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# Valorization of Oleuropein Via Tunable Acid-Promoted Methanolysis

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**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 hydroxytyrosol 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 × $10^8$ trees worldwide)[1] 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).[4] Recent methodologies for the extraction of Oleuropein include nanofiltration by using imprinted polymers (1.75 g product per kg of 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 functionalized 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 Oleacein (**6**) through Krapcho decarbomethoxylation (E, Scheme 1)[13].

The acid treatment of **1** have also been reported using sulphuric acid, 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 methanolysis could result in the creation of a diverse chemical platform, comprising **9** and **10** (I, 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* 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 Brønsted acids (HCl, *p*-toluenesulfonic acid (PTSA), triflic acid (TfOH), trifluoroacetic acid (TFA), acid ion-exchange resins (Amberlyst® 15, Amberlyst® 16, Amberlyst® 36, Amberlite® IRC86 and Amberlite® IR120) and Preyssler heteropolyacids ($H_{14}[NaP_5W_{29}MoO_{110}]$ and $H_{14}[NaP_5W_{30}O_{110}]$), as catalysts for the methanolysis of **1** at 70ºC. 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 TfOH or PTSA.[18]

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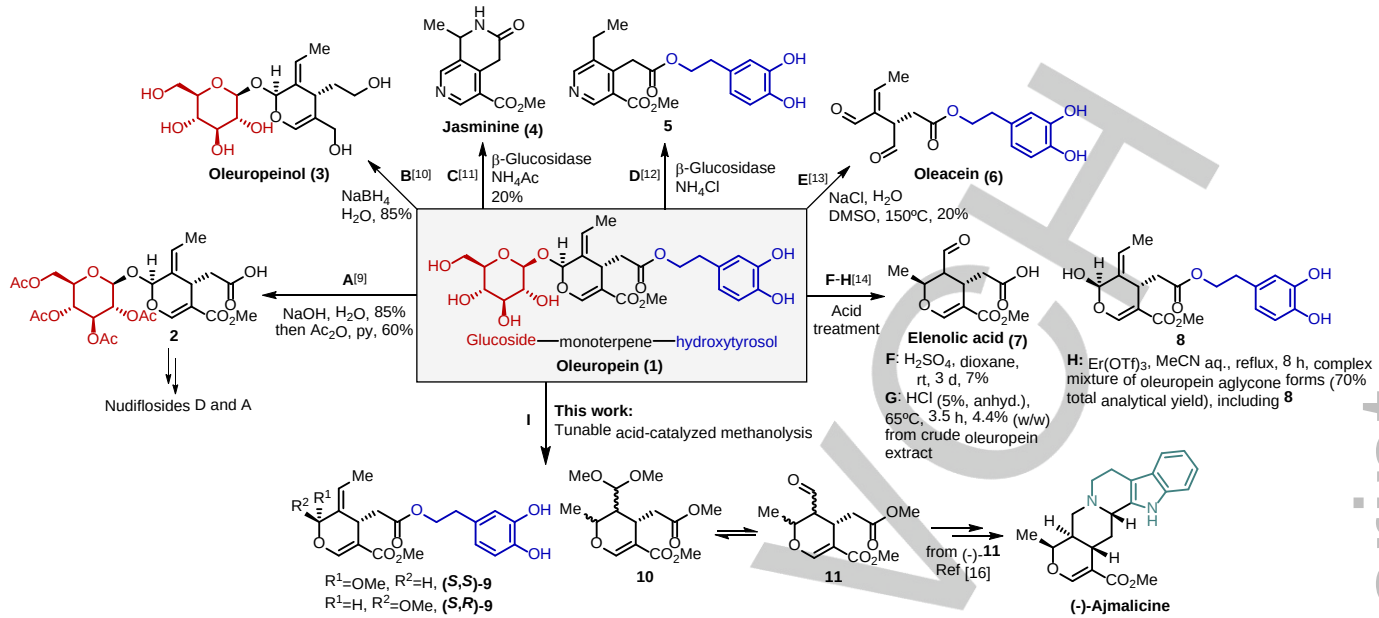



**Scheme 1.** Synthetic transformations of Oleuropein (**1**).

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 **(*S*,*R*)-9** and **10**, however, formation of **(*S*,*S*)-9** was not drastically affected. Remarkably, the most efficient promoter for the formation of **(*S*,*S*)-9** was Amberlyst® 15, affording 90% of **(*S*,*S*)-9** after 1 h. Amberlite® resins were not as efficient as the other acid resin tested (<60% conversion of **1**).[18] 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 deacetalization 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**).[18] 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 **10** in 59% yield after 2 h.[18] Furthermore, longer reaction times led to lower yields, indicating possible degradation of the product.

