverse areas. Some of these applications are summarized in Table 1.¹

The preparation of LA is not difficult, and a number of approaches have been reported for its synthesis. The most widely used approach is the dehydrative treatment of biomass or carbohydrates with acid [20–23]. LA has also been produced by hydrolysis of acetyl succinate esters [24], by acid hydrolysis of furfuryl

Table 1
Selected levulinic acid applications

Application	Reference
Chiral reagents	[3]
Biologically active materials	[4]
Polyhydroxyalkanoates	[5]
Polymers	[6,7]
Polymerization initiators	[8]
Antifouling compounds	[9]
Personal care products	[10]
Lubricants	[11]
Adsorbents	[12]
Printing/inks	[13]
Coatings	[14]
Electronics	[15]
Photography	[16]
Batteries	[17]
Drug delivery	[18]
Corrosion inhibitors	[19]

¹ The applications cited in Table 1 and subsequent tables are illustrative but not exhaustive. Many additional examples exist in the patent and open literature. In each case, LA or its derivatives are listed as useable in the given application, but may not be the primary focus of the citation.

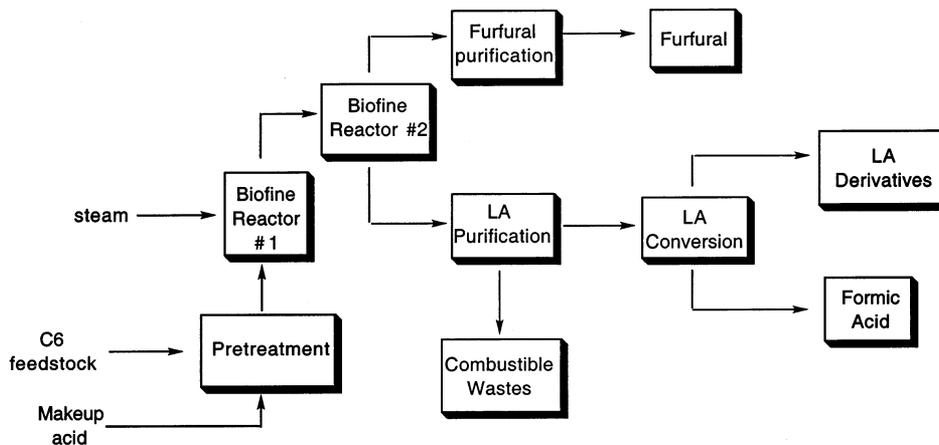


Fig. 1. The Biofine process.

alcohol [25], by oxidation of ketones with ozone [26] or with $\text{Mn}(\text{OAc})_3$ [27]. LA has been produced by Pd-catalyzed carbonylation of ketones [28] and by alkylation of nitroalkanes [29]. However, these methods frequently form large amounts of side products and intractable materials, or require expensive starting feedstocks.

Recently, a new process developed by Biofine Corporation eliminated many of the existing problems with LA production. The Biofine process uses acid hydrolysis of 6-carbon sugars as the key step for LA production, and minimizes side product formation and the resulting separation problems by significantly improving the traditional engineering of the LA production process through a novel, two reactor system (Fig. 1). [30,31].

The process supplies carbohydrate containing materials to a first reactor where they are hydrolyzed at 210–230°C for 13–25 s in the presence of 1–5% mineral acid. This initial hydrolysis produces hydroxymethylfurfural, which is removed continuously and supplied to a second reactor. In the second reactor, the hydroxymethylfurfural is hydrolyzed further at 195–215°C for 15–30 min to produce LA, which is again continuously removed. The LA yield is $\geq 60\%$, based on the hexose content of the carbohydrate-containing starting material, one of the highest reported in the literature. The result is a cost effective production of LA, making it suitable as a starting material for a wide variety of products. The technology can be successfully employed using diverse cellulose-containing waste materials such as paper mill sludge, urban waste paper, agricultural residues and cellulose fines from papermaking as starting materials. Economic projections indicate that the LA production cost could fall as low as \$0.04–\$0.10/lb depending on the scale of the operation. Furthermore, the impact on waste reduction and domestic energy use is large. Department of Energy metrics project energy savings of 75.6 trillion Btu/year and waste reduction of 26.2 million tons/year by 2020. Biofine is operating a 1 ton/day pilot plant facility in South Glens Falls, New York to demonstrate the ability to scale this process to an industrially useful size.²

² Projections are based on MTHF as a fuel oxygenate, addressing a potential market of 8 billion lb/year.

