Abstract: The acid-promoted methanolysis 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 hydroxyrosyl ester and subsequent intramolecular rearrangement were observed upon identification of the most efficient catalyst and experimental conditions. Furthermore, selected conditions 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 × 10^9 trees worldwide) as a byproduct of the cultivation of Mediterranean native olive trees (Olea europaea) for the production of both olive oil and table olives. Practical applications of these leaves are limited to the use of their extracts for dietetic purposes due to its reported health benefits.

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-flavonols). Recent methodologies for the extraction of Oleuropein include nanofiltration by using imprinted polymers (1.75 g product per kg adsorbent per hour) and solvent-free microwave-assisted extraction (0.06 ppm).

Oleuropein structure can be divided in three subunits – glucoside, monoterpene and hydroxyrosyl (red, black and blue, respectively, Scheme 1). The monoterpene unit is a highly functionalized moiety that includes two esters (including the bond between the hydroxyrosyl 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. These transformations are summarized in Scheme 1, and include selective hydrolysis of the hydroxyrosyl ester (A, Scheme 1); formation of Oleuropein 3 through reduction of both methyl and hydroxyrosyl esters (B, Scheme 1); enzymatic acetal cleavage by β-glucosidase to form either pyridine alkaloid Jasmine (4, C, Scheme 1) or compound 5 (D, Scheme 1), depending on the ammonium salt used; and formation of Oleacein (6) through Krapcho decarbomethoxylation (E, Scheme 1).

The acid treatment of 1 have also been reported using sulphuric acid, anhydrous hydrochloric acid and Erbium(III) trifluoromethanesulfonate (F-H, Scheme 1). In general, complex mixtures of Oleuropein aglycone derivatives are obtained, including Elendol acid (4) and compound 8. Nevertheless, we foresee that cleavage of the β-glucosidic 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 methanolysis 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 methanolysis of a secoiridoid extracted from the plant Fraxinus ornus hydroxynoside containing the same monoterpene subunit of 1. 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.

Currently, 11 is obtained mainly by isolation from the medicinal plant Catharanthus roseus or via bioprocesses.

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® IRC86 and Amberlite™ IR120) and Preysler heteropolyacids (H_3[NaP_5W_20MoO_10] and H_3[NaP_5W_30O_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.

Supporting information for this article is given via a link at the end of the document.
Scheme 1. Synthetic transformations of Oleuropein (1).

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 TfOH (Figure 1C). The use of PTSA and TfOH adsorbed onto silica resulted in general trace formations of TfOH (Figure 1C). The use of PTSA and TfOH adsorbed onto silica resulted in general trace formations of TfOH (Figure 1C).

Remarkably, the most efficient promoter for the formation of (S,S)-9 was Amberlyst® 15, affording 90% of (S,S)-9 after 1 h. Amberlyst® resins were not as efficient as the other acid resin tested (<60% conversion of 1). Finally, both Preyssler heteropolyacids tested proven to be very efficient promoters for the formation of 10 (>86% yield after 23 h). It is noteworthy that deacetylation of 10 was observed upon contact with silica gel under reduced pressure at 40ºC, yielding dimethyl ester 11 as a mixture of diastereoisomers 6:2:2:1 (major isomer is (-)-methyl elenolate 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 80ºC resulted in increased performance of the reaction, resulting in the formation of 10in 59% yield after 2 h. Furthermore, longer reaction times led to lower yields, indicating possible degradation of the product.

Figure 1. Reaction progress profiles (A: (S,S)-9; B: (S,R)-9; C: 10) for the methanolysis of 1 using different promoters. All reactions were conducted using 20 mg of 1, 2 mmol of acid (1 M) in dry MeOH (2 mL) at 70ºC under argon atmosphere and the yields determined by HPLC-UV analysis.
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.[18] DFT calculations performed at ωB97X-D/def2-TZVPP/SMD(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.[18] 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 transesterification 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)[19] 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%.

![Scheme 2](image)

**Scheme 2.** Proposed mechanism for the acid-promoted methanolysis of 1.

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 monoterpene-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.

