Valorization of Oleuropein Via Tunable Acid-Promoted Methanolation


Abstract: The acid-promoted methanolation of Oleuropein was studied using a variety of homogeneous and heterogeneous acid catalysts. Exclusive cleavage of the acetal bond between the glucoside and the monoterpene subunits or further hydrolysis of the hydroxytyrosol ester and subsequent intramolecular rearrangement were observed upon identification of the most efficient catalyst and experimental conditions. Furthermore, selected samples were tested using Oleuropein under continuous flow and using a crude mixture extracted from olive leaves under batch. Formation of (-)-methyl elenolate was also observed in this study, which is a reported precursor for the synthesis of the antihypertensive drug (-)-ajmalicine.

Substantial quantities of olive leaves are generated every year (10-30 kg/tree, 6 × 10^5 trees worldwide)[11] as a byproduct of the cultivation of Mediterranean native olive trees (Olea europaea) for the production of both olive oil and table olives.[2] Practical applications of these leaves are limited to the use of their extracts for dietetic purposes due to its reported health benefits.[2d,3]

Oleuropein (1) is one of the major secoiridoids found in the olive leaf (0.5-2% w/w on dry basis) together with other related secoiridoids (e.g., elenolic acid) and a variety of phenolic compounds, such as simple phenols (e.g., phenylethanoids, hydroxybenzoic acids, hydroxycinnamic acids) and flavonoids (e.g., flavones, flavanones, flavonols, 9-flavanols).[5] Recent methodologies for the extraction of Oleuropein include nanofiltration by using imprinted polymers (1.75 g product per kg adsorbent per hour)[5] and solvent-free microwave-assisted extraction (0.06 ppm)[6].

Oleuropein structure can be divided in three subunits – glucoside, monoterpene and hydroxytyrosol (red, black and blue, respectively, Scheme 1).[7] The monoterpene unit is a highly functionalyzed moiety that includes two esters (including the bond between the hydroxytyrosol and the monoterpene subunits), one alkene, one enol ether, one acetal (bond between the glucoside and the monoterpene subunits) and a stable chiral center at C-4. This multifunctional structure makes it difficult to be obtained by other means than extraction from natural sources. In this context, we became interested in the valorization of 1 towards the synthesis of diverse and synthetically rich building blocks.

A variety of synthetic transformations of 1 have been reported by several authors.[8] These transformations are summarized in Scheme 1, and include selective hydrolysis of the hydroxytyrosol ester (A, Scheme 1)[9]; formation of Oleuropeinol 3 through reduction of both methyl and hydroxytyrosol esters (B, Scheme 1)[10]; enzymatic acetal cleavage by β-glucosidase to form either pyridine alkaloid Jasminine (4, C, Scheme 1)[11] or compound 5 (D, Scheme 1)[12]; depending on the ammonium salt used; and formation of Oleacone (6) through Krapcho decarbomethoxylation (E, Scheme 1)[13].

The acid treatment of 1 have also been reported using sulphuric, anhydrous hydrochloric acid and Erbium(III) trifluoromethanesulfonate (F-H, Scheme 1).[14] In general, complex mixtures of Oleuropein aglycone derivatives are obtained, including Elenolic acid (4) and compound 8. Nevertheless, we foresee that cleavage of the β-glycosidic bond is crucial for an efficient valorization of 1 due to the inherent solubility problems in organic solvents rendered by the glucoside subunit. Thus, we envisioned that a selective acid-promoted methanolation could result in the creation of a diverse chemical platform, comprising 9 and 10 (L, Scheme 1). Precedent literature for the formation of acetal 10 remotes to 1995, where Iossifova et al. reported its formation by the H_2SO_4-promoted methanolation of a secoiridoid extracted from the plant Fraxinus ornus hydroxyornoside containing the same monoterpene subunit of 1.[15] Furthermore, removal of acetal would form 11, which, in its enantiopure form, has been reported as a precursor for the straightforward three steps synthesis of the natural product (-)-ajmalicine, approved as an antihypertensive drug.[16] Currently, 11 is obtained mainly by isolation from the medicinal plant Catharanthus roseus or via bioprocesses.[17]