Table 2
Products from LA and potential LA markets demand

Product	Use	Potential LA market (million lb/year)
MTHF	Fuel extender	10 000–100 000
DALA	Biodegradable herbicide	175–350
Diphenolic acid	Monomer	35
THF	Solvent	200
BDO	Monomers	200

Typically, however, a biomass derived material must pass a second test: what can the material be used for and is there a market? To address this issue, a research consortium was established in 1996. The consortium brought together two industrial partners, Biofine and Chemical Industry Services, with the National Renewable Energy Laboratory (NREL), the Pacific Northwest National Laboratory (PNNL), and the New York State Energy Research and Development Authority (NYSERDA). This consortium has been developing technology to convert LA into a larger suite of chemical products. Laboratory research has studied three products: methyltetrahydrofuran (MTHF), a fuel additive with a huge potential market, δ -amino levulinic acid (DALA) a broad spectrum herbicide/pesticide with a projected market of 200–400 million pounds/year, and diphenolic acid (DPA), a substitute for bisphenol A in polymer manufacture. These products have the potential to expand the market need for LA into the hundreds of millions of pounds. Table 2 summarizes possible market demand for LA from a group of LA derivatives. In the past, LA has been investigated as a starting material for several of these materials, however, its traditionally high cost has prevented widespread use of known technology (MTHF: [32,33]; DALA: [34]; DPA: [35]). The combination of a low cost source of LA with new technology has opened up new opportunities for LA as a chemical feedstock.

2. Results — new approaches to derivatives of levulinic acid

2.1. Methyltetrahydrofuran

Large scale use of LA has recently been linked to automobile fuel extenders, such as MTHF. It is miscible with gasoline at all proportions and has favorable oxygenate and vapor pressure properties [1]. Since the U.S. uses about 100 billion gallons of gasoline/year, replacement of as little as 1% (similar in volume to the usage of ethanol in gasohol) would result in a yearly demand of 1 billion gallons of MTHF, equivalent to over 10 billion pounds of LA. Early work in the 1980s [1,36] investigated the use of two LA derivatives, MTHF and angelicalactone (AL), as fuel blending agents. Direct conversion of LA to MTHF is reported to occur in only low yield [37]. However, several indirect LA processing routes are reported that lead to MTHF (Fig. 2).

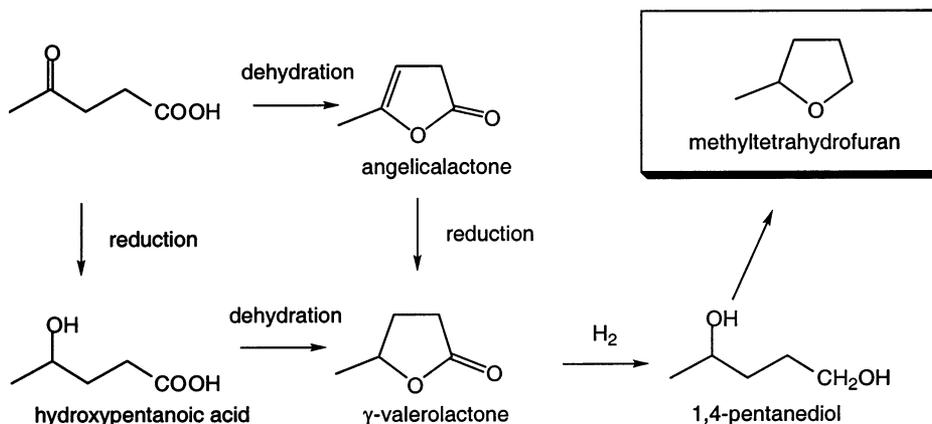


Fig. 2. Conversion of LA to MTHF.

An intermediate central to LA based MTHF processes is γ -valerolactone (GVL). This material can be prepared by several different routes. Simple heating of LA to about 160°C in the presence of acid gives a high yield of AL [1,38]. A subsequent reduction step converts AL to GVL, and then to 1,4-pentanediol (PDO). PDO is readily dehydrated to MTHF upon heating in the presence of acid [39]. Alternatively, LA can also be reduced to 4-hydroxypentanoic acid (HPA). This material can undergo cyclization to GVL and conversion to MTHF, again via PDO.

The conversion of LA to GVL has been investigated by several groups. Schutte and Thomas hydrogenated LA using a platinum oxide catalyst to give GVL in 87% yield [40]. LA was hydrogenated to GVL in the neat liquid phase with a Raney nickel catalyst in 94% yield [37,41]. Changing to a copper–chromite catalyst produced a complex mixture of GVL, PDO and MTHF. This is the first report of MTHF as a byproduct, although its ready formation from PDO by thermal decomposition/dehydration explains its presence. Rhenium catalysts [Re black, Re(IV) oxide hydrate] for hydrogenation of LA to GVL have also been described [42]. The subsequent reduction of GVL to PDO has also been studied. Hydrogenation of GVL over copper–chromite catalyst gave 79% PDO [43]. In a later study up to 83% yield of PDO was achieved. At higher reaction temperatures, PDO yields dropped and MTHF was found in a low-boiling fraction [37].

