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The total synthesis of chrysophanol and aloesaponarin II, anthraquinone natural products from bio-renewable cashew nut shell liquid-derived phenolics

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Dedicated to our friend and colleague Professor HG Schmalz (Hagga). Thank you for your contributions to chemistry and to the South African chemistry community.

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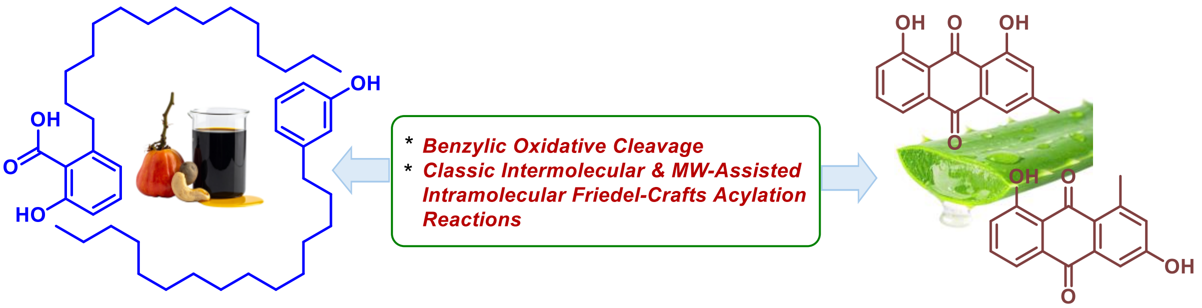
Abstract

The valorization of bio-renewable feedstocks provides a sustainable pathway for the synthesis of high-value natural products. Here, we report the total synthesis of the anthraquinone natural products chrysophanol and aloesaponarin II from cashew nut shell liquid (CNSL)-derived phenolics. Cardanol was converted to *m*-cresol, which underwent a classic Friedel-Crafts acylation reaction with 3-methoxyphthalic anhydride prepared from anacardic acids to furnish 3-hydroxy-2-(2-hydroxy-4-methylbenzoyl)benzoic acid and 3-hydroxy-2-(4-hydroxy-2-methylbenzoyl)benzoic acid in a single step. The acids were individually cyclized via novel microwave-assisted intramolecular Friedel–Crafts acylation reactions to afford chrysophanol and aloesaponarin II in 30% overall yields. This work demonstrates the utility of CNSL phenolics as versatile precursors for constructing natural products.



Keywords: Bio-renewable, anthraquinones, cardanol, anacardic acid, natural products

Introduction

The growing emphasis on sustainable chemistry has spurred significant interest in bio-renewable feedstocks as viable alternatives to petroleum-derived resources in organic synthesis.[1,2] Among these, agricultural waste streams represent an abundant, low-cost, and environmentally benign source of starting materials.[3,4] Such feedstocks containing chemical building blocks can, in theory, be transformed into structurally complex and biologically active natural products, including anthraquinones.

Anthraquinones **1** are tricyclic aromatic compounds forming an important subclass of the quinone family, particularly within the polyketide group.[5,6] First discovered serendipitously in antiquity, these compounds were originally isolated from plants, fungi, and lichens and valued in ancient Chinese, Indian, and Mediterranean cultures for their vivid pigments and medicinal properties.[7-10] As illustrated in Figure 1, several anthraquinone-derived natural products such as rhein (**2**), danthron (**3**), chrysophanol (**4**), aloesaponarin II (**5**), and aloe-emodin (**6**) have been the focus of extensive studies. In recent years, these compounds have attracted attention as potential anti-SARS-CoV-2 agents[11], while ongoing investigations continue to reveal their broad therapeutic relevance, including anticancer, anti-inflammatory, anti-tumor, and antioxidant activities.[12,13]

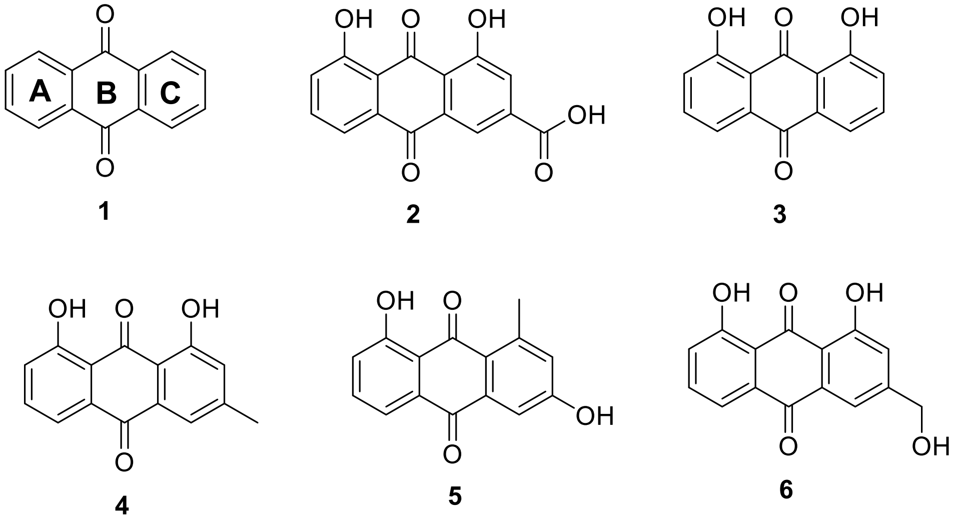


Figure 1. Chemical structure of the anthraquinone framework and naturally occurring anthraquinones.

Owing to their broad spectrum of biological activities, anthraquinones have long been a focal point in the development of new synthetic methodologies. Their synthesis has been traditionally accomplished through cyclization strategies such as the Friedel-Crafts acylation of phthalic anhydrides with benzene derivatives or of aromatic benzoyl derivatives,[14-16] the Diels-Alder reaction of juglone with dienes,[17-18] the Hauser annulation reaction[19-20] and transition metals-mediated cyclization reactions,[21] among others. Although these approaches are well established, they are often hampered by significant drawbacks, including modest yields, long reaction times and the formation of intractable by-products.[22] A more fundamental limitation is their dependence on fossil fuel-derived precursors, which undermines their long-term sustainability.[23,24] The finite nature of fossil fuel reserves, combined with the well-documented role of their extraction and consumption, is driving environmental change, particularly global warming.[25] Hence, there is a pressing need to design synthetic routes that rely on bio-renewable resources. In this context, cashew nut shell liquid (CNSL) has emerged as a promising agricultural waste feedstock. Its phenolic constituents, mainly including anacardic acids (**7**), cardanols (**8**), and cardols (**9**), shown in Figure 2, offer versatile and sustainable building blocks for the synthesis of key organic intermediates.[26-29-20]

