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ORIGINAL PAPER

Sustainable Process for Production of Azelaic Acid Through Oxidative Cleavage of Oleic Acid

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Abstract This work describes two sustainable methods for production and purification of azelaic acid (AA) to replace the current process of ozonolysis of oleic acid (OA). The first proceeds in two steps, coupling smooth oxidation of OA to 9,10-dihydroxystearic acid (DSA) with subsequent oxidative cleavage by sodium hypochlorite. An alternative methodology is also proposed, using a chemocatalytic system consisting of H_2O_2/H_2WO_4 for direct oxidative cleavage of the double bond of OA at 373 K. A convenient technique for separation and purification of azelaic acid is also proposed.

Keywords Oleic acid · Azelaic acid · Pelargonic acid · Hydrogen peroxide · Tungstic acid · Sodium hypochlorite

Introduction

Among the wide variety of biomass materials, fats and oils play an important role as they have competitive cost, are available in different geographical areas, and display functional groups suitable for many industrial applications [1, 2]. Their most abundant components are fatty acids (FA), i.e., monocarboxylic acids with an aliphatic chain, mostly present in the form of free acids or as ester derivatives of glycerol. Among these, long-chain fractions play a relevant role. They can be transformed into methyl esters for production of biodiesel or functionalized to produce surfactants, plasticizers, monomers, and new solvents [2, 3]. These include *cis*-9-octadecenoic acid (oleic acid, OA in Scheme 1), which is a very interesting raw material, since it is renewable, inexpensive, and available in different geographical areas.

Its most common transformations are epoxidation, hydroxylation, and oxidative cleavage of the double bond. The latter reaction is particularly interesting because it selectively produces azelaic acid (AA) and pelargonic acid (PA) (Scheme 1).

Azelaic acid has important applications in textiles (polyesters and polyamides) and pharmaceuticals (antiacne). Industrially, oxidative cleavage of the double bond is carried out by ozonolysis [4]. However, use of ozone and molecular oxygen at high temperatures represents a serious drawback of this process, since these oxidants present combustion hazards. It is therefore required to find new processes that meet the standards of sustainability.

A valid alternative is hydrogen peroxide, because it is capable of oxidizing with excellent atom economy and is safer than gaseous reactants [5]. Many of the known strategies couple H_2O_2 with catalytic systems such as RuO_2, $Na_3PO_4\{[WO(O_2)_2]\}$, $H_2WO_4/Co(OAc)_2$, and Re_2O_7 [6–16]. These synthetic routes (path *i* of Scheme 1) typically include a first step of dihydroxylation that gives 9,10-dihydroxystearic acid (DSA). In a second step (*ii*) a new catalyst is introduced, either in the same reaction environment [14] or on the purified diol [15], for oxidative cleavage of the CH(OH)–CH(OH) bond.

Recently, an efficient one-pot strategy (*iii* in Scheme 1) was proposed with a catalyst based on the quaternary ammonium salt $Q_3\{PO_4[WO(O_2)_2]_4\}$ [17]. Even in this case, there are some disadvantages, namely high catalyst

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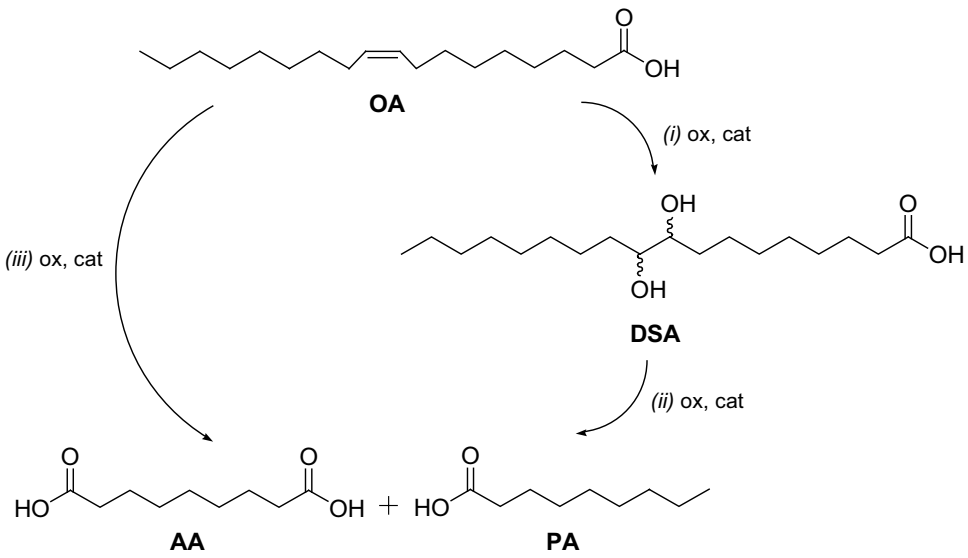
Scheme 1 Oxidative cleavage of oleic acid (OA)