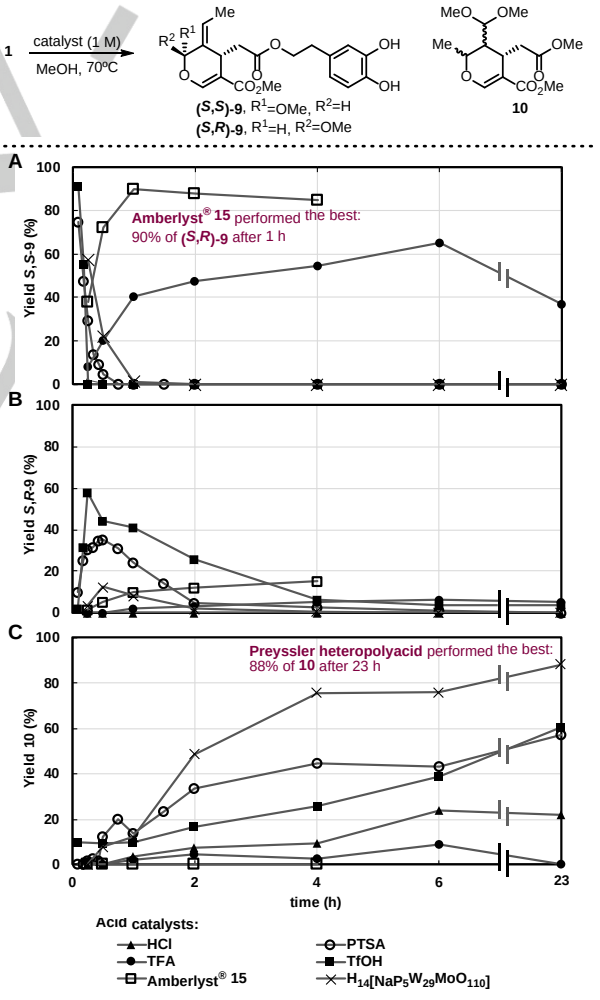
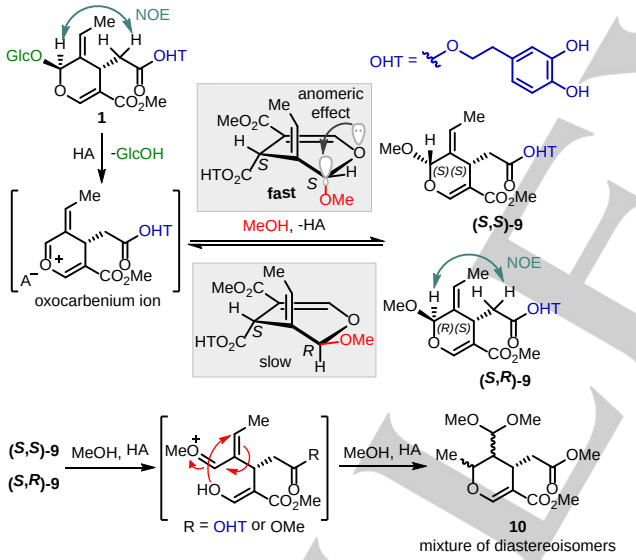



**Figure 1.** Reaction progress profiles (A: **(*S*,*S*)-9**; B: **(*S*,*R*)-9**; C: **10**) for the methanolysis of **1** using different promoters. All reactions were conducted using 20 mg of **1**, 2 mmol of acid (1 M) in dry MeOH (2 mL) at 70ºC under argon atmosphere and the yields determined by 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** occur 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**.




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

As compound **(*S*,*S*)-9** is not stable under this 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)[18] 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%.

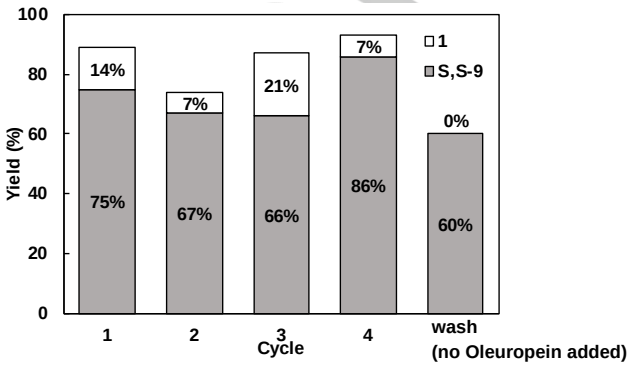



**Figure 2.** Methanolysis of **1** under continuous flow using Amberlyst® 15.

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.