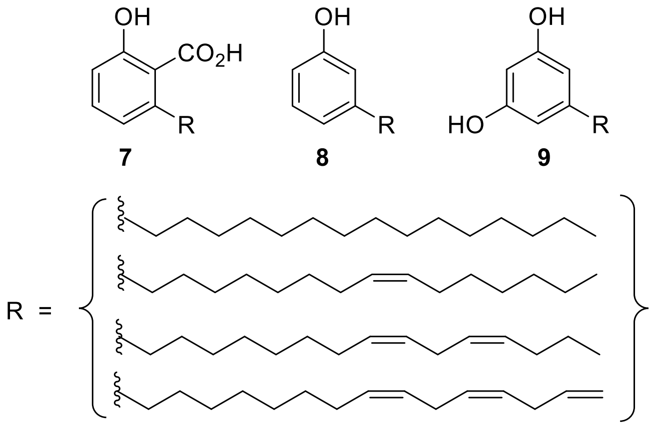
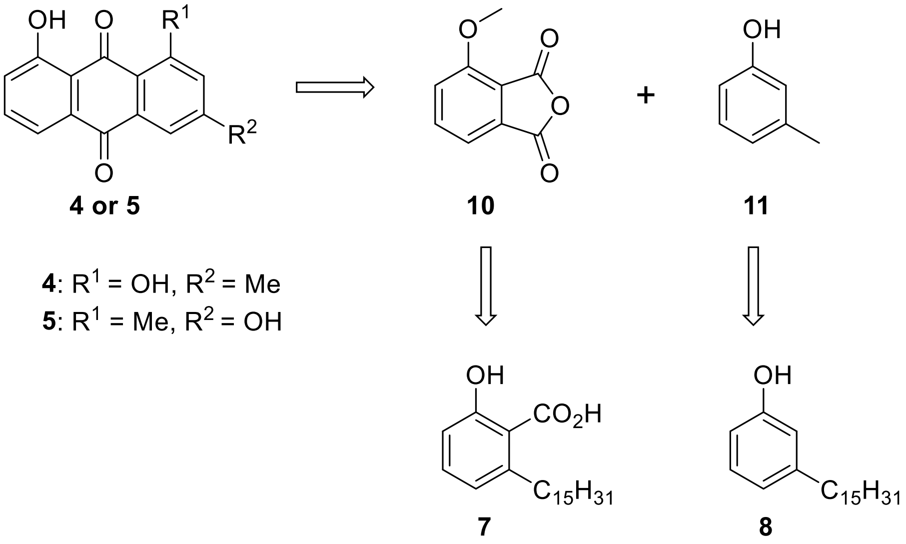


Figure 2. Cashew nut shell liquid-derived constituents.

Our group has previously showcased the versatility of CNSL phenolics in synthesizing various classes of UV filters.[30,31] Expanding on this work, we now report, for the first time, a novel bio-based strategy for the total synthesis of the anthraquinone natural products chrysophanol (**4**) and aloesaponarin II (**5**) using CNSL-derived anacardic acids and hydrogenated cardanol. This approach provides a sustainable route to these valuable compounds, contributing to the reduction of fossil fuel dependence in organic synthesis.

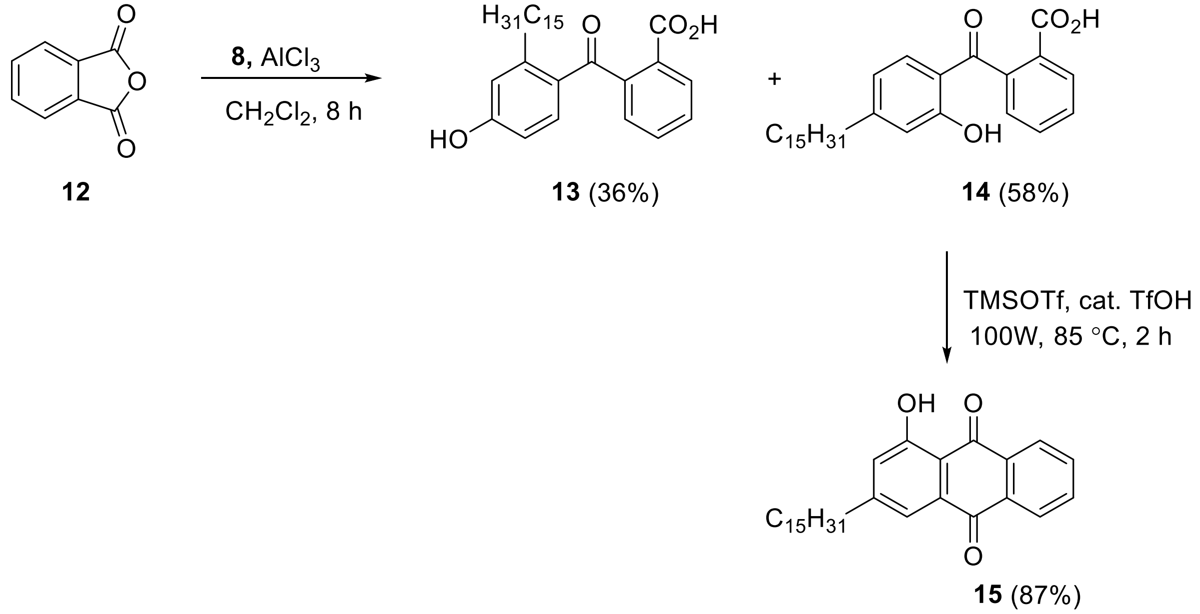
Results and Discussion

We envisaged that the anthraquinone natural products **4** and **5** could be accessed through Friedel-Crafts acylation reactions of phthalic anhydride (**10**), prepared from anacardic acids (**7**) and *m*-cresol (**11**) assembled from hydrogenated cardanol (**8**), as exhibited in Scheme 1.



Scheme 1. Retrosynthetic strategy for chyrosophanol (**4**) and aloesaponarin II (**5**).

Before synthesizing the anthraquinones, we validated our anthraquinone synthetic strategy using commercially available phthalic anhydride (**12**) and hydrogenated cardanol (**8**)**,** as shown in Scheme 2. Applying a method similar to Ullman and Schmidt's classical $AlCl_3$-promoted Friedel-Crafts acylation of phenols,[32] a reaction between **12** and **8** yielded *ortho* and *para* hydroxy benzophenone regioisomers **13** and **14** in 36% and 58% yields, respectively. The isolation of the *O*-acylated intermediate at lower temperatures suggests that some of the *C*-acylated products may have formed via a Fries rearrangement mechanism. Further investigation is, however, required to verify the feasibility of this reaction pathway under the present reaction conditions. It is worth noting that dichloromethane, although hazardous, was used as the solvent for this reaction because it uniquely provided homogenous dissolution of both the aromatic substrate and Lewis acid catalyst, facilitating efficient complexation. Its performance was superior to that of other solvents tested (see attached supplementary information). To enhance the environmental and safety profile of this reaction, future optimization efforts will explore safer solvent alternatives, such as benzotrifluoride and hexafluoro-2-propanol, both of which have demonstrated utility in facilitating Friedel-Crafts-type reactions.[33,34] Under microwave irradiation and using TMSOTf and a catalytic amount of TfOH as optimized conditions, an intramolecular Friedel-Crafts acylation reaction of **14** efficiently furnished the desired anthraquinone **15** in 87% yield.