The study was initiated by evaluating a variety of Brensted acids (HCl, p-toluenesulfonic acid (PTSA), triflic acid (TIOH), trifluoroacetic acid (TFA), acid ion-exchange resins (Amberlyst® 15, Amberlyst® 16, Amberlyst® 36, Amberlite® IRC66 and Amberlite® IR120) and Preyssler heteropolyacids (H_{14}[NaP_{5}W_{29}MoO_{110}] and H_{14}[NaP_{5}W_{30}O_{110}]), as catalysts for the methanolysis of 1 at 70°C. The identification of various products led us to study the reaction progress profiles for each reaction by expressing the yield of (S,S)-9 and (S,R)-9 and 10 as a function of the reaction time. A selection of these results is summarized in Figure 1. In general, full conversion of 1 was achieved after 6 h reaction time, occurring exceptionally fast (<5 min) when using TIOH or PTSA.[18]
Based on the precedent results on the methanolysis of crude Oleuropein extracts, HCl was the first acid studied. The methanolysis of 1 using HCl afforded 10 in 24% yield after 6 h, which did not significantly change throughout the 23 h reaction time.

In addition, compound (S,S)-9 was found in trace amounts during the initial moments (<30 min) of the reaction. In contrast, compound (S,S)-9 was observed in good yields for the reactions promoted by the organic acids TFA, PTSA, and TfOH (Figure 1A). Furthermore, the maximum yield observed for (S,S)-9 follows the acidity trend of the acids (65% (6 h), 75% (5 min) and 91% (5 min) using TFA, PTSA, and TfOH, respectively). Similarly, the maximum yield for the formation of 10 is directly proportional to the acidity of the promoter used, reaching 60% after 23 h using TfOH (Figure 1C). The use of PTSA and TfOH adsorbed onto silica resulted in general trace formations of silica treated with HCl afforded 10 after 23 h. Amberlyst® 15 performed the best: 90% of (S,R)-9 after 1 h. Finally, both Preyssler heteropolyacids tested proved to be very efficient promoters for the formation of 10 (>86% yield after 23 h). It is noteworthy that deacetalization of 10 was observed upon contact with silica gel under reduced pressure at 40°C, yielding diethyl ester 11 as a mixture of diastereoisomers 6:2:2:1 (major isomer is (-)-methyl enololate 11). The temperature effect on the reaction selectivity was evaluated using PTSA as promoter. The use of lower temperature resulted in slower kinetics whereas an increase to 80°C resulted in increased performance of the reaction, resulting in the formation of 10 in 59% yield after 2 h. Furthermore, longer reaction times led to lower yields, indicating possible degradation of the product.
On the basis of these reaction progress profiles, which suggest that 9 is an intermediate for the formation of product 10, we propose the reaction mechanism depicted in Scheme 2. We hypothesize that an initial methanolysis of the acetal moiety occurs via formation of an oxocarbenium ion intermediate to form both epimers (S,S)-9 and (S,R)-9. The stereochemistry of (S,R)-9 was determined by NOESY experiment. DFT calculations performed at ωB97X-D/def2-TZVP/SMO/Methanol)/B3LYP/6-31G(d) level of theory show that these epimers have similar free energies, however, different effects are involved in their stabilization – the anomeric effect in (S,S)-9 and steric effects in (S,R)-9 with the methoxy substituent preferring the equatorial orientation. We tentatively explain the initial selective formation of epimer (S,S)-9 by the presence of the anomeric effect involving the C-O(methoxy) bond formed. We suggest that epimerization into the more stable epimer (S,R)-9 occurs via the reversibility showed in Scheme 2, and highlight that the stereochemistry of (S,R)-9 is the same as the natural product 1. A transterification into the corresponding methyl ester and an acetal ring opening followed by a 1,4-addition (favourable 6-endo-trig) of the oxygen to the exocyclic double bond are believed to occur to afford the corresponding cyclized product as a mixture of diastereoisomers, which undergo acetal formation to yield 10.