loading (7 % in moles based on W), use of phase-transfer agents, and addition of hydrochloric acid for product recovery. Very efficient systems based on gold catalysts have also recently been described, although some doubts can be raised due to the high cost of this noble metal [18]. Therefore, many efforts have been made to find a successful strategy for production of azelaic acid. This was also demonstrated by the launch in 2014 of the industrial Matrica process, which does not use ozone in the vegetable oil oxidative scission reaction. The present work fits into this context and aims to identify new processes for oxidation of oleic acid that do not require organic solvents or phase-transfer agents, and use low catalyst loading. A clean protocol for isolation of azelaic acid is also proposed.

Materials and Methods

General

Solvents, oleic acid (90 %), and the other reagents were purchased from Sigma Aldrich. Aqueous hydrogen peroxide (aqueous solution 60 %) was supplied by Solvay (Rosignano, Italy).

The collected samples were quantified by gas chromatography (GC) on a PerkinElmer instrument coupled to a flame ionization detector (FID), equipped with a PerkinElmer Elite series 5 capillary column (0.10 μm, 0.32 mm ID, 15 m). The carrier gas was helium at pressure of 1.72 bar at the head of the column. The injector temperature was 423 K, and the detector temperature was 523 K. The oven temperature was held at 313 K for 1 min, then ramped to 453 K at 7 K/min and kept for 1 min, finally being increased to 503 K at 7 K/min and kept for 4 min.

All samples [25 mg mixture dissolved in 500 μL tetrahydrofuran (THF)] were derivatized with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA, 300 μL). *n*-Undecane was added as internal standard (1 % v/v) to 5 mL hexane.

^{1}H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ at 400 MHz.

Oxidative Cleavage in Two Steps

In a 250-mL round-bottom flask equipped with a condenser, tungstic acid (0.040 g, 0.160 mmol) was suspended in aqueous solution of H_2O_2 (60 % w/w, 1.36 g, 24 mmol), and the system was stirred at 343 K. Oleic acid (5.1 mL, 16 mmol) was added as soon as complete dissolution of tungstic acid was observed. After 2 h, the mixture was allowed to cool down to room temperature and NaOCl (4.5 % active Cl_2, 150 mL, 95.4 mmol) was added. The system was stirred at room temperature for 2 h, and pH was then adjusted to 1 using aqueous hydrochloric acid solution (37 % w/w). The reaction mixture was extracted with ethyl acetate (4 × 200 mL). The combined organic layers were dried with anhydrous sodium sulfate and evaporated under reduced pressure. The products were analyzed by ^{1}H NMR without further purification of the crude material and through GC after derivatization (t_r AA = 11 min, t_r PA = 4.2 min).