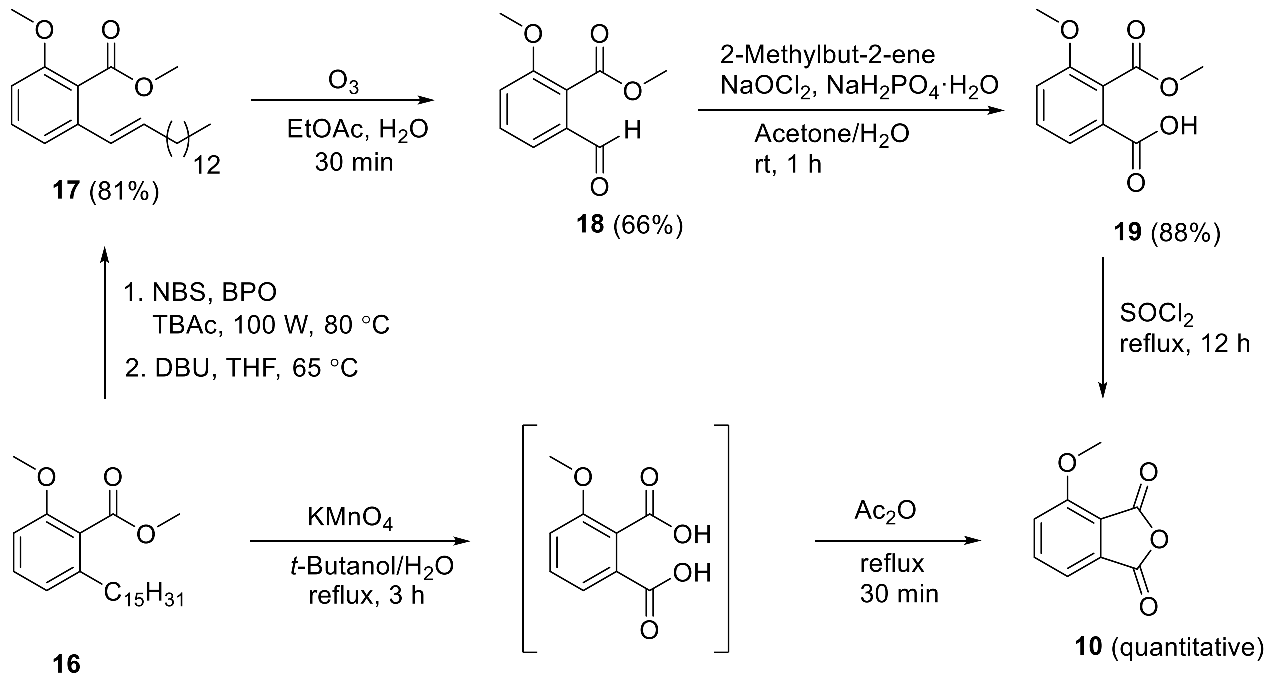


Scheme 2. Model study for the assembly of anthraquinone scaffolds.

Pleased with the construction of the anthraquinone **15**, our attention turned to the synthesis of the target natural products using the developed and optimized conditions. As a first step, it was necessary to prepare the key precursor, 3-methoxy phthalic anhydride (**10**)**,** from anacardic acids (**7**), following established literature procedures.[35]

Synthesis of 3-methoxy phthalic anhydride (10)

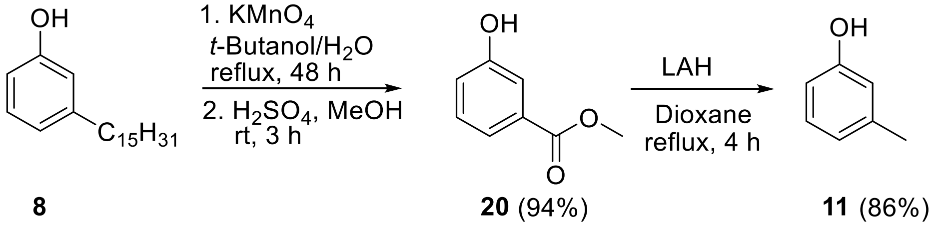
Methylated hydrogenated anacardic acid (**16**) was synthesized from calcium anacardate salt using known methods.[30,36] Benzylic bromination of **16** utilizing NBS and the green solvent *t*-butyl acetate, followed by DBU-mediated elimination, afforded alkene **17**, which underwent oxidative cleavage with ozone to yield benzaldehyde **18**. Pinnick oxidation of **18** provided benzoic acid **19**, which, upon exposure to thionyl chloride, gave phthalic anhydride (**10**) in 47% overall yield over five steps.[35] Although the synthesis of compound **10** was achieved, the reliance on problematic reagents like thionyl chloride presented a significant drawback. Strategies exist to mitigate its use, such as using it stoichiometrically in toluene[37] or replacing it with oxalyl chloride. While these approaches could have been considered in our case, we reasoned that the overall step economy would remain suboptimal. Instead, to circumvent thionyl chloride entirely and streamline the synthesis, we adopted a $KMnO_4$-mediated oxidative cleavage strategy, which we envisioned would furnish the desired compound **10** through a more efficient one-pot, two-step reaction. To achieve this, **16** was subjected to $KMnO_4$-mediated oxidative cleavage reaction in *tert*-butanol, yielding a diacid intermediate, alongside tetradecanoic acid, which was used as a building block in another project. The diacid was promptly exposed to a dehydrative cyclization reaction[38] with acetic anhydride, furnishing 3-methoxy phthalic anhydride (**10**) in quantitative yield (Scheme 3).



Scheme 3. Two approaches to the synthesis of 3-methoxy phthalic anhydride (**10**).

The Synthesis of *m*-cresol (11)

In line with the retrosynthetic strategy outlined in Scheme 1, the synthesis of chrysophanol (**4**) and aloesaponarin II (**5**) required the use of phenol **11**, which we envisaged could be prepared from **8** as highlighted in Scheme 4.