As compound (S,S)-9 is not stable under these conditions, we envisioned that flow conditions would allow its easy and selective preparation because the contact between the compound and the acid is reduced. Thus, the feasibility of using Amberlyst® 15 under continuous flow conditions for the methanolysis of 1 was tested by passing a methanolic solution of 1 through a column (reactor) packed with this resin. Optimization of residence time revealed that 5 minutes (ca. 86 µL/min for our specific reactor) is the best for the selective synthesis of (S,S)-9. With optimal conditions in hand, we then evaluated the robustness of the resin. For that, we continuously injected 1 through the reactor for 4 cycles and one final wash with pure solvent (methanol). As summarized in Figure 2, (S,S)-9 was obtained in 66-86% yield in each cycle, together with <21% of unreacted 1 and <5% of (S,R)-9 (not shown). The overall yield of (S,S)-9 obtained in this process, including 4 cycles and 1 final wash, was 89%.

Finally, we applied this methodology to the crude mixture extracted from olive leaves and the results are summarized in Table 1. Remarkably, methanolysis of a crude mixture (gram-scale) containing 1 using 10% w/w Amberlyst® 15 afforded 53 mg of 9 per gram of crude mixture extract (Table 1, entry 2). As a maximum of 15 mg 9/g crude would be expected based on the reported amount of Oleuropein in the olive leaf (2% w/w), we believe that this over 100% yield is due to the presence of additional Oleuropein-like monoterpenes-containing products in the crude extract. This result is also in accordance with the quantitative yield of 9 obtained from the methanolysis of pure 1 using the same promoter (Table 1, entry 1). Similarly, an over 100% yield of 10 was obtained in the methanolysis of crude extract by using PTSA as promoter (31 mg/g of crude, Table 1, entry 4). Overall, these results are very promising as it allows the valorization of 1 avoiding the tedious purification step of 1 after extraction from olive leaves.

Table 1. Acid-promoted methanolysis of crude mixture extract containing 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Promoter</th>
<th>t (h)</th>
<th>Major product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crude</td>
<td>Amberlyst® 15</td>
<td>1</td>
<td>(S,S)-9</td>
<td>Quantitative&lt;sup&gt;[2]&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Crude</td>
<td>Amberlyst® 15</td>
<td>1</td>
<td>(S,S)-9</td>
<td>53 mg/g crude&lt;sup&gt;[2]&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Crude</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;[NaP&lt;sub&gt;2&lt;/sub&gt;W&lt;sub&gt;20&lt;/sub&gt;MoO&lt;sub&gt;41&lt;/sub&gt;]</td>
<td>12</td>
<td>10</td>
<td>66%</td>
</tr>
<tr>
<td>4</td>
<td>Crude</td>
<td>PTSA</td>
<td>23</td>
<td>10</td>
<td>31 mg/g of crude&lt;sup&gt;[2]&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> All the reactions were carried out in a pressure tube at 70°C. For the specific reaction conditions see experimental section. <sup>[b]</sup> Mixture of isomers (S,S)-9/(S,R)-9 1:0.2, determined by <sup>[1]</sup>H NMR. <sup>[c]</sup> Yield determined by HPLC-UV analysis of crude reaction mixture.
In conclusion, we described a new sustainable approach for the diverse valorization of 1. Our studies revealed that tuning of the reaction conditions and acid promoter result in highly selective methanolysis. Identified products include cleavage of the glucoside acetal, to yield \((S, S)-9\), followed by epimerization to give \((S,R)-9\) and downstream formation of acetal 10 and the biological active \((-\text{methyl elenolate})\).

Preparation of Preysler heteropolycarids \(H_2[Na_3PW_{29}MoO_{110}]\) and \(H_2[Na_3PW_{29}MoO_{110}]\). The Preysler salt, \(K_{Na_3PW_{29}MoO_{110}}\) \(\cdot\) \(H_2O\), was prepared from \(Na_3PW_{29}2H_2O\) according to a reported method.[21] In a typical experiment, \(Na_3PW_{29}2H_2O\) (30 g, 0.09 mol) was dissolved in boiling water (20 mL), and concentrated phosphoric acid (\(H_2PO_4\)) was poured carefully into the solution (27 g, 0.27 mol). Then, the mixture was refluxed for 24 h, and concentrated nitric acid (1 mL) was added to the solution. Preysler salt was precipitated by adding \(KCl\) (10 g, 0.13 mol). The \(K_{Na_3PW_{29}MoO_{110}}\) \(\cdot\) \(H_2O\) was converted to the corresponding acid \(H_2[Na_3PW_{29}MoO_{110}]\) by passing it through a Dowex-50WX-8 ion exchange column.