Procedure for Obtaining a Fraction Enriched in the Intermediate Peroxo Species (PS)

In a 250-mL round-bottom flask equipped with a condenser, tungstic acid (0.040 g, 0.160 mmol) was suspended in aqueous solution of H_2O_2 (60 % w/w, 1.36 g, 24 mmol)

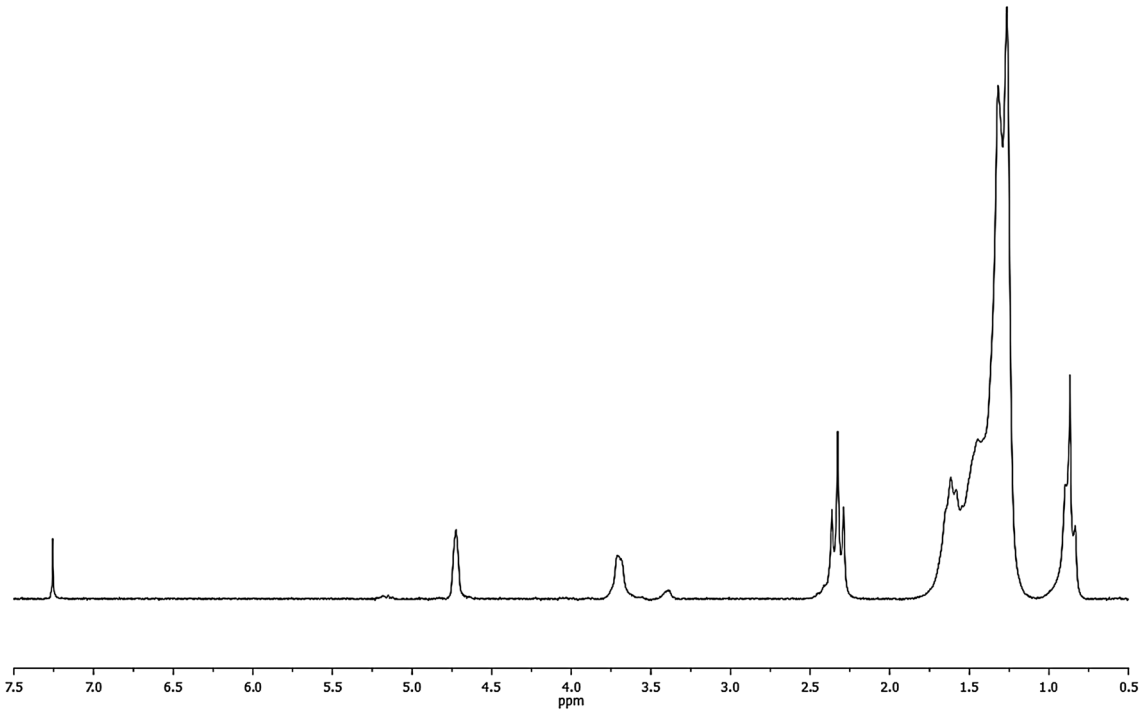


Fig. 1 ^{1}H NMR spectrum of the peroxo species (PS)-rich fraction (in $CDCl_3$)

and the system was stirred at 343 K. Oleic acid (5.1 mL, 16 mmol) was added as soon as complete dissolution of tungstic acid was observed. After 2 h, the mixture was allowed to cool down to room temperature. The oily residue was melted, and hexane was added. After cooling at 273 K, the resulting white solid was filtered (mainly DSA), and washed with hexane. The solvents were removed under vacuum from the mother liquor, and hexane was added at 273 K to the resulting oily residue. The resulting white solid was again filtered (mainly DSA), and washed with hexane. The solvents were removed under vacuum from the mother liquor, affording a fraction enriched in PS (90 % according to the NMR spectrum reported in Fig. 1). *Caution: evaporation of solutions which may contain hydrogen peroxide or peroxo species at a rotary evaporator represents a serious safety risk and can cause explosion and destruction of equipment.* The peroxides value was 550 mmol O_2/kg (NFT 60-220).

Oxidative Cleavage in a Single Step

In a 250-mL round-bottom flask equipped with a condenser, tungstic acid (0.283 g, 1.13 mmol) was suspended in aqueous solution of H_2O_2 (60 % w/w, 51.2 g, 904 mmol) and the system was stirred at 343 K. Oleic acid (36.3 mL, 113 mmol) was added as soon as complete dissolution of tungstic acid was observed. The reaction mixture was stirred under reflux. After 8 h, the mixture was allowed to cool down to room temperature and cool water (50 mL) was added. The reaction mixture was extracted with hot ethyl acetate (4 × 100 mL). The combined organic layers were dried with anhydrous sodium sulfate and evaporated under reduced pressure. The products were analyzed by ^{1}H NMR without further purification of the crude material and by GC after derivatization (t_r AA = 11 min, t_r PA = 4.2 min, t_r DSA = 20 min).