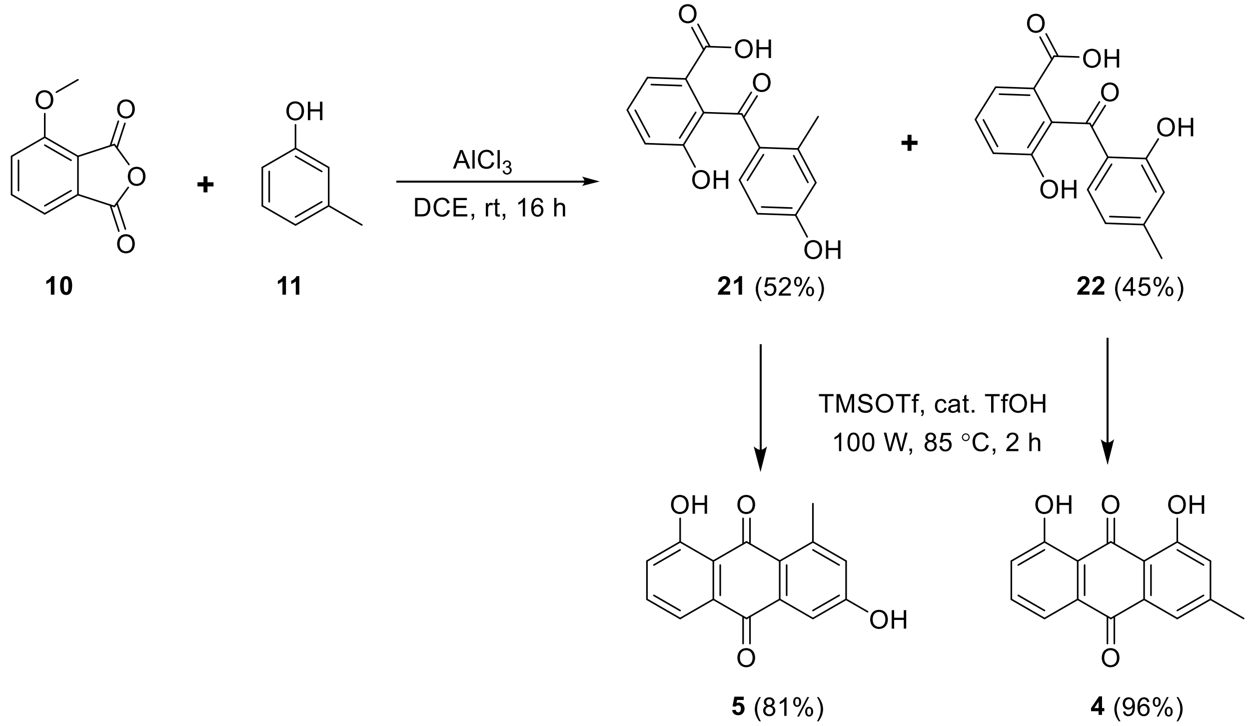


Scheme 4. Synthesis of *m*-cresol (**11**).

The synthesis of **11** commenced with a one-pot two-step oxidative cleavage reaction of cardanol (**8**) under conditions previously described. The resulting acid intermediate was esterified *in situ* with methanol under acidic conditions to yield ester **20** in excellent yield without the need for chromatographic purification.[39] The tetradecanoic byproduct from the first step was neither isolated nor purified in this instance. Using a literature procedure,[40] ester **20** was promptly reduced with excess lithium aluminium hydride (LAH) under reflux to afford m-cresol (11) in 86% yield.

The synthesis of chrysophanol (4) and aloesaponarin II (5)

In pursuit of the total synthesis of the target natural products **4** and **5**, our initial objective was to prepare the key benzoic acid precursors, **21** and **22**, which serve as advanced intermediates en route to the anthraquinones **4** and **5**, as illustrated in Scheme 5.



Scheme 5. Synthesis of chrysophanol (**4**) and aloesaponarin II (**5**).

To accomplish this, we employed the method established in the model study, where **10** and **11** were exposed to AlCl$_3$ in dichloroethane (DCE) to yield the two desired acids **21** and **22** in a single step. Gratifyingly, the reaction liberated the phenolic hydrogen of the phthalic anhydride moiety, circumventing the need for a separate demethylating step. The acid precursors were then subjected to the novel microwave-assisted IFCA reaction, which smoothly delivered the target natural products **4** and **5** in excellent yields of 96% and 81%, respectively.

Conclusions

In this work, we have showcased the utility of CNSL-derived phenolics as sustainable starting materials for the synthesis of anthraquinone-based natural products. Through the development of a novel microwave-assisted intramolecular Friedel–Crafts acylation (IFCA) reaction, we accomplished the total synthesis of chrysophanol (**4**) and aloesaponarin II (**5**), each obtained in an impressive 30% overall yield over seven linear steps from anacardic acid. While total syntheses of these natural products have been reported previously from petrochemical and/or commercial precursors, this study demonstrates, for the first time, their successful synthesis from CNSL-derived phenolics. This work not only establishes CNSL as a viable bio-renewable feedstock for natural product synthesis but also underscores its potential as a sustainable platform for accessing high-value, structurally diverse compounds.

Experimental Section

General Remarks: Solvents used for chromatographic techniques (ethyl acetate and *n*-hexane) were distilled before use by conventional distillation processes. The solvents used in reactions were first dried with a suitable drying agent and then distilled under argon or nitrogen. Dichloromethane was distilled from calcium hydride, and tetrahydrofuran was distilled from sodium with benzophenone as an indicator. 1,4-Dioxane was distilled using conventional methods and stored over molecular sieves, 3 Å beads, 4-8 mesh. All the required chemicals or reagents were obtained from Sigma–Aldrich or Merck and were used without further purification. Normal chromatography was carried out with silica gel 60 (Macherey–Nagel, particle size 0.063-0.200 mm), with both isocratic and gradient eluent systems being used. Thin-layer chromatography (TLC) was carried out on Macherey–Nagel Alugram Sil G/UV254 plates precoated with 0.25 mm silica gel 60. The TLC plates were viewed under UV light (254 nm and 366 nm). Nuclear magnetic resonance (NMR) spectra were acquired using a Bruker AVANCE III 400 MHz spectrometer. Spectra were obtained in chloroform-d, DMSO-d_6, or CD_3OD. Chemical shift values are expressed in parts per million (ppm), referenced to trimethylsilane (TMS), which is designated as zero ppm. Coupling constants (*J*-values) are reported in Hertz (Hz). The Fourier-Transform infrared (FTIR) spectra were recorded using a Bruker Tensor 27 standard system spectrometer. Samples were directly loaded onto a diamond cell for measurement. The results are presented on the wavenumber scale (cm^{-1}). High-resolution mass spectra were obtained with a Waters-LCT-Premier mass spectrometer. The sample was dissolved in methanol to a concentration of 2 ng/µL and introduced by direct infusion. The ionization mode was electrospray positive with a capillary voltage of 2500 V and a desolvation temperature of 250 °C using nitrogen gas at 250 L/hr. The intensity data was recorded on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K3 radiation (50 kV, 30 mA) with temperature of measurement at 173(2) K, using the APEX 2 data collection software. The collection method involved 4-scans of width 0.5 and 512×512 bit data frames. The data reduction was achieved by means of the program SAINT+ and face-indexed absorption corrections were made using XPRE. Melting points were determined using a Reichert hot stage microscope. Microwave chemical reactions were conducted using a CEM Discover microwave, equipped with a top-tier 300 mL single-mode microwave cavity. Cashew nut shell liquid was purchased from DIY AGRO PRODUCTS LTD, Mtwara, Tanzania. Some of the cardanol was obtained by vacuum distillation of the cashew nut shell liquid, which results in the decarboxylation of the anacardic acids to afford the cardanols. In addition, some of the cardanol was obtained commercially from Sigma-Aldrich and used without further purification. Calcium anacardate was prepared as its calcified salt from cashew nut shell liquid following established literature procedures.[25]

The synthesis of 2-(4-hydroxy-2-pentadecylbenzoyl)benzoic acid 13 and 2-(2-hydroxy-4-pentadecylbenzoyl)benzoic acid (**14**)