![Figure 2](image)

**Figure 2.** Methanolysis of 1 under continuous flow using Amberlyst® 15.

| Entry | Substrate | Promoter | t (h) | Major product | Yield |
|-------|-----------|----------|-------|---------------|-------|
| 1     | 1         | Amberlyst® 15 | 31 mg/g crude | (S,S)-9 | Quantitative[^3] |
| 2     | Crude     | Amberlyst® 15 | 1      | (S,S)-9 | 53 mg/g crude[^3] |
| 3     | 1         | NaH2O2/PtO2 | 12     | 10 | 68% |
| 4     | Crude     | PTSA     | 23     | 10 | 31 mg/g crude[^4] |

[^1]: All the reactions were carried out in a pressure tube at 70°C. For the specific reaction conditions see experimental section.[^2]: Mixture of isomers (S,S)-9/(S,R)-9 1:0.2, determined by 1H NMR.[^3]: 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 methanolation. 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 (-)-methyl elenolate 11. In addition, both 10 and 9 can be obtained in high yield from the crude extract of olive leaves. We also demonstrated the viability of a continuous flow approach towards the fast and facile production of (S,S)-9 in good yields. Both synthesized compounds 9 and 10 possess very appealing structures, as chiral synthons due to the presence of several chiral centers and potential reactive sites that would be difficult to obtain by other ways. Thus, the identified products are foreseen as a potential versatile building block platform for the synthesis of promising novel scaffolds.

Experimental Section

General Information. All solvents were distilled from commercial grade sources. Anhydrous solvents were prepared according to usual procedures. Chemicals were obtained from commercial sources and used without further purification: Acetyl chloride (Merk. Ref 1.00031, KP56353), p-Toluene sulfonic acid monohydrate (PTSA, Fluka, 89762-1kg, 1372419), Triflic acid (TOH, Fluka 91738-50mL, 1297369), Trifluoroacetic acid (TFA, Alfa, A12198-500g, 10202568), Amberlyst® 15 dry (Aldrich, 216399-500g, MBK7833V), Amberlyst® 16 wet (Fluka, 88317-250g, BCB5787V), Amberlyst® 36 wet (Aldrich, 43762-250g, 11605SEJv), Amberlite® IRC86 (Fluka, 05455-250g, BCB1822V) and Amberlite® IR120 (Aldrich, 10322, 45049V). HCl was prepared in situ by reaction of acetyl chloride and dry MeOH. Olive leaves from Olea europaea were collected from different regions in Portugal, over the year. They were dried at room temperature under atmospheric conditions. The NMR spectra were recorded at 300 MHz (1H) and 100 MHz (13C) in a Bruker Fourier 300 spectrometer. The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Hα and Hβ refer to geminal protons.

HPLC analysis were performed on a Thermo Scientific Dionex Ultimate 3000 apparatus with a LPG -3400SD Pump, a UV MWD -3000 (RS) apparatus with a LPG -3400SD Pump, a UV MWD -3000(RS) detector and an autosampler ACC-3000, equipped with a 20 µL loop, using a reversed-phase EC 250/4 Guardian 100-5 C18sec column (250x4 mm; 5 µm) Thermo Scientific Dionex®. The following conditions were used to analyse the reaction mixtures: A mixture of (A) H2O/1% TFA and (B) ACN/1% TFA was used as mobile phase in a LC-MS (ES+): m/z cald. for C25H32NaO13 [M+Na]+ 563.17406, [M+Cl]- = 575.13605. General procedure for the methanolation 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 (2mmol, 1 M). The resulting reaction mixture was stirred at 70°C (or 60°C and 80°C 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 µL) at specific time and diluted them in HPLC grade acetonitrile to 0.4 mM concentration.