Separation and Purification of Azelaic Acid (Single Step)

The reaction mixture was extracted with cool water (100 mL) and then with hot ethyl acetate (3 × 200 mL). The volume of the organic phase was reduced under vacuum and extracted with hot water (3 × 50 mL). On cooling the aqueous phase, a white precipitate of azelaic acid formed, which was collected, washed with cool water, and dried (isolated yield 60 %). The ^{1}H NMR spectrum of isolated AA is given in Fig. 2.

Results and Discussion

General Strategies

Two different strategies (a and b) were identified, as summarized in Scheme 2.

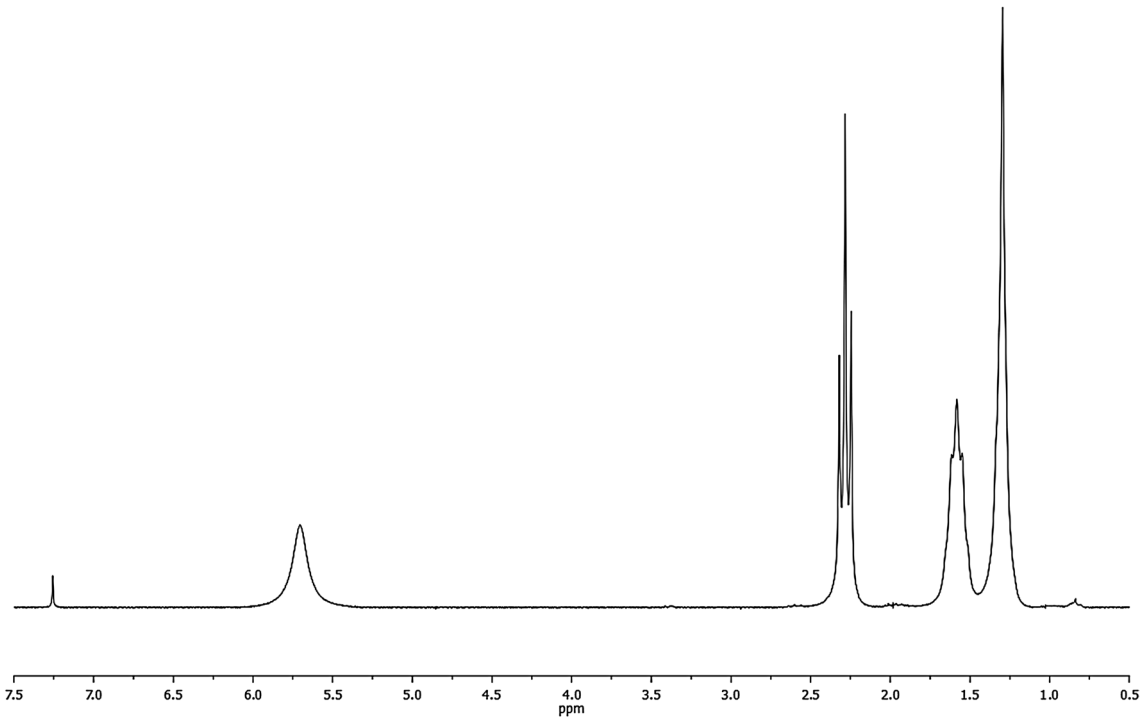
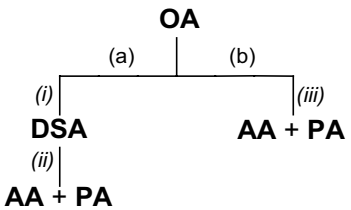


Fig. 2 ^{1}H NMR spectrum in $CDCl_3$ of isolated azelaic acid (AA)