More recent studies have focused on homogeneous catalysis of the hydrogenation steps. Both ruthenium and rhodium complexes catalyze hydrogenation of LA at low temperature (60°C) in aqueous solutions [44,45]. GVL is also produced from LA in 85–100% yield using ruthenium iodocarbonyl complexes [46]. Ruthenium triphenylphosphine complexes give 99% conversion and 86% yield of GVL in toluene solution [47].

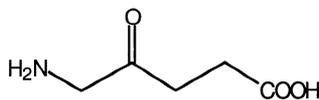
The major projected use of MTHF is as a transportation fuel extender. Because it is miscible with gasoline at all proportions and hydrophobic, MTHF could be blended at the refinery and transported by pipeline. In contrast, ethanol must be

added later in the distribution process because contamination with water can cause phase separation. MTHF can be blended in gasoline up to 60% by volume without adverse engine performance [48]. MTHF has a higher specific gravity than gasoline; therefore, mileage from MTHF blended fuel would not decrease. As a component of 'P-series' fuels (recently approved by the Department of Energy), MTHF can be used to meet the requirements for alternative fuel fleet vehicles stipulated by the Energy Policy Act of 1992. The 'P-series' fuels are blended such that they have a minimum antiknock index of 87 and a maximum vapor pressure of 15 psi. P-series fuel emissions are generally below those for reformulated gasoline using methyltertiarybutyl ether (MTBE) and are well below federal emissions standards.

Work carried out at PNNL has built upon the background chemical research in LA reactions. Batch reactor tests were performed to screen a series of catalyst formulations and processing conditions for use in hydrogenating levulinic acid. Initial tests in dilute phase with 1,4-dioxane solvent have provided the basis of continuous-flow reactor tests with the Biofine LA product from their demonstration plant. Laboratory-scale work has shown the conversion of LA into MTHF with a single-bed catalytic hydrogenation process that uses a catalyst consisting of palladium and rhenium metals on carbon at elevated temperature and pressure. The LA undergoes multiple hydrogenations (3 mol of hydrogen per mole of LA) and two dehydrations in a single reaction step. PNNL was recently issued a patent for the catalyst composition and the operating parameters [49]. Operating conditions are 240°C and 1500 psig using liquid hourly space velocities around 1 l of LA/l of catalyst bed/h. Lab tests have indicated an 83% yield on a theoretical (molar) basis. On a weight basis, the yield is 63 pounds of MTHF for every 100 pounds of LA. Literature values using competing processes give low yields (3%) of MTHF as a minor by-product. Efforts are under way to scaleup production of MTHF from LA in a mobile processing unit at Biofine's demonstration plant. MTHF production is projected at about 20 gallons per day.

2.2. *Δ*-aminolevulinic acid (DALA)

DALA (**2**) is a broad spectrum, biodegradable herbicide that shows high activity toward dicotyledonous weeds while showing little activity toward monocotyledonous crops such as corn, wheat, or barley. DALA is completely biodegradable with a broad spectrum of activity rivaling and possibly exceeding that of Monsanto's Roundup®. DALA exerts its effects by stimulating overproduction of tetrapyrroles in the plant at night. In daylight, the accumulated tetrapyrroles photosensitize the formation of singlet oxygen in the plant, leading to its death [50,51]. More recently, DALA has been found to be useful as an insecticide and as a component in photodynamic therapy as a cancer treatment [52,53].



2, DALA

A variety of synthetic routes for DALA have been reported. DALA can be prepared from N-substituted amino acids [54], and through stepwise buildup of the carbon chain [55]. More elegant strategies used cyclic starting materials such as furfurylamine [56], 5-hydroxy-2-pyridone [57], N-methoxycarbonyl-3-piperidinones [58], and 5-hydroxymethyl-2-furfural [59]. The biological activity of DALA has also led to a search for processes that can be applied at commercial scales. A number of DALA production patents have been issued [60–63].

The obvious starting material for the preparation of DALA is LA, which requires formation of a C–N bond at the C5 carbon. Several amination methods have been successful on laboratory scale, but none of them have been scaled up to commercial levels. The most common approach for activating the C5 position toward amination is bromination of LA in an alcohol medium to give mixtures of 5-bromo- and 3-bromoesters that are separated by distillation [64]. The 5-bromo-levulinic acid is aminated using nucleophilic nitrogen species such as sodium azide [65]. These various steps are combined to give the conventional DALA synthesis shown in Fig. 3 [34]. LA (1) is brominated to give 5-bromo-levulinic acid 3. To introduce the key amino group, 3 is treated with potassium phthalimide, giving intermediate 4. Acid hydrolysis of 4 gives DALA. The major difficulties with this approach are the relatively low yields in the first two steps and the generation of a large amount of a waste product, 5. Introduction of the amino group into DALA is highly inefficient because only a single atom from the potassium phthalimide is used. The remainder of the structure is waste. More generally, none of the reported approaches are suitable for large scale manufacture of DALA because of the need for multistep syntheses, expensive starting materials, or toxic intermediates.