**Table 1.** Acid-promoted methanolysis of crude mixture extract containing **1**.[a]

| Entry | Substrate | Promoter | t (h) | Major product | Yield |
|---|---|---|---|---|---|
| 1 | **1** | Amberlyst® 15 | 1 | **(*S*,*S*)-9** | Quantitative[b] |
| 2 | Crude | Amberlyst® 15 | 1 | **(*S*,*S*)-9** | 53 mg/g crude[b] |
| 3 | **1** | $H_{14}[NaP_5W_{29}MoO_{110}]$ | 12 | **10** | 68% |
| 4 | Crude | PTSA | 23 | **10** | 31 mg/g of crude[c] |

[a] All the reactions were carried out in a pressure tube at 70ºC. For the specific reaction conditions see experimental section. [b] Mixture of isomers **(*S*,*S*)-9**/**(*S*,*R*)-9** 1:0.2, determined by $^1$H NMR. [c] 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 (-)-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.[19] Chemicals were obtained from commercial sources and used without further purification: Acetyl chloride (Merk. Ref 1.00031, KP56353), *p*-Toluenesulfonic acid monohydrate (PTSA, Fluka, 89762-1kg, 1372419), Triflic acid (TfOH, Fluka 91738-50ml, 1297369), Trifluoroacetic acid (TFA, Alfa, A12198-500g, 10202568), Amberlyst® 15 dry (Aldrich, 216399-500g, MKBR7383V), Amberlyst® 16 wet (Fluka, 86317-250g, BCBKS787V), Amberlyst® 36 wet (Aldrich, 436712-250g, 11605EJV), Amberlite® IRC86 (Fluka, 06455-250g, BCBL1928V) and Amberlite® IRC120 (Aldrich, 10322, 45094V). 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 ($^1$H) and 100 MHz ($^{13}$C) 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). $H_a$ and $H_b$ 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) detector and an autosampler ACC-3000, equipped with a 20 $\mu$L loop, using a reversed-phase EC 250/4 Nucleodur 100-5 C18ec column (250×4 mm; 5 $\mu$m) Thermo Scientific™ Dionex™. The following conditions were used to analysis the reaction mixtures: A mixture of (A) $H_2O$/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); 35% B – 75% B (25-45 min), recorded at 230 nm. The retention times of **1**, **(*S*,*S*)-9**, **(*S*,*R*)-9**, and **10** were 20.6 min, 34.6 min, 34.4 min and 32.1 min, respectively.

TLC analysis were performed in silica gel 60 $F_{254}$ plates (HX69787354). Purifications were performed using silica gel 60A (P2050017, Carlo Erba) and (TA2045967, Merck) for flash column chromatography (using automated system Combi Flash® Rf Teledyne Isco) and preparative TLC purifications, respectively.

ESI MS spectra were carried out on an ion trap mass analyzer (Thermo Scientific LCQ Fleet Ion Trap LC/MS) equipped with an electrospray interface. Pro Mass for Xcalibur (Version 2.8) was used as software. HRMS were carried out on an Orbitrap Thermo Scientific apparatus.

Density functional theory (DFT) calculations were performed with Gaussian 09[20] at ωB97X-D/def2-TZVPP/SMD(Methanol)//B3LYP/6-31G(d) level of theory.[18]

**Preparation of Preyssler heteropolyacids $H_{14}[NaP_5W_{30}O_{110}]$ and $H_{14}[NaP_5W_{29}MoO_{110}]$.** The Preyssler salt, $K_{14}[NaP_5W_{30}O_{110}]\cdot nH_2O$, was prepared from $Na_2WO_4\cdot 2H_2O$ according to a reported method.[21] In a typical experiment, $Na_2WO_4\cdot 2H_2O$ (30 g, 0.09 mol) was dissolved in boiling water (20 mL), and concentrated phosphoric acid ($H_3PO_4$) 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. Preyssler salt was precipitated by adding KCl (10 g, 0.13 mol). The $K_{14}[NaP_5W_{30}O_{110}]\cdot nH_2O$ was converted to the corresponding acid $H_{14}[NaP_5W_{30}O_{110}]$ by passing it through a Dowex-50W-X8 ion exchange column.