(*i*) H_2WO_4, H_2O_2, 343 K; *(ii)* NaOCl, RT; *(iii)* H_2WO_4, H_2O_2, reflux

Scheme 2 Strategies for oxidative cleavage of oleic acid (OA)

The first procedure (a) involves a smooth and relatively fast oxidation of oleic acid to 9,10-dihydroxystearic acid (*i*) using commercially available H_2WO_4 as the only catalytic ingredient and H_2O_2 (60 % v/v). It should be noted that this concentration is higher than that usually adopted in oxidation reactions (up to 35 %). This step is followed by oxidative cleavage with a stoichiometric amount of NaOCl at room temperature (*ii*), which implies energy savings in terms of both cost and emissions. In fact, these experimental conditions are considered advantageous according to the criteria of the EcoScale, which is a semiquantitative tool to assess the impact of chemical synthesis [19].

In the alternative approach (b) the synthesis takes place in one step (*iii*). The two-phase system does not require addition of further solvents, and it operates in reflux conditions. In both cases, the conversion was preliminarily assessed by ^{1}H NMR spectroscopy. Identification and quantification of the products were carried out via GC analysis of the reaction mixtures.

Oxidative Cleavage in Two Steps (a)

The process was conducted in a single batch, and screening was performed as reported in Table 1.

The spectrum of a typical reaction mixture (*i*) revealed that DSA was not the only oxidation product, as three diagnostic signals appeared in the region of the protons geminal to oxygenated functions. The signals were associated to three different species, which, also on the basis of GC, mass spectroscopy, and number of peroxides (550 mmol O_2/kg, NFT 60–220), were identified as DSA (δ 3.4), its parent epoxide EPOXY (δ 2.8), and PS (δ 3.7). The latter is an intermediate peroxo species (Fig. 3) whose formation has been mentioned in literature [16].

A fraction largely enriched in PS was also isolated, and its proton spectrum is reported in Fig. 1. The signal at δ 88.0 in the carbon spectrum confirms this assignment. Other relevant signals are at δ 77.2 (–CHOH–) and 179.4 (C=O). However, the presence of byproducts was not a drawback because subsequent cleavage of the σ–C–C bond (*ii*) easily occurred upon addition of NaOCl.

Using an OA/H_2O_2 ratio of 1/1.5, complete conversion of OA was achieved within 60 min (entries 1 and 2). Increasing the amount of oxidant (entries 3 and 4) was

Table 1 Conversion of oleic acid (OA) at 343 K (first step)

Entry	OA/H_2WO_4	OA/H_2O_2	OA conversion (%)[a]	EPOXY (%)[a,b]	DSA (%)[a,b]	PS (%)[a,b]	*t* (min)
1	100/1	1/1.5	90 ± 4	7 ± 1.1	45 ± 1.0	10 ± 1.1	30
2	100/1	1/1.5	>99	–	52 ± 1.1	16 ± 2	60
3	100/1	1/2	>99	–	47 ± 1.0	43 ± 4	120[c]
4	100/1	1/4	>99	–	45 ± 1.0	45 ± 5	240[c]
5	200/1	1/1.5	80 ± 4	7 ± 1.1	40 ± 1.0	15 ± 2	60
6	400/1	1/1.5	>99	–	40 ± 1.0	20 ± 2	120
7	1600/1	1/1.5	>99	10 ± 2	40 ± 1.0	20 ± 2	>240

[a] Evaluated by ^{1}H NMR spectroscopy. Values are averages of three runs. Errors reported as standard deviations