Protocol for the synthesis and isolation of 9 (Table 1, entry 1). Amberlyst® 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

Preparation of Preyssler heteropolyacids H2[Nα1Pγ9Wδ9O45] and H2[Nα1Pγ9Wδ9MoO45]. The Preyssler salt, K8[Nα1Pγ9Wδ9O45]nH2O, was prepared from Na2W2O7·2H2O according to a reported method. In a typical experiment, Na2W2O7·2H2O (30 g, 0.09 mol) was dissolved in boiling water (20 mL), and concentrated phosphoric acid (H3PO4) was poured carefully into the solution (27 g, 0.27 mol). Then, the mixture was refluxed for 24 h, and concentrated nitric acid (1 mol) was added to the solution. Preyssler salt was precipitated by adding KCl (10 g, 0.13 mol). The K8[Nα1Pγ9Wδ9O45]nH2O was converted to the corresponding acid H2[Nα1Pγ9Wδ9O45] by passing it through a Dowex-50WX-8 ion exchange column. This article is protected by copyright. All rights reserved.
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 \times 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 1:2.0). R₁ (DCM/MeOH 9:1) = 0.77.

Major (S,R)-¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.53 (s, 1H, H₁), 4.41 (d, J = 3 Hz, 1H, H₈), 4.21–4.11 (m, 2H, H₇), 3.68 (s, 3H, H₁₅), 3.67 (s, 3H, H₁₄), 3.36 (s, 3H, -OCH₃), 3.34 (s, 3H, -OCH₂), 3.28–3.19 (m, 2H, H₅), 2.63 (dd, J = 3 Hz, 15 Hz, 1H, H₁₆), 2.38 (dd, J = 3 Hz, 15 Hz, 1H, H₆), 1.93–1.87 (m, 1H, H₉), 1.39 (d, J = 6 Hz, 3H, H₁₀).¹3C NMR (100 MHz, CDCl₃) δ (ppm) 173.2 (C₁₇), 172.4 (C₁₄), 156.3 (C₃), 109.0 (C₄), 106.1 (C₈), 71.5 (C₁₅), 55.7 (C₁₂), 54.3 (C₁₃), 51.8 (C₁₄), 51.6 (C₁₅), 43.6 (C₉), 37.3 (C₆), 28.8 (C₅), 19.5 (C₂), 13.5 (C₁₀).

Minor (S,S)-¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.54 (s, 1H, H₁), 4.40 (d, J = 3 Hz, 1H, H₈), 4.21–4.11 (m, 2H, H₇), 3.68 (s, 3H, H₁₅), 3.67 (s, 3H, H₁₄), 3.37 (s, 3H, -OCH₃), 3.34 (s, 3H, -OCH₂), 3.28–3.19 (m, 2H, H₅), 2.63 (dd, J = 3 Hz, 15 Hz, 1H, H₁₆), 2.38 (dd, J = 3 Hz, 15 Hz, 1H, H₆), 1.93–1.87 (m, 1H, H₉), 1.39 (d, J = 6 Hz, 3H, H₁₀).¹3C NMR (100 MHz, CDCl₃) δ (ppm) 173.2 (C₁₇), 172.4 (C₁₄), 156.3 (C₃), 109.0 (C₄), 106.1 (C₈), 71.5 (C₁₅), 55.7 (C₁₂), 54.3 (C₁₃), 51.8 (C₁₄), 51.6 (C₁₅), 43.6 (C₉), 37.3 (C₆), 28.8 (C₅), 19.5 (C₂), 13.5 (C₁₀).

Protocol for the synthesis of 9 from crude mixture extract (Table 1, entry 2). To a pressure tube (15 mL, L \times OD 10.2 \times 25.4 cm, Ref. Z181099-1EA, Aldrich) equipped with a condenser and containing 1 (251 g, 0.5 mmol) dissolved in dry MeOH (25 mL), was added PTSA (4.75 g, 25 mmol, 1 M) 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 \times 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 11 as a brown oil, as a mixture of diastereoisomers (10.6 mg, 9%, ratio of 6:2:2:1). R₁ (DCM/MeOH 3:1) = 0.85. NMR spectra is in agreement with the reported data.¹[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 (d, J = 3 Hz, 6H, 1H, H₁), 3.73 (s, 3H, H₁₄), 3.69 (s, 3H, H₁₆), 3.39 (m, 1H, H₅), 2.93 (dd, J = 3 Hz, 18 Hz, 1H, H₁₆), 2.64 (m, 1H, H₈), 2.25 (dd, J = 12 Hz, 18 Hz, 1H, H₆), 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 (C₈), 38.4 (C₆), 28.0 (C₅), 17.9 (C₁₀). ESI-MS (+) m/z [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.

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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.