The Preyssler heteropolyacid $H_{14}[NaP_5W_{29}MoO_{110}]$ was synthesized following a literature method.[21-22] The method was similar to that of $H_{14}[NaP_5W_{30}O_{110}]$. Briefly, $Na_2WO_4\cdot 2H_2O$ (23 g, 0.07 mol) and $Na_2MoO_4\cdot 2H_2O$ (2 g, 8.3 mmol) were dissolved in water (20 mL) and mixed at 333 K for 30 min. Then, $H_3PO_4$ (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 $K_{14}[NaP_5W_{29}MoO_{110}]$, this salt was converted to its corresponding acid $H_{14}[NaP_5W_{29}MoO_{110}]$, by passing it through a column filled with Dowex50W-X8 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[14b] 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. $R_f$ (DCM/MeOH 9:1) = 0.49; (reported $R_f$ (DCM/MeOH 8:1) = 0.5)[12a]). NMR spectra of **1** are in agreement with reported data.[13]

**$^1$H NMR (300 MHz, $CD_3OD$) δ (ppm)** 7.52 (s, 1H, *H3*), 6.72–6.67 (m, 2H, *H7'*, *H4'*), 6.56 (dd, *J* = 8.0, 1.8 Hz, 1H, *H8'*), 6.09 (q, *J* = 6.9 Hz, 1H, *H8*), 5.92 (s, 1H, *H1*), 4.73 (d, *J* = 7.6 Hz, 1H, *H1''*), 4.26– 4.08 (m, 2H, *$H_a$1'*, *$H_b$1'*), 3.99 (dd, *J* = 9.0, 4.4 Hz, 1H, *H5*), 3.90 (d, *J* = 12.1 Hz, 1H, *$H_a$6''*), 3.72 (s, 3H, *H12*), 3.70–3.66 (m, 1H, *$H_b$6''*), 3.33–3.30 (m, 4H, *H2''*, *H3''*, *H4''*, *H5''*), 2.80–2.69 (m, 3H, *H2'*, *$H_a$6*), 2.46 (dd, *J* = 14.1, 9.1 Hz, 1H, *$H_b$6*), 1.68 (d, *J* = 7.0, 3H, *H10*); **$^{13}$C NMR (100 MHz, $CD_3OD$) δ (ppm)** 173.2 (*C7*), 168.7 (*C11*), 155.2 (*C3*), 146.2 (*C5'*), 144.9 (*C6'*), 130.7 (*C9*), 130.5 (*C3'*), 124.7 (*C8*) 121.3 (*C8'*), 117.1 (*C4'*), 116.4 (*C7'*), 109.4 (*C4*), 100.9 (*C1''*), 95.1 (*C1*), 78.4 (*C3''*), 77.9 (*C5''*), 74.8 (*C2''*), 71.5 (*C4''*), 66.9 (*C1'*), 62.7 (*C6''*), 51.9 (*C12*), 41.3 (*C6*), 35.4 (*C2'*), 31.8 (*C5*), 13.6 (*C10*); **LC-MS (ESI+):** *m/z* cald. for $C_{25}H_{32}NaO_{13}$ $[M+Na]^+$ 563.17406, found 563; ESI (-): $[M-H]^-$ = 539 *m/z*; $[M+Cl]^-$ = 575 *m/z*.

**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 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

stirred at 70ºC for 1 h. The resin was removed by filtration, and the reaction was diluted in water (20 mL) and extracted with DCM (20 mL × 3). The combined organic phases were dried with anhydrous $Na_2SO_4$ 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). $R_f$ (DCM/MeOH 9:1) = 0.77.

*Major* (*S,R*)- **$^1$H NMR (300 MHz, $CDCl_3$) 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, *H1*), 4.28–4.09 (m, 2H, *H1'*), 3.87 (dd, *J* = 3 Hz, 9 Hz, 1H, *H5*), 3.78 (s, 3H, H*12*), 3.44 (s, 3H, -OC$H_3$), 2.90–2.75 (m, 6H, $H_a$*6*, *H2'*), 2.71–2.65 (m, 2H, $H_b$*6*), 1.58 (d, *J* = 9 Hz, 3H, *H10*); **$^{13}$C NMR (100 MHz, $CDCl_3$) 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 (C8), 121.3 (C8'), 117.1 (C7'), 115.0 (C4'), 108.7 (C4), 104.8 (C1), 65.2 (C1'), 56.3 (-OC$H_3$), 51.9 (C12), 38.7 (C6), 34.3 (C2'), 28.7 (C5), 13.3 (C10).