The Preysler heteropolycarids \(H_2[Na_3PW_{29}MoO_{110}]\) was synthesized following a literature method.[21-22] The method was similar to that of \(H_2[Na_3PW_{29}MoO_{110}]\). Briefly, \(Na_3PW_{29}2H_2O\) (23 g, 0.07 mol) and \(Na_3MoO_2\) \(2H_2O\) (2 g, 8.3 mmol) were dissolved in water (20 mL) and mixed at 333 K for 30 min. Then, \(H_2PO_4\) (27 mL) was added, and the solution was refluxed for 24 h. The solution was cooled to room temperature, and \(KCl\) (10 g, 0.13 mol) dissolved in \(H_2O\) (30 mL) was added with vigorous stirring for 30 min. The solid was obtained by crystallization in warm water (70 mL) and then was cooled down to room temperature, obtaining yellow crystals corresponding to \(K_{Na_3PW_{29}MoO_{110}}\). This salt was converted to its corresponding acid \(H_2[Na_3PW_{29}MoO_{110}]\) by passing it through a column filled with Dowex50WX-8 ion-exchange resin.

Isolation of oleuropein (1) from olive leaves
Milled dried olive leaves (200 g) were suspended in 2 L of distilled water inside a pyrex beaker and heated in a domestic microwave at medium/high potency for 15 minutes. Leaves were removed by filtration, followed by water evaporation under reduced pressure. Acetone (100 mL) was added to the brown oily mixture and stirred overnight at room temperature. The insoluble material was filtered out and the solvent removed under reduced pressure to give a brown oil containing 1, which was purified by flash chromatography silica column using DCM/MeOH (1:0 to 8:2) to yield 1 [3 g, 1.5\% (w/w dried olive leaves) as a yellow amorphous solid. R\(_d\) (DCM/MeOH 9:1) = 0.49; (reported R\(_d\) (DCM/MeOH 8:1) = 0.57)[23]. NMR spectra of 1 are in agreement with reported data.[13]

**General Information.** All solvents were distilled from commercial grade sources. Anhydrous solvents were prepared according to usual procedures.[18] Chemicals were obtained from commercial sources and used without further purification: Acetyl chloride (Merk. Ref 1.00031, KP56353), p-Toluensulfonic acid monohydrate (PTSA, Fluka, 89762-1kg, 1372419), Triflic acid (TOH, Fluka 91738-50ml, 1297369), Trifluoroacetic acid (TFA, Alfa, A12198-500g, 10202568), Amberlyst\(_R\) 15 dry (Alridch, 216399-500g, MKBR7383V), Amberlyst\(_R\) 16 wet (Fluka, 86317-250g, CBKBS787V), Amberlyst\(_R\) 36 wet (Alridch, 43612-250g, 11605EJV), Amberlyst\(_R\) IRC86 (Fluka, 06455-250g, BCB1923V) and Amberlit\(_R\) IRC120 (Alridch, 10322, 45094V). 

**Preparative TLC.** Purifications were performed using silica gel 60A (P2050017, Carlo Erba) and 60B (0.20 mmol) in MeOH (8 mL) was added to the tube. The reaction was continued until no further reaction was observed. The reaction mixture was then filtered through a short column of silica gel, and the filtrate was concentrated to dryness under reduced pressure. The residue was then purified by preparative TLC on silica gel plates (Kieselgel 60F254, H2O/1% TFA and (B) ACN/1% TFA was used as mobile phase in a multistep gradient: 5% B – 28% B (0 -19 min); 28% B – 35% B (19 -25 min) and 35% B – 100% B (25 -32 min).

**General procedure for the synthesis of 9 (Table 1, entry 1).** Amberlyst\(_R\) 15 (72 mg, 2 equiv) was placed in a pressure tube (15 mL, L×OD 10.2×25.4 cm, Ref. Z181099-1EA Aldrich). A solution of milled dried olive leaves (200 g) was suspended in 2 L of distilled water inside a pyrex beaker and heated in a domestic microwave at medium/high potency for 15 minutes. Leaves were removed by filtration, followed by water evaporation under reduced pressure. Acetone (100 mL) was added to the brown oily mixture and stirred overnight at room temperature. The insoluble material was filtered out and the solvent removed under reduced pressure to give a brown oil containing 1, which was purified by flash chromatography silica column using DCM/MeOH (1:0 to 8:2) to yield 1 [3 g, 1.5\% (w/w dried olive leaves) as a yellow amorphous solid. R\(_d\) (DCM/MeOH 9:1) = 0.49; (reported R\(_d\) (DCM/MeOH 8:1) = 0.57)[23]. NMR spectra of 1 are in agreement with reported data.[13]