[b] Other minor oxidation products are present but have not been identified

[c] Time to completion

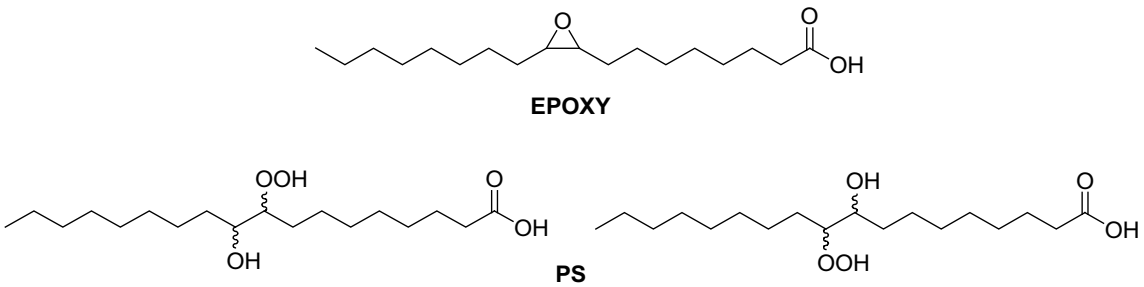


Fig. 3 Structures of EPOXY and peroxo species (PS)

found to be detrimental to the reaction, plausibly due to the resulting dilution of the catalyst.

Variation of the catalyst loading was attempted to identify the lowest substrate/catalyst ratio capable of promoting the reaction within a reasonable reaction time (entries 5–7). It is evident that excessive reduction of the amount of catalyst (1600/1, entry 7) resulted in an extended reaction time. Instead, a loading of 400/1 (entry 6) was found convenient, as complete conversion of OA was achieved in only 2 h. Regarding the subsequent oxidation with NaOCl, it should be stressed that the feasibility of this process has already been described on isolated DSA [20]. In the present work, the reaction was carried out with a NaOCl:OA molar ratio of 6:1, and was followed by monitoring the disappearance of the signals at δ 2.8–3.7. Complete conversion of DSA, PS, and EPOXY occurred within 2 h at room temperature, and AA was obtained in maximum yield of 54 % starting from the conditions of entry 4, as quantified by gas chromatography.

Oxidative Cleavage in a Single Step (b)

In the single step (*iii* in Scheme 2), the $OA/H_2O_2/H_2WO_4$ ratio was set at 100/400/1 as initial conditions. A first general consideration is that, at 343 K, the reaction did not give appreciable amounts of the desired carboxylic acids, but only formation of DSA (entry 1 of Table 2).

A run performed without any tungstic acid indicated that the presence of a catalytic ingredient is required (entry 2). Under reflux, however, conversion of oleic acid into pelargonic and azelaic acid was already significant within 4 h (entry 3). The system was then refined by tuning the substrate/catalyst and substrate/oxidant ratios, the modality of addition of the oxidant, and the reaction time. Increasing the catalyst loading was not beneficial for the performance of the catalyst (entry 3 versus 4). The yields of AA and PA, in fact, did not exhibit any appreciable changes. Therefore, a substrate/catalyst ratio of 100/1 was considered as a fair compromise between an acceptable reaction rate and minimization of the catalyst loading. It should be noted that this level of concentration is sevenfold lower (based on W atoms) than that proposed in a recent study based on phosphotungstic acid [17]. Translated to mass, this means that our system uses a catalyst loading about 10 times lower for the same amount of oleic acid (taking into account the additional mass derived from phase-transfer agents [17]). Subsequently, the effect of varying the amount of oxidant was evaluated, assuming that the high temperature could degrade the hydrogen peroxide. Actually, the data reported in entries 5–7 suggest that the yield of azelaic acid

Table 2 Results of oxidative cleavage of oleic acid (OA) in a single step (at 373 K)

Entry	*t* (h)	OA/H_2WO_4	OA/H_2O_2	DSA (%)[a,b]	PA (%)[a,b]	AA (%)[a,b]
1[c]	4	100/1	1/4	90 ± 2	–	–
2	4	–	¼	20 ± 1.0	14 ± 1.0	10 ± 1.1
3	4	100/1	¼	26 ± 1.1	36 ± 2	43 ± 1.3
4	4	50/1	¼	5.0 ± 0.2	24 ± 1.3	41 ± 2
5	4	100/1	1/8	4.0 ± 0.2	52 ± 3	64 ± 3
6	4	50/1	1/8	–	44 ± 2	72 ± 4
7	4	100/1	1/(4 + 4)	1.0 ± 0.1	33 ± 2	72 ± 4
8	8	50/1	¼	3.0 ± 0.2	26 ± 1.4	43 ± 2
9	8	100/1	1/4	5.0 ± 0.4	55 ± 1.2	64 ± 2
10	8	100/1	1/8	–	69 ± 1.5	91 ± 2