In a two-necked round-bottom flask equipped with a stirrer bar and CH_2Cl_2 (50 mL) were added a mixture of phthalic anhydride (**12**) (3.143 g, 21.20 mmol) and aluminium chloride (8.484 g, 63.60 mmol). This was followed by the addition of cardanol (**8**) (4.301 g, 14.13 mmol), and the resulting mixture was heated under reflux for 12 hours. The reaction mixture was allowed to cool to room temperature and quenched with ice-cold 10% aqueous HCl. The reaction mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers were washed with 20% aqueous NaOH. The NaOH solution was further washed with ethyl acetate (2 x 15 mL) and the aqueous layer was acidified with 32% aqueous HCl and adjusted to pH=1. The acidic aqueous layer was further extracted with ethyl acetate (4 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was purified using silica gel column chromatography eluting with 10-50% ethyl acetate/*n*-hexane to afford both 2-(4-hydroxy-2-pentadecylbenzoyl)benzoic acid (**13**) (3.452 g, 7.62 mmol, 36%) and 2-(2-hydroxy-4-pentadecylbenzoyl)benzoic acid (**14**) (5.641 g, 12.37 mmol, 58%) as colorless solids.13 R_f = 0.22, in 50/50 ethyl acetate/*n*-hexane, v/v. m.p**.**: 94–96 °C. FTIR (ν/cm^{-1}): 3357, 3347, 1697, 1650, 1615, 1570, 1413, 1341, 1290, 1172, 1114. ^{1}H-NMR (400 MHz, CD_3OD): δ 7.99 (dd, *J* = 7.7, 1.4 Hz, 1H, H-3), 7.65–7.53 (m, 2H, H-4, H-5), 7.32 (dd, *J* = 7.5, 1.4 Hz, 1H, H-6), 7.09 (d, *J* = 8.6 Hz, 1H, H-6'), 6.73 (d, *J* = 2.5 Hz, 1H, H-3'), 6.51 (dd, *J* = 8.6, 2.5 Hz, 1H, H-5'), 3.01–2.94 (m, 2H, H-1''), 1.66 (ddd, *J* = 12.0, 9.8, 6.3 Hz, 2H, H-2''), 1.46 – 1.22 (s, 24H, H-3''–H-14''), 0.93–0.86 (m, 3H, H-15''). ^{13}C-NMR (101 MHz, CD_3OD): δ 200.0 (CO), 169.3 (COOH), 162.4 (C4'), 149.7 (C2), 136.9 (C6'), 133.0 (C1), 132.0 (C3), 131.2 (C1), 130.4 (C2'), 129.8 (C5), 128.9 (C4), 128.9 (C6), 118.9 (C3'), 112.9 (C5'), 35.7 (C1''), 33.1 (C3''), 32.4 (C2''), 31.0–30.5 (C4' –C13''), 23.7 (H-14''), 14.5 (C15''). HRMS (TOF-ESI): calculated for $C_{29}H_{41}O_4^+$, [M+H]$^+$: 453.2999, found 453.3031. 14; R_f = 0.52, in 50/50 ethyl acetate/*n*-hexane, v/v. m.p.: 134–136 °C. FTIR (ν/cm^{-1}): 3251, 2959, 2915, 2849, 1693, 1630, 1576, 1503, 1470, 1416, 1335, 1302. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.93 (s, 1H, OH), 10.14 (br-s, 1H, COOH), 8.15–8.09 (m, 1H, H-3), 7.67 (td, *J* = 7.5, 1.3 Hz, 1H, H-4), 7.58 (td, *J* = 7.7, 1.3 Hz, 1H, H-5), 7.38–7.33 (m, 1H, H-6), 6.96 (d, *J* = 8.1 Hz, 1H, H-6'), 6.87 (d, *J* = 1.6 Hz, 1H, H-3'), 6.57 (dd, *J* = 8.2, 1.6 Hz, 1H, H-5'), 2.58 (t, *J* = 7.8 Hz, 2H, H-1''), 1.66–1.54 (m, 2H, H-2''), 1.41–1.20 (m, 24H, H-3''–H-14''), 0.88 (t, *J* = 6.7 Hz, 3H, 15'') ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 201.9 (CO), 170.7(COOH), 162.9 (C2'), 153.3 (C1), 141.1 (C2), 133.3 (C4), 132.6 (C6'), 131.3 (C3), 129.8 (C5), 127.7 (C6), 127.6 (C1'), 119.7 (C5'), 118.1 (C4'), 117.8 (C3'), 36.4 (C1''), 32.1 (C2''), 30.7 (C3''), 29.8 (C2''), 29.8–29.5 (C4''–C13''), 22.8 (C14''), 143 (C15'') ppm. HRMS (TOF-ESI): Calculated for $C_{29}H_{41}O_4^+$, [M+H]$^+$: 453.3000, found 453.3031.

1-Hydroxy-3-pentadecylanthraquinone (**15**)

In a 35 mL capped microwave tube equipped with a stirrer bar and DCE (10 mL), were combined 2-(2-hydroxy-4-pentadecylbenzoyl)benzoic acid (**14**) (250 mg, 552.3 mmol), TMSOTf (0.15 mL, 828.5 mmol), and TfOH (2.57 µL, 27.62 mmol). The mixture was then heated under reflux (open vessel) for 2 hours while irradiating with 100 W. Once complete, the reaction mixture was poured onto 10 mL of ice-cold water. The resulting aqueous mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with 15 mL of brine. After drying over $MgSO_4$ and concentration in vacuo, the residual orange oil was purified using silica-gel column chromatography eluting with 5/95 ethyl acetate/ *n*-hexane, v/v to furnish anthraquinone **15**) (207.6 mg, 478.2 mmol, 87%) as a yellow powder. R_f = 0.42, in 5/95 ethyl acetate/ *n*-hexane, v/v. m.p.: 94 – 96 °C FTIR (ν/cm^{-1}): 3346, 3327, 3251, 3108, 2911, 2561, 1715, 1641, 1602, 1566, 1521, 1494, 1325. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.59 (s, 1H, OH), 8.33 – 8.26 (m, 2H, H-5 & H-8), 7.83 – 7.76 (m, 2H, H-6 & H-7), 7.66 (d, *J* = 1.64 Hz, 1H, H-2), 7.11 (d, *J* = 1.64 Hz, 1H, H-4), 2.70 (t, *J* = 7.72 Hz, 2H, H-1'), 1.73 – 1.62 (q, 2H, H-2'), 1.39 – 1.15 (m, 24H, H-3' – H-14'), 0.87 (t, *J* = 6.71 Hz, 3H, H-15'). ^{13}C-NMR (101 MHz, CDCl$_3$): δ 188.2 (C9), 182.9 (C10), 163.0 (C1), 153.8 (C3), 134.6 (C6), 134.2 (C7), 133.8 (C4a), 133.5 (C8a), 133.4 (C5a), 127.5 (C8), 126.9 (C5), 123.7 (C2), 120.4 (C4), 114.4 (C1a), 36.6 (C1'), 32.1 (C2'), 30.6 – 22.8 (C3' – C14'), 14.3 (C15'). HRMS (TOF-ESI): Calculated for $C_{29}H_{39}O_3^+$, [M+H]$^+$: 435.2894, found 435.2894.