**H\(_1\) NMR (300 MHz, CD\(_3\)OD) \(\delta\) ppm: 7.52 (s, 1H, H3), 6.72–6.67 (m, 2H, H7, H4'), 3.36 (m, 2H, H5'), 2.89 (m, 3H, H5, H8').**

**General procedure for the methanolysis of 1 (Figure 1).** To a flame dried pressure tube (15 mL, L×OD 10.2×25.4 cm, Ref. Z181099-1EA Aldrich) and under argon atmosphere, was added 1 (20 mg, 0.04 mmol) dissolved in dry MeOH (2 mL), followed by addition of the acid promoter (2 mmol, 1. M). The resulting reaction mixture was stirred at 70ºC (or 60ºC and 80ºC for the temperature study) in a GC oven for a maximum of 23 h. The progress of the reaction was followed by reversed-phase HPLC-UV, by cooling down the reactor, taking aliquots (65 \(\mu\)L) at specific time and diluted them in HPLC grade acetonitrile to 0.4 \(\mu\)L concentration.

**Protocol for the synthesis and isolation of 9 (Table 1, entry 1).** Amberlyst\(_R\) 15 (72 mg, 2 equiv) was placed in a pressure tube (15 mL, L×OD 10.2×25.4 cm, Ref. Z181099-1EA Aldrich). A solution of 1 (86 mg, 0.20 mmol) in MeOH (8 mL) was added to the tube. The reaction was...
stirred at 70°C for 1 h. The resin was removed by filtration, and the reaction was diluted in water (20 mL) and extracted with DCM (20 mL x 3). The combined organic phases were dried with anhydrous Na₂SO₄ and the solvent was removed under reduced pressure to afford 9 as a brown oil (77 mg, quantitative yield) as a mixture of diastereoisomers ([S,S]-9/([S,R]-9) 1:0.2). Rᵣ (DCM/MeOH: 9:1) = 0.77.

Major ([S,R]-9) 1H NMR (300 MHz, CDCl₃) δ (ppm) 7.51 (s, 1H, H3), 7.01 (d, J = 1.98 Hz, 1H, H7), 6.79 (d, J = 6 Hz, 1H, H4'), 6.62 (dd, J = 3 Hz, 9 Hz, 2H, H8), 5.74 (q, J = 6 Hz, 1H, H8'), 5.12 (d, J = 0.86 Hz, 1H, H7'), 4.28–4.09 (m, 2H, H1'), 3.87 (dd, J = 3 Hz, 9 Hz, 1H, H5), 3.78 (s, 3H, H12), 3.44 (s, 3H, -OCH₃), 2.90–2.75 (m, 5H, H6, H₂', H2'), 2.71–2.65 (m, 2H, H6, H2'), 1.58 (d, J = 9 Hz, 3H, H10). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 172.1 (C7), 168.4 (C11), 153.4 (C3), 143.4 (C5'), 143.2 (C6'), 130.6 (C3), 130.0 (C9), 128.9 (C6), 121.3 (C8'), 117.1 (C7'), 115.0 (C4'), 108.7 (C4), 104.8 (C1), 162.5 (C11), 156.3 (-OCH₃), 51.9 (C12), 38.7 (C8), 34.3 (C2'), 28.7 (C5), 13.3 (C10).

Minor ([S,S]-9) 1H NMR (300 MHz, CDCl₃) δ (ppm) 7.50 (s, 3H, H3); 6.98 (d, J = 2 Hz, H7); 6.79 (d, J = 9 Hz, H4'); 6.00 (d, J = 3 Hz, 9 Hz, H8); 5.28 (t, H1'); 4.28–4.09 (m, 2H, H1'); 3.76 (s, H12); 3.47 (s, -OCH₃); 1.67 (d, J = 6 Hz, H10). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 172.3 (C7), 168.1 (C11), 152.8 (C3), 143.5 (C5), 143.1 (C6'), 130.7 (C3), 130.5 (C9), 129.8 (C6), 121.2 (C8'), 116.8 (C7), 115.1 (C4'), 109.0 (C9'), 99.2 (C2'), 65.5 (C11), 56.5 (-OCH₃); 51.8 (C12), 39.2 (C8), 34.6 (C2'), 30.6 (C5), 13.2 (C10).