[a] As chromatography yields. Values are averages of three runs. Errors reported as standard deviations

[b] Other minor oxidation products are present but have not been identified

[c] At 343 K

increases with the amount of oxidant. The effects of the modality of addition of H_2O_2 were also taken into account. Therefore, a test was conducted in which eight equivalents of hydrogen peroxide were added in two steps at an interval of 2 h. The increase in yield of AA up to 72 % indicates that the addition of the "new" hydrogen peroxide enhances the performance of the system.

Finally, the increase in product yield on doubling the reaction time was determined (entries 8–10). After 8 h of reaction, an excellent yield of AA (91 %) was obtained by using the conditions described in entry 10. After the optimization of the reaction conditions, a convenient methodology for isolation and purification of azelaic acid was also developed (Fig. 4). This was inspired by classical methods of extraction [21], previously used for separation of dicarboxylic from monocarboxylic acids [22], and also applied in the specific case of the azelaic and pelargonic couple [23].

The reaction was quenched by adding cold water to the reaction mixture, and the resulting suspension was extracted with hot ethyl acetate (AcOEt). The aqueous phase contained the catalyst and the residual H_2O_2, while the organic phase captured the crude reaction products. After evaporation under vacuum of the organic solvent, white suspension was obtained, which was extracted with boiling water. On cooling, azelaic acid crystallized into white microcrystals. ^{1}H NMR confirmed a high degree of product purity (Fig. 2). It should be noted that this convenient procedure for isolation of azelaic acid was found less feasible when applied to the crude reaction mixture of the oxidative cleavage in two steps (a).

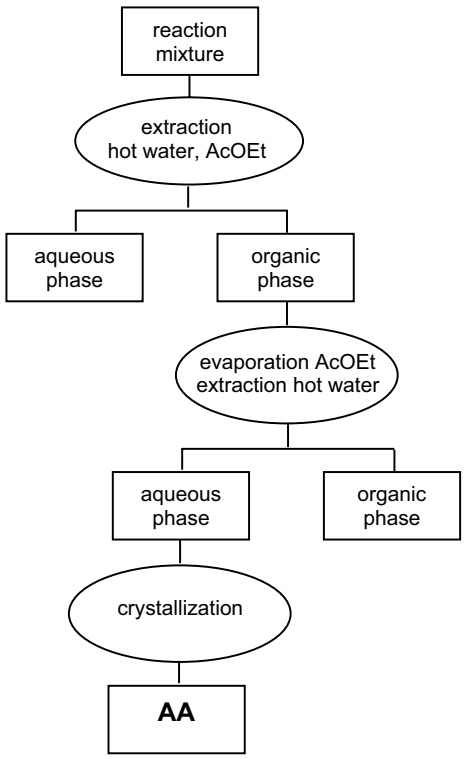


Fig. 4 Flowchart for isolation of azelaic acid (AA)

Conclusions

The present work aims to identify methodologies for sustainable production of azelaic acid (AA) from oleic acid (OA). The first method couples a system based on H_2O_2/H_2WO_4 with subsequent addition of sodium hypochlorite. It has the advantage of mild reaction conditions, but it has not been possible to obtain AA in yields higher than 51 %. The second approach requires the same catalytic ingredient as the first procedure and is capable of producing AA at 373 K with an unprecedented chromatographic yield of 91 %. Neither of these methods uses phase-transfer agents, and they both employ low catalyst loading. Furthermore,

tungstic acid has a more favorable ecotoxicological profile than phosphotungstic acid. A convenient method for purification of the product has also been highlighted. Future developments will focus on further optimization of the isolation procedures and recovery of the catalytic ingredients.