Methyl 2-methoxy-6-pentadecylbenzoate (16)[36]

In a 100 mL reaction vessel containing 15 mL methanol, were added methylated anacardic acids (**7**) (28.17 g, *ca.* 75.84 mmol) and Pd/C (403.3 mg, 3.801 mmol). The mixture was then fitted to the hydrogen reactor and purged with hydrogen gas for 10 seconds. Afterwards, the reaction vessel was sealed, and the hydrogen gas pressure was adjusted to 3 bar, and the reaction was left to stir at room temperature for 24 hours. Once the reaction was completed (TLC monitoring), the reaction mixture was filtered through a pad of Celite and concentrated under vacuum to afford methyl 2-methoxy-6-pentadecylbenzoate (**16**), as a colorless crystalline solid: (26.88 g, 71.37 mmol, 94%). Rf = 0.36, in 10/90, ethyl acetate/ *n*-hexane, v/v. m.p.: 31–33 °C. FTIR (ν/cm^{-1}): 2996, 2841, 2271, 1702, 1666, 1514, 1491, 1477, 1301, 994, 843. ^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.26 (t, *J* = 8.1 Hz, 1H, H-4), 6.82 (d, *J* = 7.7 Hz, 1H, H-3), 6.75 (d, *J* = 8.4 Hz, 1H, H-5), 3.91 (s, 3H, C1-CO$_2$C$\underline{H_3}$), 3.81 (s, 3H, C2-OC$\underline{H_3}$), 2.54 (t, *J* = 7.9 Hz, 2H, H-1'), 1.58 (p, *J* = 7.3 Hz, 2H, H-2'), 1.36-1.21 (m, 22H, H-3'–H-14'), 0.88 (t, *J* = 6.4 Hz, 3H, H-15'). ^{13}C-NMR (101 MHz, CDCl$_3$): δ 169.1 (C1-$\underline{C}$O$_2$CH$_3$), 156.4 (C2), 141.5 (C6), 130.3 (C5), 123.6 (C1), 121.6 (C4), 108.5 (C3), 55.9 (C1-CO$_2$$\underline{C}H_3$), 52.2 (C2-O$\underline{C}H_3$), 33.6–22.1 (C-3'–C-14'), 14.2 (C-15'). HRMS (TOF-ESI): [M+H], Calculated for $C_{24}H_{40}O_3$, [M+H]: 377.3530, found 377.3539. The spectroscopic data is consistent with reported literature.

Methyl 2-methoxy-6-(pentadec-1-en-1-yl)benzoate (17)[36]

In three separate 100 mL long-necked round-bottom flasks, each equipped with a stirrer bar, 30 mL of *tert*-butyl acetate was added. To each flask, methyl 2-methoxy-6-pentadecylbenzoate (**16**) (7.261 g, 19.28 mmol), *N*-bromosuccinimide (3.431 g, 19.28 mmol), and benzoyl peroxide (467.7 mg, 1.928 mmol) were introduced. The resulting mixtures were individually irradiated at 100 W, with reflux (open vessel) maintained at 80 ºC for 1 hour. Following this duration, the resulting three reaction mixtures were combined, and the volatile components were removed under reduced pressure. The remaining precipitate was dissolved in 50 mL of ethyl acetate and washed with water (3 x 30 mL). The organic layer was subsequently desiccated over MgSO$_4$ and underwent purification via silica-gel column chromatography, eluting with a solvent mixture of 10/90, ethyl acetate/ *n*-hexane, v/v to isolate methyl 2-(1-bromopentadecyl)-6-methoxybenzoate, which was used as an intermediate. The bromo intermediate (10.11 g, 26.92 mmol) was charged into a 250 mL round-bottom flask equipped with a stirrer bar and 35 mL THF. To this solution, DBU (10.18 g, 67.32 mmol) was added. The resulting reaction mixture was stirred under reflux for 6 hours. After cooling to room temperature, the reaction mixture was poured onto an ice-cold 75 mL solution of 10% aqueous HCl. The aqueous solution was extracted with ethyl acetate (3 x 15 mL) and washed with brine solution (2 x 10 mL). The organic layers were combined and dried over MgSO$_4$ and concentrated under reduced pressure. The resulting crude product was purified using silica-gel column chromatography eluting with 30/70, ethyl acetate/ *n*-hexane, v/v to yield methyl 2-methoxy-6-(pentadec-1-en-1-yl)benzoate (**17**) as a colorless solid: (5.849 g, 15.61 mmol, 81%). R$_f$ = 0.31, in 30/70, ethyl acetate/ *n*-hexane, v/v). m.p.: 34–36 °C. FTIR (ν/cm^{-1}): 2923, 2852, 1768, 1736, 1652,1577, 1464, 1434, 1262, 1187, 1111, 1107. ^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.28 (t, *J* = 8.2 Hz, 1H, H-4), 7.12 (d, *J* = 7.9 Hz, 1H, H-5), 6.78 (d, *J* = 8.3 Hz, 1H, H-3), 6.32 (d, *J* = 15.8 Hz, 1H, H-1'), 6.22 (dt, *J* = 15.5, 6.6 Hz, 1H, H-2'), 3.93 (s, 3H, CO$_2$C$\underline{H_3}$), 3.82 (s, 3H, OC$\underline{H_3}$), 2.19 (q, *J* = 7.2 Hz, 2H, H-3'), 1.45 (q, *J* = 7.3 Hz, 3H, H-4'), 1.40–1.21 (s, 22H, H-5'–H-14'), 0.91 (t, 3H, H-15'). ^{13}C-NMR (101 MHz, CDCl$_3$): δ 168.8 ($\underline{C}$O$_2$CH$_3$), 156.5 (C2), 136.8 (C6), 134.9 (C1'), 130.3(C4), 126.2 (C2'), 122.3 (C1), 117.9 (C5), 109.2 (C3), 56.0 (CO$_2$$\underline{C}H_3$), 52.3 (O$\underline{C}H_3$), 33.3 (C3'), 32.0–22.8 (C4'–C14'), 29.8, 14.2

(C15'). HRMS (TOF-ESI): Calculated for $C_{24}H_{39}O_3^+$, [M+H]$^+$: 375.2894, found 375.2894. The spectroscopic data is consistent with reported literature.