HRMS (ESI+) m/z calld. for C₉H₁₂NaO₇ [M + Na]+ 415.1363, found 415.13638.

Protocol for the synthesis and isolation of 9 from crude mixture extract (Table 1, entry 2).

To a pressure tube (15 mL, L × OD 10.2 × 25.4 cm, Ref. Z181099-1EA, Aldrich) loaded with Amberlyst® 15 (120 mg, 10% w/w) was added a solution of oleuropein (20 mg, oleuropein content of 15 mg/g) dissolved in dry MeOH (2 mL), was added PTSA (0.381 g, 2.0 mmol) under argon atmosphere. The reaction mixture was stirred at 80°C for 6 h and then neutralized with a sat. aq. sol. of NaHCO₃ followed by solvent evaporation under reduced pressure. The crude residue was dissolved in water (5 mL) and extracted with EtOAc (4 × 15 mL). The combined organic phases were dried with anhydrous Na₂SO₄ and the solvent removed under reduced pressure. The crude mixture was adsorbed in silica (0.5 g) at 40°C for 30 min. under reduced pressure and then purified by flash chromatography column (DCM/EtOAc 3:1) to give 9 as a brown oil, as a mixture of diastereoisomers (10.6 mg, 9%, ratio of 6:2:1); Rᵣ (DCM/EtOAc 3:1) = 0.85; NMR spectra is in agreement with the reported data.[14] Major diastereoisomer – ¹H NMR (300 MHz, CDCl₃) δ (ppm) 9.64 (d, J = 3 Hz, 1H, H8), 7.64 (s, 1H, H3), 4.20 (dd, J = 3 Hz, 6 Hz, 1H, H1'), 3.73 (s, 3H, H14), 3.69 (s, 3H, H16), 3.39 (m, 1H, H10), 2.93 (dd, J = 3 Hz, 18 Hz, 1H, H6), 2.24 (m, 1H, H8), 1.57 (d, J = 6 Hz, 3H, H10); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 199.6 (C8), 171.7 (C11), 167.0 (C7), 156.7 (C3), 106.5 (C4), 69.5 (C1), 51.9 (C15), 51.5 (C14), 50.8 (C9), 38.4 (C6), 28.0 (C5), 17.9 (C10); ESI+ MS – ([M + H] +) = 257 m/z; [M+Na] = 279 m/z.

General procedure for the continuous flow experiments. An empty HPLC column (ID = 4.6 mm, L = 3 mm) was filled with Amberlyst® 15 (for the specific amount used in each experiment, see S1) and equilibrated by injection of methanol (for the specific volume used in each experiment, see S1). Then, the column was submersed in a water bath at 70°C while a solution of 1 (10 mg in 1 mL MeOH) was passed through the reactor at a specific flow using a pump from New Era Pump Systems, Inc. At the end, the column was washed with 1 mL of MeOH to remove the remaining product and the samples were analyzed by HPLC-UV using the conditions described before. For the reuse experiments, the column was washed only after 4 injection of solutions containing 1.

Acknowledgements

The authors acknowledge Fundação para a Ciência e a Tecnologia (FCT) (refs UID/DTP/04138/2013, SFRH/BPD/100433/2014, SFRH/BPD/109470/2015 PD/BD/128316/2017), COMPETE Programme (SAICTPAC/0019/2015) and European Research Area Network; ERANet LAC (ref ELAC2014/BI/F/ 0341) for financial support.

Keywords: biomass • heterogeneous catalysis • homogeneous catalysis • solvolyis • oleuropein


[17] For further details, see Supporting Information.


[19] Gaussian 09 (Revision D.01), M. J. Frisch et al., see Supporting Information.


A new strategy towards valorization of Oleuropein was explored by acid-promoted methanolysis. Tune of the acidity (promoter) and control of the reaction conditions allowed the selective formation of diverse products. This approach was successfully applied to olive leaves crude extract. In addition, continuous flow conditions allowed the selective production of one intermediate in good yield.