The key areas of study at NREL for DALA manufacture have been the improvement of each of these synthesis steps with particular focus on overall cost effectiveness. The NREL work has significantly improved the yield of the first two steps and the efficiency of the second (Fig. 4).

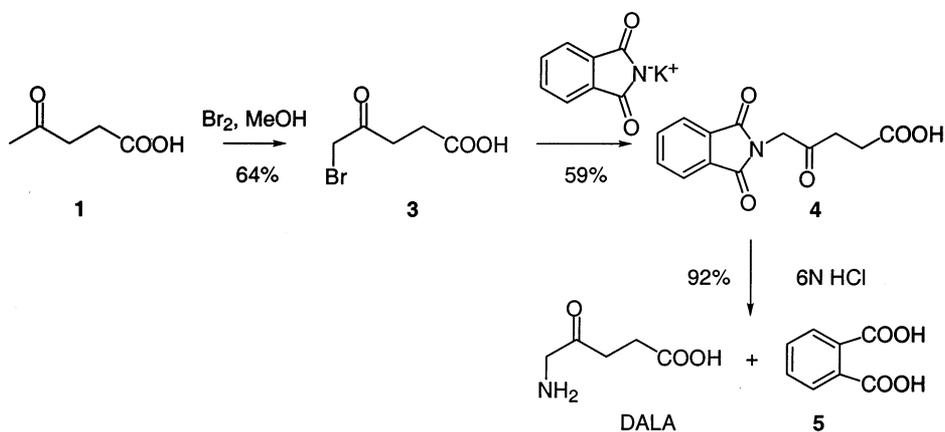


Fig. 3. Conventional synthesis of DALA.

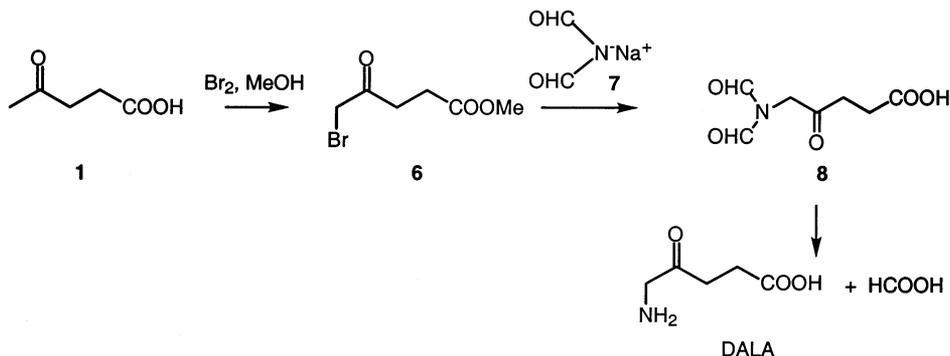
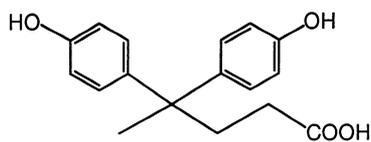


Fig. 4. NREL Synthesis of DALA.

The NREL synthesis also begins with LA, which is brominated in MeOH to give methyl 5-bromolevulinate **6**. This ester is treated with diformylamide anion **7** (easily prepared from NaOMe and formamide) to give **8** [66]. Acid hydrolysis of this intermediate leads to DALA. The only side product observed from the hydrolysis is formic acid. Each of the steps proceeds in high (> 80%) yield and affords DALA (as the hydrochloride salt) in >90% purity, giving a process that could be commercially viable [67]. The material prepared by this process has been submitted for herbicide testing at the University of Illinois. The first samples were 85% as effective as a control sample of DALA. More recently, the process has been improved further by use of a different amination reagent for the second step of the process. This new reagent generates much less waste, and can be used in several solvents.

2.3. Diphenolic acid

Diphenolic acid (**9**) is a material that has found wide application in the production of polymers and other materials.



9, diphenolic acid

The material is easily prepared from the reaction of LA with two moles of phenol [68]. DPA can serve in many of the same applications as bisphenol A (BPA), but the lower cost of the latter has reduced the DPA market. Since the Biofine process offers LA at a much lower cost, it is reasonable to again consider DPA as a renewables based polymer precursor. Work sponsored by NYSERDA has started at Rensselaer Polytechnic Institute on near term applications for DPA, particularly

ones that displace currently marketed BPA products. Researchers are exploring DPA/BPA copolycarbonate and copolyarylate combinations that could partially or wholly displace BPA formulations. Within these combinations, researchers are also studying the use of dibrominated DPA in fire retardants. Brominated DPA also has some promise as an environmentally acceptable marine coating that could replace the toxic tributyltin. Further development of DPA uses will concentrate on highly crosslinked polymers and charged polyesters, or ‘ionomers’.