Synthesis of methyl 2-formyl-6-methoxybenzoate (18)[36]

In a 250 mL Schlenk flask equipped with a stirrer bar and 30 mL ethyl acetate/water (20:10; v/v), was added methyl 2-methoxy-6-(pentadec-1-en-1-yl)benzoate (**17**) (7.771 g, 20.68 mmol). The resulting mixture was purged with oxygen gas (O_2) before applying a stream of ozone for 35 minutes while stirring at room temperature. After the reaction was completed (TLC monitoring), the organic layer was isolated and washed with brine (1 x 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting white precipitate was purified using silica-gel column chromatography, eluting with 30/70, ethyl acetate/*n*-hexane, v/v. This process afforded the desired methyl 2-formyl-6-methoxybenzoate (**18**) as a colorless solid: (2.668 g, 13.84 mmol, 66%). The ozonolysis procedure liberates tetradecanal as a white solid byproduct (1.916 g, 8.422 mmol, 41%). R_f = 0.36, in 30/70, ethyl acetate/ *n*-hexane, v/v. m.p.: 66–68 °C. FTIR (ν/cm^{-1}): 2955, 1738, 1698, 1472, 1268, 1101, 976. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H, C$\underline{H}$O), 7.52 (t, *J* = 7.9 Hz, 1H, H-4), 7.43 (d, *J* = 7.7 Hz, 1H, H-3), 7.19 (d, *J* = 8.3 Hz, 1H, H-5), 3.94 (s, 3H, $CO_2C\underline{H_3}$), 3.85 (s, 3H, $OC\underline{H_3}$). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 190.4 ($\underline{C}$HO), 167.3 ($\underline{C}O_2CH_3$), 156.7 (C6), 134.3 (C2), 131.1 (C4), 123.5 (C1), 123.3 (C3), 117.1 (C-5), 56.4 ($CO_2\underline{C}H_3$), 52.9 ($O\underline{C}H_3$). The spectroscopic data is consistent with reported literature.

3-Methoxy-2-(methoxycarbonyl)benzoic acid (19)[36]

In a round bottom flask equipped with a stirrer bar and 15 mL acetone/water (10:5; v/v), were added methyl 2-formyl-6-methoxybenzoate (**18**) (2.523 g, 12.98 mmol) and 2-methyl-2-butene (4.4 mL, 41.54 mmol) followed by the addition of sodium chlorite ($NaOCl_2$), (7.042 g, 77.89 mmol) and sodium phosphate monobasic dihydrate ($NaH_2PO_4{\cdot}2H_2O$) (12.15 g, 77.89 mmol). The resulting mixture was stirred at room temperature for 1 hour. The resulting yellow mixture was quenched with 10% aqueous HCl and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were further washed with brine (2 x 15 mL) and then dried under $MgSO_4$ and concentrated under reduced pressure. The crude yellow solid was purified using silica-gel column chromatography eluting with 30/70 ethyl acetate/*n*-hexane to furnish 3-methoxy-2-(methoxycarbonyl)benzoic acid (**19**) as a colorless solid (2.414 g, 11.47 mmol, 88 %). R_f = 0.32, in 30/70, ethyl acetate/ *n*-hexane, v/v. m.p.: 141–143 °C. FTIR (ν/cm^{-1}): 1722, 1702, 1699, 1623, 1501, 1455, 1323. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 7.9, 1.0 Hz, 1H, H-6), 7.46 (t, *J* = 8.1 Hz, 1H, H-5), 7.19 (dd, *J* = 8.4, 0.9 Hz, 1H, H-4), 3.93 (s, 3H, $OC\underline{H_3}$), 3.87 (s, 3H, $CO_2C\underline{H_3}$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.6 ($\underline{C}O_2H$), 167.8 ($\underline{C}O_2CH_3$), 156.6 (C3), 130.5 (C6), 127.8 (C1), 125.9 (C2), 122.8 (C5), 116.5 (C4), 56.5 ($CO_2\underline{C}H_3$), 52.9 ($O\underline{C}H_3$). HRMS (TOF-ESI): Calculated for $C_{10}H_{11}O_5^+$, [M+H]$^+$: 211.0601, found 211.0601. The spectroscopic data is consistent with reported literature.

4-Methoxyisobenzofuran-1,3-dione (10)[35]

Method 1: In a single-necked round-bottom flask, equipped with a stirrer bar and thionyl chloride (8.081 mL, 132.3 mmol), was added the 3-methoxy-2-(methoxycarbonyl)benzoic acid (**19**) (2.364 g, 11.23 mmol) and the resulting mixture was heated under reflux for 12 hours. After this time, the volatiles were removed under vacuum and the resulting yellow powder was purified using silica-gel column chromatography, eluting with 50/50, ethyl acetate/ *n*-hexane, v/v to afford 4-methoxyisobenzofuran-1,3-dione (**10**) as a white solid (1.962 g, 11.00 mmol, 98%).

Method 2: To a 250 mL single-necked round-bottom flask equipped with a stirrer bar and *tert*-butanol and water (40:60; v/v) were added 2-methoxy-6-pentadecylbenzoate (**7**; 10.56 g, 28.04 mmol) and potassium permanganate (28.80 g, 182.3 mmol). The resulting mixture was heated to reflux for 3 hours. After this time, the reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite. The clear solution was acidified with 32% aqueous HCl to achieve a pH=1. This solution was then washed thoroughly with diethyl ether (3 x 15 mL). After which the acidic aqueous layer was concentrated by gentle heating at 80 °C in a

400 mL beaker for 2.5 hours. After this time, 35 mL of methanol was added to the beaker and dried over $MgSO_4$ and concentrated in vacuo to furnish 3-methoxyphthalic acid, which was used as an intermediate. To this intermediate, acetic anhydride (25 mL) was added and the mixture was heated to reflux for 30 minutes. After this time, the mixture was allowed to cool to room temperature and placed in the refrigerator for 5 hours at -15.6 ºC. The resulting precipitate was filtered off and washed with n-hexane to furnish 4-methoxyisobenzofuran-1,3-dione (**10**) as white crystals (4.872 g, 27.34 mmol, 99%). Rf = 0.57, in 50/50, ethyl acetate/ *n*-hexane, v/v. m.p.: 161–163 °C. FTIR (ν/cm^{-1}): 1847, 1788, 1617, 1602, 1541, 1421. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84 (t, *J* = 8.1 Hz, 1H, H-6), 7.56 (d, *J* = 7.0 Hz, 1H, H-7), 7.34 (d, *J* = 8.6 Hz, 1H, H-5), 4.07 (s, 3H, $OC\underline{H}_3$). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.9 (C1), 160.8 (C3), 158.4 (C7a), 138.6 (C7), 133.5 (C4), 118.8 (C6), 117.5 (C5), 117.1 (C3a), 56.8 ($O\underline{C}H_3$). The spectroscopic data is consistent with reported literature.