*Minor* (*S,S*) - **$^1$H NMR (300 MHz, $CDCl_3$) δ (ppm)** 7.50 (s, *H3*); 6.98 (d, *J* = 2 Hz, *H7'*); 6.79 (d, *J* = 9 Hz, *H4'*); 6.00 (dq, *J* = 3 Hz, 9 Hz, *H8*); 5.28 (t, *H1*); 4.28–4.09 (m, 2H, *H1'*); 4.01 (dd, *J* = 3 Hz, 9 Hz, *H5*); 3.76 (s, *H12*); 3.47 (s, -OC$H_3$); 1.67 (d, *J* = 6 Hz, *H10*); **$^{13}$C NMR (100 MHz$CDCl_3$) δ (ppm)** 172.3 (*C7*), 168.1 (*C11*), 152.8 (*C3*), 143.2 (*C5'*), 143.1 (*C6'*), 130.7 (*C3'*), 130.5 (*C9*), 129.3 (*C8*), 121.2 (*C8'*), 116.8 (*C7'*), 115.1 (*C4'*), 109.0 (*C4*), 99.2 (*C1*), 65.5 (*C1'*), 56.5 (-OC$H_3$), 51.8 (*C12*), 39.2 (*C6*), 34.6 (*C2'*), 30.6 (*C5*), 13.2 (*C10*).

**HRMS** (ESI+) *m/z* cald. for $C_{20}H_{24}NaO_8$ $[M + Na]^+$ 415.13634, 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 crude extract from leaves (1.2 g) dissolved in dry MeOH (5 mL). The reaction was allowed to stir at 70ºC for 1 h. The resin was removed by filtration, and the reaction was diluted in water (20 mL) and extracted with DCM (20 mL × 3). The combined organic phases were dried with anhydrous $Na_2SO_4$ and the solvent was removed under reduced pressure to afford **9** (64 mg, 53 mg/g crude) as a mixture of diastereoisomers (**(S,S)-9/(S,R)-9** 1:0.2). $R_f$ (DCM/MeOH 9:1) = 0.77.

**Protocol for the synthesis and isolation of 10 (Table 1, entry 3).** To a pressure tube (15 mL, L×OD 10.2×25.4 cm, Ref. Z181099-1EA Aldrich) was added a solution of **1** (40 mg, 0.074 mmol) in MeOH (4 mL). Then, $H_{14}[NaP_5W_{29}MoO_{110}]$ (2 g) was added and the reaction was stirred at 70ºC for 12 h. The catalyst was precipitated by addition of diethyl ether (20 mL) and the catalyst removed by filtration. The crude reaction was washed with water (10 mL × 2) and the organic phase was dried with anhydrous $Na_2SO_4$ and the solvent removed under reduced pressure to give a crude residue containing **10** and hydroxytyrosol (83% yield, 34 mg, 1:1 mixture of **10**/hydroxytyrosol, *i.e.*, 22 mg of **10** and 12 mg of hydroxytyrosol). The crude residue was passed through a pad of silica (Hex/EtOAc 8:2) to give pure **10** as a brown oil (19 mg, 68% yield). $R_f$ (DCM/MeOH - 9:1) = 0.88. NMR spectra of **10** are in agreement with the reported data.[15]

*Major* – **$^1$H NMR (300 MHz, $CDCl_3$) δ (ppm)** 7.53 (s, 1H, *H3*), 4.41 (d, *J* = 3 Hz, 1H, *H8*), 4.21–4.11 (m, 2H, *H1*), 3.68 (s, 3H, *H15*), 3.67 (s, 3H, *H14*), 3.36 (s, 3H, -OC$H_3$), 3.34 (s, 3H, -OC$H_3$), 3.28–3.19 (m, 2H, *H5*), 2.63 (dd, *J* = 3 Hz, 15 Hz, 1H, $H_a$*6*), 2.38 (dd, *J* = 3 Hz, 15 Hz, 1H, $H_b$*6*), 1.93–1.87 (m, 1H, *H9*), 1.39 (d, *J* = 6 Hz, 3H, *H10*), **$^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm)** 173.2 (*C7*), 172.4 (*C11*), 156.3 (*C3*), 109.0 (*C4*), 106.1 (*C8*), 71.5 (*C1*), 55.7 (*C12*), 54,3 (*C13*), 51.8 (*C14*), 51.6 (*C15*), 43.6 (*C9*), 37.3 (*C6*), 28.8 (*C5*), 19.5 (*C10*).