Market penetration of Biofine’s DPA has near term potential; DPA has been produced commercially for many years by reacting LA with phenol. LA’s price is the most important component of DPA’s price, which is currently around \$3/lb. If LA were produced for \$1/lb, DPA could likely be produced for \$1.20/lb. The market for BPA is estimated to be over 500 million lb/year. A \$1.20/lb DPA might not only capture 20% of this market, but also recapture some 5 million lb/year of its old use as a coating material. DPA may even perform better in some applications. The goal is to achieve a DPA market size of 15 million lb/year over the next 5 years, creating a 7 million lb/year market for LA.

DPA’s widest use is as a component in polymers, however, it has also found applications in several other area. Applications are summarized in Table 3.

3. Conclusions

The availability of inexpensive LA from the Biofine process will open up new opportunities for the cost-effective production of chemicals from renewable feed

Table 3
Selected diphenolic acid applications

Application	Reference
Thermoplastics	[69]
Polysulfones	[70]
Polyphenylene ethers	[71]
Hyperbranched and dendrimeric polyesters	[72]
Thermally reversible isocyanates	[73]
Phenolic and polyester resins	[74]
Polycarbonates	[75]
Heat sensitive recording media	[76]
Electronics	[77]
Printing/inks	[78]
Fragrances	[79]
Medicinals	[80]
Dyes/pigments	[81]
Lubricants	[82]
Fire retardant materials	[83]
Polymeric coatings	[84]
Adhesives	[85]
Paints	[86]

stocks. More broadly, the work described in this paper is an early example of a 'biomass refinery', taking complex raw materials from renewable sources, and converting them into a wider slate of discrete products. Further research will undoubtedly reveal other examples of these types of technology.

Acknowledgements

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References

- [1] Thomas JJ, Barile RG. Conversion of cellulose hydrolysis products to fuels and chemical feedstocks. *Energy Biomass Wastes* 1984;8:1461–94.
- [2] Kitano M, Tanimoto F, Okabayashi M. Levulinic acid, a new chemical raw material. Its chemistry and use, *Chem Econ Eng Rev* 1975;7:25–29.
- [3] Meyers AI, Seefeld MA, Lefker BA, Blake JF, Williard PG. Stereoselective alkylations in rigid systems. Effect of remote substituents on π -facial additions to lactam enolates. Stereoelectronic and steric effects, *J Am Chem Soc* 1998;120:7429–7438 and other papers in the series.
- [4] Bitonti AJ, McDonald IA, Salituro FG, Whitten JP, Jarvi ET, Wright PS. Novel indole derivatives useful to treat estrogen-related neoplasms and disorders. World patent 9522524 to Merrell Dow Pharmaceuticals, 1995.
- [5] Jang J-H, Rogers PL. Effect of levulinic acid on cell growth and poly- β -hydroxyalkanoate production by *Alcaligenes* sp. SH-69. *Biotechnol Lett* 1996;18:219–24.
- [6] van Aert HAM, van Genderen MHP, van Steenpaal GJML, Nelissen L, Meijer EW, Liska J. Modified poly(2,6-dimethyl-1,4-phenylene) ethers prepared by redistribution. *Macromolecules* 1997;30:6056–66.
- [7] Taylor TJ, Kiemeyer WH, Golino CM. Emulsified furan resin-based binding compositions for glass fibers. World patent 9426677 to Schuller International, 1995.
- [8] Lai JT. Preparation of mixed symmetrical azonitrile polymerization initiators. US patent 5010179 to BF Goodrich, 1991.
- [9] Bush JH. Acylated nitrogen-based fouling control agents by reaction of amines with acylcarboxylic acids and alkenes. US patent 5851377 to The Lubrizol Corporation, 1998.
- [10] Tsucha J, Yoshida K. Skin cosmetics containing levulinate, glycyrrizates, and resorcinol or isopropylmethylphenol. Japanese patent 05320023 to Kanebo, 1994.
- [11] Adams PE, Lange RM, Yodice R, Baker MR, Dietz JG. Intermediates useful for preparing dispersant-viscosity improvers for lubricating oils. European patent 882745 to The Lubrizol Corporation, 1998.
- [12] Raidel M, Aschenbrenner F. Absorbent item. World patent 9843684 to Kimberly-Clark G.m.b.H., 1998.
- [13] Gundlach KB, Sanchez LA, Hanzlik CA, Brodsky K, Colt RL, Montes AM. Ink compositions for thermal ink-jet printing. US patent 5769929 to Xerox Corp, 1998.
- [14] Nakazato M, Konishi Y. Bakable composition for blackening metal surface. Japanese patent 06280041 to Nippon Dacro Shamrock, 1995.
- [15] Oono T, Saito S, Shinohara S, Takakuwa, K. Fluxes for electric circuit board soldering and electric circuit boards. Japanese patent 08243787 to Tamura Kaken, 1996.
- [16] Shimizu A, Nishio S, Wada Y, Metoki I. Photographic processing method for processing silver halide photographic light-sensitive material. European patent 704756 to Konica Corporation, 1996.