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References

1. Gunstone FD (2008) Imports by commodity and by country. Lipid Technol 20:264
2. Biermann U, Bornscheuer U, Meier MAR, Metzger JO, Schäfer H (2011) Oils and fats as renewable raw materials in chemistry. Angew Chem Int Ed 50:3854–3871
3. Dierker M, Schäfer HJ (2010) Surfactants from oleic, erucic and petroselinic acid: synthesis and properties. Eur J Lipid Sci Technol 112:122–136
4. Brown AC, Goebel CG, Oehlschlaeger HF, Rolfes RP (1957) Method of making azelaic acid. US Patent 2,813,113
5. Nojori R, Aoku M, Sato K (2003) Green oxidation with aqueous hydrogen peroxide. Chem Commun 16:1977–1986
6. Köckritz A, Martin A (2011) Synthesis of azelaic acid from vegetable oil-based feedstocks. Eur J Lipid Sci Technol 113:83–91
7. Warwel S, Rüsch gen. Klaas M (1997) Oxidative cleavage of unsaturated fatty acids without ozone. Lipid Technol 9:10–14
8. Herrmann AT, Warwel S, Rüsch gen. Klaas M (1977) Production of compounds containing carboxylic acid. German Patent 19,724,736
9. Antonelli E, D'Aloisio R, Gambaro M, Fiorani T, Venturello C (1998) Efficient oxidative cleavage of olefins to carboxylic acids with hydrogen peroxide catalyzed by methyltrioctylammonium tetrakis(oxodiperoxotungsto)phosphate(3-) under two-phase conditions. Synthetic aspects and investigation of the reaction course. J Org Chem 63:7190–7206
10. Song HY, Chen J, Tong J (2005) Study on synthesis of azelaic acid by catalytic oxidation using phase transfer catalyst. Huaxue Shiji 27:65–67
11. Santacesaria E, Sorrentino A, Rainone F, Di Serio M, Speranza F (2000) Oxidative cleavage of the double bond of monoenic fatty chains in two steps: a new promising route to azelaic acid and other industrial products. Ind Eng Chem Res 39:2766–2771
12. Haimov A, Cohen H, Neumann R (2004) Alkylated polyethyleneimine/polyoxometalate synzymes as catalysts for the oxidation of hydrophobic substrates in water with hydrogen peroxide. J Am Chem Soc 126:11762–11763
13. Santacesaria E, Ambrosio M, Sorrentino A, Tesser R, Di Serio M (2003) Double bond oxidative cleavage of monoenic fatty chains. Catal Today 79–80:59–65
14. Oakley MA, Woodward S, Coupland K, Parker D, Temple-Heald C (1999) Practical dihydroxylation and C–C cleavage of unsaturated fatty acids. J Mol Catal A Chem 150:105–111
15. Köckritz A, Blumenstein M, Martin A (2010) Catalytic cleavage of methyl oleate or oleic acid. Eur J Lipid Sci Technol 112:58–63
16. Behr A, Tenhumberg N, Wintzer A (2013) Efficient ruthenium-catalysed oxidative cleavage of methyl oleate with hydrogen peroxide as oxidant. RSC Adv 3:172–180
17. Godard A, De Caro P, Thiebaud-Roux S, Vedrenne E, Mouloungui Z (2013) New environmentally friendly oxidative scission of oleic acid into azelaic acid and pelargonic acid. J Am Oil Chem Soc 90:133–140
18. Kulik K, Martin A, Pohl M-M, Fischer C, Köckritz A (2014) Insights into gold-catalyzed synthesis of azelaic acid. Green Chem 16:1799–1806
19. Van Aken K, Strekowski L, Patiny L (2006) EcoScale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters. Beilstein J Org Chem 3:2
20. Lemaire M, Favre-Reguillon A, Paquit B, Claude S, Raoul Y (2011) Method for preparing carboxylic acids by oxidative cleavage of a vicinal diol. WO 2011(107721):A1
21. Levey M (1959) Chemistry and technology in ancient Mesopotamia. Elsevier, Amsterdam, pp 33–34
22. Heuser A, Stoehr O (1891) Ueber methylierte dipyridyle. J Prakt Chemie 44:404–410
23. Zaidman B, Kisilev A, Sasson Y, Garti N (1988) Double bond oxidation of unsaturated fatty acids. J Am Oil Chem Soc 65:611–615