*Minor* - **$^1$H NMR (300 MHz, $CDCl_3$) δ (ppm)** 7.58 (s, 1H, *H3*); 4.28 (d, *J* = 9 Hz, 1H, *H8*); 4.21–4.11 (m, 2H, *H1*); 3,70 (s, 3H, *H14*); 3.69 (s, 3H, *H15*); 3.31 (d, *J* = 3 Hz, 6H, -OC$H_3$); 3,28–3,19 (m, 2H, *H5*); 2.82 (dd, *J* = 9 Hz, 18 Hz, 1H, $H_a$*6*); 2.23 (dd, *J* = 9 Hz, 18 Hz, 1H, $H_b$*6*); 1.98 (dt, *J* = 3 Hz, 9 Hz, 1H, *H9*); 1.43 (d, *J* = 9 Hz, 3H, H10) ppm; **$^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm)** 167.7 (*C7*), 167.6 (*C11*), 155.2 (*C3*), 107.6 (*C4*), 101.5 (*C8*), 71.1 (*C1*), 55.4 (*C12*), 51.6 (*C13*), 51.4 (*C14*), 51.3 (*C15*), 41.2 (*C9*), 39.7 (*C6*), 29.1 (*C5*), 18.8 (*C10*).

**HRMS** (ESI+) *m/z* cald. for $C_{14}H_{22}NaO_7$ $[M + Na]^+$ 325.12577, found 325.12573.

**Protocol for the synthesis of 10 from crude mixture extract (Table 1, entry 1).** To a pressure tube (15 mL, L × OD 10.2 × 25.4 cm, Ref. Z181099-1EA, Aldrich) with crude extract from leaves (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 70ºC in a GC oven and the progress analyzed by HPLC-UV as described before. The analytic yield of product **10** after 23 h was 31 mg/g of crude.

**Protocol for the synthesis and isolation of 11.** To a round bottom flask equipped with a condenser and containing **1** (0.251 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 80ºC for 6 h and then neutralized with a sat. aq. sol. of $NaHCO_3$, followed by solvent evaporation under reduced pressure. The obtained crude residue was dissolved in water (5 mL) was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried with anhydrous $Na_2SO_4$ and the solvent removed under reduced pressure. The crude mixture was adsorbed in silica (0.5 g) at 40ºC 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); $R_f$ (DCM/EtOAc 3:1) = 0.85; NMR spectra is in agreement with the reported data.[14a]

*Major diastereoisomer* – **$^1$H NMR (300 MHz, $CDCl_3$) δ (ppm)** 9.64 (d, *J* = 3 Hz, 1H, *H8*), 7.64 (s, 1H, *H3*), 4.20 (dq, *J* = 3 Hz, 6 Hz, 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, $H_a$*6*), 2.64 (m, 1H, *H9*), 2.25 (dd, *J* = 12 Hz, 18 Hz, 1H, $H_b$*6*), 1.57 (d, *J* = 6 Hz, 3H, *H10*); **$^{13}$C NMR (100 MHz, $CDCl_3$) 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 SI) and equilibrated by injection of methanol (for the specific volume used in each experiment, see SI). Then, the column was submersed in a water bath at 70ºC 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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**Keywords:** biomass • heterogeneous catalysis • homogeneous catalysis • solvolysis • oleuropein

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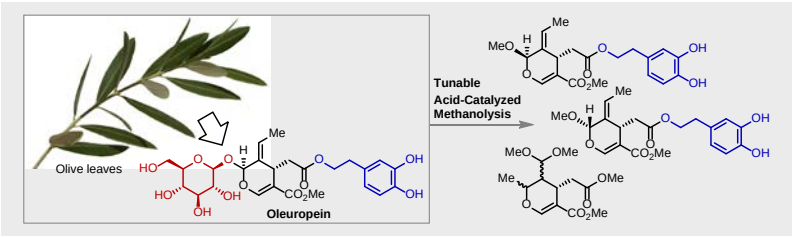
**Entry for the Table of Contents**

Layout 2:

COMMUNICATION




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.

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**Valorization of Oleuropein Via Tunable Acid-Promoted Methanolysis**