- [17] Maekawa Y, Miyaki Y. Nonaqueous secondary batteries with anodes containing amorphous chalcogen compounds or oxides. Japanese patent 09190820 to Fuji Photo Film, 1997.
- [18] Hille T. Transdermal resorption of pharmaceuticals from supercooled melts. German patent 4446600 to LTS Lohmann Therapie-Systeme GmbH und Co Kg, 1996.
- [19] Armstrong WP, Phillips E. Corrosion-inhibiting coating compositions containing metal or amine salts of ketoacids. European patent 496555 to Ciba-Geigy A.-G., 1993.
- [20] Lourvanij K, Rorrer GL. Dehydration of glucose to organic acids in microporous pillared clay catalysts. *Appl Catal A* 1994;109:147–65.
- [21] Jow J, Rorrer GL, Hawley MC, Lampion DTA. Dehydration of D-fructose to levulinic acid over LZY zeolite catalyst. *Biomass* 1987;14:185–94.
- [22] Dahlmann J. Preparation of levulinic acid. *Chem Ber* 1968;101:4251–3.
- [23] Farone WA, Cuzens JE. Hydrolytic method for the production of levulinic acid and its derivatives from biomass and sugars. World patent 9819986 to Arkenol, 1998.
- [24] Farnleitner L, Stueckler H, Kaiser H, Kloimstein E. Preparation of stable levulinic acid. German patent 3920340 to Chemie Linz G.m.b.H., 1991.
- [25] Itaya H, Shiotani A, Toriyahara Y. Preparation of levulinic acid from furfuryl alcohol. Japanese patent 62252742 to Ube Industries, 1998.
- [26] Edwards WB III. Oxocarboxylic acids. US patent 4612391 to Philip Morris, 1986.
- [27] Vaerman JM, Bertrand JNM. Selective oxidation of ketones. German patent 2125162 to Labofina S.A., 1972.
- [28] Cavinato G, Toniolo L. Levulinic acid synthesis via regiospecific carbonylation of methyl vinyl ketone or of its reaction products with hydrochloric acid or an alkanol or of a mixture of acetone with a formaldehyde precursor catalyzed by a highly active palladium-hydrochloric acid. *J Mol Catal* 1990;58:251–67.
- [29] Ballini R, Petrini M. Facile and inexpensive synthesis of 4-oxoalkanoic acids from primary nitroalkanes and acrolein, *Synthesis* 1986:1024–1026.
- [30] Fitzpatrick SW. Manufacture of furfural and levulinic acid by acid degradation of lignocellulosic. World patent 8910362 to Biofine Incorporated, 1990.
- [31] Fitzpatrick SW. Production of levulinic acid by the hydrolysis of carbohydrate-containing materials. World patent 9640609 to Biofine Incorporated, 1997.
- [32] Hachihama Y, Imoto M. Synthesis of high-molecular compounds from furfural. II. A synthesis of 1,4-pentanediol from furfural. *J Chem Soc Jpn* 1942;45:19–20.
- [33] Hayashi I, Negoro E, Hachihama Y. Levulinic acid and its derivatives. II. Preparation and reduction of [gamma]-valerolactone by catalytic hydrogenation. *J Chem Soc Jpn* 1954;57:67–9.
- [34] Benedikt E, Kost H-P. Synthesis of 5-aminolevulinic acid. *Z Naturforsch B: Anorg Chem Org Chem* 1986;41(B):1593–4.
- [35] Bader A. US Patent 2933472, to SC Johnson and Son, 1960.
- [36] Rudolph TW, Thomas JJ. NO_x, NMHC, and CO emissions from biomass derived gasoline extenders. *Biomass* 1988;16:33–49.
- [37] Christian RV Jr., Brown HD, Hixon RM. Derivatives of γ -valerolactone, 1,4-pentanediol, and 1,4-di-(β -cyanoethoxy)-pentane. *J Am Chem Soc* 1947;69:1961–3.
- [38] Leonard RH. Method of converting levulinic acid into alpha angelica lactone. US patent 2809203, 1957.
- [39] Olah GA, Fung AP, Malhotra R. Synthetic methods and reactions; 99. Preparation of cyclic ethers over superacidic perfluorinated resin/sulfonic acid (Nafion-h) catalyst, *Synthesis* 1981:474–476.
- [40] Schutte HA, Thomas RW. Normal valerolactone. III. Its preparation by the catalytic reduction of levulinic acid with hydrogen in the presence of platinum oxide. *J Am Chem Soc* 1930;52:3010–2.
- [41] Kyrides LP, Groves W, Craver JK. Process for the production of lactones. US Patent 2368366, 1945.
- [42] Broadbent HS, Campbell GC, Bartley WJ, Johnson JH. Rhenium and its compounds as hydrogenation catalysts. III. Rhenium heptoxide. *J Org Chem* 1959;24:1847–54.
- [43] Folkers K, Adkins H. The catalytic hydrogenation of esters to alcohols II. *J Am Chem Soc* 1932;54:1145–54.

- [44] Joó F, Tóth Z, Beck MT. Homogeneous hydrogenation in aqueous solutions catalyzed by transition metal phosphine complexes. *Inorg Chim Acta* 1977;25:L61–2.
- [45] Joó F, Somsák L, Beck MT. Peculiar kinetics of hydrogenations catalyzed by chlorotris-(sulphonated triphenylphosphine) rhodium (I) in aqueous solutions. *J Mol Catal* 1984;24:71–5.
- [46] Bracca G, Raspolli-Galletti AM, Sbrana G. Anionic ruthenium iodocarbonyl complexes as selective dehydroxylation catalysts in aqueous solution. *J Organomet Chem* 1991;417:41–9.
- [47] Osakada K, Ikariya T, Yoshikawa A. Preparation and properties of hydride triphenylphosphine ruthenium complexes with 3-formyl (or acyl) propionate. *J Organomet Chem* 1982;231:79–90.
- [48] Lucas SV, Loehr DA, Meyer ME, Thomas JJ. Exhaust emissions and field trial results of a new, oxygenated, non-petroleum-based, waste-derived, gasoline blending component, 2-methyltetrahydrofuran. Soc. Auto. Eng. Fuels and Lubricants Sect. Mtg., Philadelphia, PA, October 1993.
- [49] Elliott DC, Frye JG Jr. Hydrogenated 5-carbon compound and method of making oxopentanoic acid, catalytic hydrogenation and ring opening and withdrawal of a hydrogenated product. US patent 5883266 to Battelle Memorial Institute, 1999.
- [50] Rebeiz CA, Montazer-Zouhoor A, Hopen HJ, Wu SM. Photodynamic herbicides: 1. Concept and phenomenology. *Enzy Microb Technol* 1984;6:390–401.
- [51] Rebeiz CA, Amindari S, Reddy KN, Nandihalli UB, Moubarak MB, Velu JA. δ -Aminolevulinic acid based herbicides and tetrapyrrole biosynthesis modulators, In: *Porphyric Pesticides: Chemistry, Toxicology, and Pharmaceutical Applications*. ACS Symposium Series 559, 1994.
- [52] Rebeiz CA, Juvik JA, Rebeiz CC. Porphyric insecticides 1. Concept and phenomenology. *Pestic Biochem Physiol* 1988;30:11–27.
- [53] Rebeiz N, Arkins S, Rebeiz CA, Simon J, Zachary JF, Kelley KW. Induction of tumor necrosis by δ -aminolevulinic acid and 1,10-phenanthroline photodynamic therapy. *Cancer Res* 1996;56:339–44.
- [54] Wang J, Scott AI. An efficient synthesis of δ -aminolevulinic acid (ala) and its isotopomers. *Tetrahedron Lett* 1997;38:739–40.
- [55] Appleton D, Duguid AB, Lee S-K, Ha Y-L, Ha H-J, Leeper FJ. Synthesis of analogues of δ -aminolaevulinic acid and inhibition of 5-aminolaevulinic acid dehydratase. *J Chem Soc Perkin Trans* 1998;1:89–101.
- [56] Kawakami H, Ebata T, Matsushita H. A new synthesis of 5-aminolevulinic acid. *Agric Biol Chem* 1991;55:1687–8.
- [57] Herdeis C, Dimmerling A. Eine dreistufige synthese der δ -aminolaevulinsäure. *Arch Pharm (Weinheim)* 1984;317:304–6.
- [58] Matsumura Y, Takeshima Y, Okita H. A convenient method for introducing oxo group into the β -position of cyclic amines and its application to synthesis of δ -aminolevulinic acid. *Bull Chem Soc Jpn* 1994;67:304–6.
- [59] Cottier L, Descotes G, Eymard L, Rapp K. Synthesis of γ -oxo acids or γ -oxo esters by photooxygenation of furanic compounds and reduction under ultrasound: application to the synthesis of 5-aminolevulinic acid hydrochloride. *Synthesis* 1995:303–306.
- [60] Aronova N, Makhova NN, Zavyalov SI, Volkenshtein JB, Kunitskaya GM. Method of producing Zeta-aminolevulinic acid hydrochloride. US Patent 3846490, 1974.
- [61] Kawakami T, Kawakami H, Matsumoto K, Koseki K, Matsushita H. Method of preparing an acid additional salt of delta-aminolevulinic acid. US Patent 5284973 to Japan Tobacco, 1994.
- [62] Descotes G, Cottier L, Eymard L, Rapp K. Process for the preparation of n-acyl derivatives of 5-aminolevulinic acid, as well as the hydrochloride of the free acid. US Patent 5344974 to Sudzucker Aktiengesellschaft Mannheim/Ochensfurt, 1994.
- [63] Takeya H, Shimizu T, Ueki H. Process for preparing 5-aminolevulinic acid. US Patent 5380935 to Cosmo Research institute and Cosmo Oil, 1995.
- [64] MacDonald SF. Methyl 5-bromolevulinate. *Can J Chem* 1974;52:3257–8.
- [65] Ha H-J, Lee S-K, Ha Y-J, Park J-W. Selective bromination of ketones. A convenient synthesis of 5-aminolevulinic acid. *Synth Commun* 1994;24:2557–62.
- [66] Yinglin H, Hongwen H. A convenient synthesis of aminomethyl ketones (α -amino ketones). *Synthesis* 1990:615-618.
- [67] Moens L. Synthesis of an acid addition salt of delta-aminolevulinic acid from 5-bromo levulinic acid esters. US patent 5907058 to Midwest Research Institute, 1999.

- [68] Isoda Y, Azuma M. Preparation of bis(hydroxyaryl)pentanoic acids. Japanese patent 08053390 to Honshu Chemical Ind., 1996.
- [69] Weber M, Weiser-Elbl K. Thermoplastic molding compositions and their use. European patent 855430 to BASF A.-G., 1998.
- [70] Weber M, Heckmann W. Compatibilization of polysulfone/polyamide blends by reactive polysulfones. Evidence for copolymer formation. *Polym Bull (Berlin)* 1998;40:227–34.
- [71] Tagle LH, Diaz FR, Cerda G, Oyarzo M, Penafiel G. Polymerization by phase transfer catalysis. Part 22. Synthesis of poly(amide-carbonates) and poly(amide-thiocarbonates) derived from diphenols with the amide group in the side chain. *Polym Bull (Berlin)* 1997;39:9–14.
- [72] Chu F, Hawker CJ, Pomery PJ, Hill DJT. Intramolecular cyclization in hyperbranched polyesters. *J Polym Sci Part A Polym Chem* 1997;35:1627–33.
- [73] Markle RA, Brusky PL, Cremeans GE. Thermally-reversible isocyanate polymers. World patent 9111476 to Battelle Memorial Institute, 1991.
- [74] Demmer CG, Irving E. Modified phenolic resins. European patent 184553 to Ciba-Geigy A.-G., 1986.
- [75] Hoogeboom TJ. Branched aromatic polycarbonate composition. US patent 3816373 to General Electric, 1974.
- [76] Kurisu T, Motosugi Y, Kobayashi H. Thermal recording materials having bisphenol derivatives as color developers. Japanese patent 62257884 to Ricoh, 1987.
- [77] Watanabe S, Kukemura K, Nakura S. Chemical amplification-type positive-working resist. Japanese patent 10020504 to Shin-Etsu Chemical Industry, 1998.
- [78] Malhotra SL, Naik KN, MacKinnon DN, Jones AY. Ink-jet printing sheet for transparency preparation. US patent 5683793 to Xerox, 1997.
- [79] Anderson D, Frater G, Gygax P. Fragrance precursors. World patent 9730687 to Givaudan-Roure (International) S.A., 1997.
- [80] Brooks CDW, Bhatia P, Kolasa T, Stewart AO, Gunn DE, Craig RA. Preparation of symmetrical bis(heteroarylmethoxy)phenylalkanoic acid derivatives as inhibitors of leukotriene biosynthesis. World patent 9712867 to Abbott Laboratories, 1997.
- [81] Ogawa T, Matsumoto T, Takahara K, Saiki S. Azo lake pigment compositions prepared using 4-aminobenzenesulfonic acid (salts) and bisphenol (derivatives) for inks. Japanese patent 08245899 to Sanyo Color Works, 1996.
- [82] Chafetz H, Liu CS, Papke BL, Kennedy TA. Lubricating oil containing an acylated alkenylsuccinimide from reaction of an alkenylsuccinimide with a bis(hydroxyaromatic) carboxylic acid. US patent 5445750 to Texaco, 1995.
- [83] Rosenquist N. Polycarbonate crosslinker resins and fire resistant compositions. European patent 372323 to General Electric Co, 1991.
- [84] Blegen JR. Coating compositions based on polyester resins hardenable by vapor permeation, for flexible supports. Belgian patent 891465 to Ashland Oil, 1982.
- [85] Taira K, Morofuji A, Ueno H, Kobayashi S. Hot-melt adhesive. French patent 2535336 to Toyo Seikan Kaisha, 1984.
- [86] Holmen RE, Olander SJ. Paint composition for marking paved surfaces. US patent 4031048 to Minnesota Mining and Mfg. Co., 1977.