Methyl 3-hydroxybenzoate (20)[39]

In a 100 mL round-bottom flask, equipped with a stirrer bar and *tert*-butanol and water (10:30; v/v) were added cardanol (**8**) (5.011 g, 6.600 mmol) and potassium permanganate (6.583 g, 42.90 mmol). This mixture was heated under reflux for 7 hours and after this time, the mixture was allowed to cool to room temperature and filtered through a pad of Celite. The filtrate was adjusted to pH=1 using 32% aqueous HCl, the acidic aqueous mixture was first washed with 15 mL diethyl ether to extract the tetradecanoic acid byproduct before being concentrated to ¼ of the original volume and the white precipitate was collected on a sintered funnel through filtration and washed with water. The collected precipitate was redissolved in 50 mL methanol in a 100 mL round-bottom flask and a catalytic amount of sulfuric acid was added dropwise. The resulting mixture was stirred at room temperature for 2.5 hours and after this time, sufficient sodium bicarbonate solution was added to the mixture and extracted with ethyl acetate (3 x 25 mL) and the combined organic layers were dried over $MgSO_4$ and after concentration under reduced pressure, methyl-3-hydroxybenzoate (**20**) was isolated as a colorless solid (952.2 mg, 6.261 mmol, 95%). R_f = 0.66 (15% ethyl acetate/n-hexane). m.p.: 71–73 °C. FTIR (ν/cm^{-1}): 3301, 1734, 1617, 1401, 1278, 1222, 817, 788. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.84 (s, 1H, H-3), 7.41–7.35 (m, 2H, H-3, H-6), 7.30 (t, *J* = 7.8 Hz, 1H, H-5), 7.03 (ddd, *J* = 8.0, 2.6, 1.1 Hz, 1H, H-2), 3.81 (s, 3H, $OC\underline{H}_3$). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 166.3 ($\underline{C}O_2CH_3$), 157.6 (C3), 130.9 (C1), 129.8 (C5), 120.4 (C6), 119.9 (C2), 115.7 (C4), 52.1 ($\underline{C}H_3$). The spectroscopic data are consistent with reported literature.

3-Methylphenol (11)[41]

In a 50 mL two-necked round bottom flask equipped with a stirrer bar and dry 1,4-dioxane (10 mL), were added lithium aluminium hydride ($LiAlH_4$) (1.772 g, 46.56 mmol) and methyl 3-hydroxybenzoate (**15**; 885.3 mg, 5.822 mmol) at 0 ºC under a nitrogen atmosphere. The resulting mixture was heated at reflux for 4 h and then cooled. The reaction was quenched with water (10 mL). The mixture was filtered through a pad of Celite. The filtrate was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), then filtered, and evaporated in vacuo. The residue was triturated with cold *n*-hexane to furnish *m*-cresol (**11**) as a pale-yellow liquid. R_f = 0.39, in 10/90 ethyl acetate/n-hexane, v/v. b.p. 200–204 °C. FTIR (ν/cm^{-1}): 3381, 2910, 2855, 1715, 1614, 1455, 1228, 1201, 925, 719. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35–7.29 (m, 1H, H-5), 7.17 (s, 1H, $O\underline{H}$), 7.00–6.96 (m, 1H, H-6), 6.95–6.90 (m, 2H, H-4, H-2), 2.47 (s, 3H, $C\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9 (C3), 139.9 (C1), 129.5 (C5), 121.9 (C6), 116.3 (C2), 112.5 (C4), 21.2 ($\underline{C}H_3$). HRMS (TOF-ESI): calculated for C_7H_8O, [M+H]: 109.0648, found 109.0645. The spectroscopic data is consistent with reported literature.

3-Hydroxy-2-(4-hydroxy-2-methylbenzoyl)benzoic acid 21 and 3-hydroxy-2-(2-hydroxy-4-methylbenzoyl)benzoic acid (22)

In a 2-necked round-bottom flask equipped with a stirrer bar and DCE (50 mL) were added a mixture of 3-methoxyphthalic anhydride (**112**) (3.574 g, 20.04 mmol) and aluminium chloride (8.021 g, 60.12 mmol). This was followed by the addition of *m*-cresol (**227**) (4.071 g, 13.36 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with ice-cold 10% aqueous HCl. The reaction mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers were extracted with 20 w.t% NaOH. The alkaline layer was washed with ethyl acetate (3 x 15 mL) and acidified with 32% aqueous HCl (adjusted to pH=1). The acidic aqueous layer was further extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was purified using silica-gel column chromatography eluting with 10-50% ethyl acetate/n-hexane to afford both 3-hydroxy-2-(4-hydroxy-2-methylbenzoyl)benzoic acid (**21**) (2.845 g, 10.45 mmol, 52%) and 3-hydroxy-2-(2-hydroxy-4-methylbenzoyl)benzoic acid (**22**) (2.431 g, 8.934 mmol, 45%) as colorless solids. **21:** R_f = 0.16, in 50/50 ethyl acetate/*n*-hexane, v/v. m.p.: 198–200 °C. FTIR (ν/cm^{-1}): 3191, 3074, 2981, 2893, 2834, 1635, 1661, 1605, 1501, 1435, 1336, 1324. ^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.07 (s, 1H, C3-O$\underline{H}$), 9.87 (s, 1H, C4'-O$\underline{H}$), 7.38 (d, *J* = 7.6 Hz, 1H, H-6), 7.32 (t, *J* = 8.0 Hz, 1H, H-5), 7.10 (t, *J* = 9.0 Hz, 2H, H-4, H-6'), 6.65 (s, 1H, H-3'), 6.52 (d, *J* = 8.2 Hz, 1H, H-5'), 2.49 ($\underline{C}H_3$). ^{13}C-NMR (101 MHz, DMSO-*d*$_6$): δ 195.5 ($\underline{C}$O), 167.0 ($\underline{C}$OOH), 160.2 (C4'), 154.3 (C3), 141.7 (C2), 134.2 (C4), 131.2 (C1), 130.1 (C2), 129.3 (C5), 128.6 (C1'), 120.6 (C6), 119.8 (C6'), 118.3 (C3'), 112.1 (C5'), 21.8 ($C\underline{H}_3$). HRMS (TOF-ESI): Calculated for $C_{15}H_{13}O_5^+$, [M+H]$^+$: 273.0757, found 273.0754. **22:** $\mathbf{R_f}$ = 0.47, in 50/50 ethyl acetate/*n*-hexane, v/v. m.p.: 235–237 °C. FTIR (ν/cm^{-1}): 3461, 3001, 2951, 2925, 2833, 1613, 1506, 1471, 1422, 1250, 1215, 1196. ^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.9 (d, *J* = 3.2 Hz, 1H, C2'-O$\underline{H}$), 10.2 (d, *J* = 3.3 Hz, 1H, C3-O$\underline{H}$), 7.5–7.4 (m, 2H, H-5, H-6), 7.2 (d, *J* = 7.9 Hz, 1H, H-4), 7.0 (d, *J* = 8.0 Hz, 1H, H-6'), 6.8 (s, 1H, H-3'), 6.7 (d, *J* = 8.1 Hz, 1H, H-5'), 2.3 (s, 3H, $C\underline{H}_3$). ^{13}C-NMR (101 MHz, DMSO-*d*$_6$): δ 202.1 ($\underline{C}$O), 167.0 ($\underline{C}$OOH), 161.5 (C2'), 154.8 (C3), 147.5 (C4'), 132.3 (C6'), 130.8 (C6), 130.7 (C1), 127.5 (C2), 121.1 (C5), 120.8 (C5'), 120.6 (C4), 119.3 (C1'), 117.8 (C3'), 21.9 ($C\underline{H}_3$). HRMS (ESI), calculated for $C_{15}H_{13}O_5^+$, [M+H]$^+$: 273.0757, found, 273.0758.

Chrysophanol (4)[42]

To a 50 mL high pressure glass tube charged with a stirrer bar and 10 mL dichloroethane, was added 3-hydroxy-2-(2-hydroxy-4-methylbenzoyl)benzoic acid (**22**; 807.3 mg, 2.966 mmol), followed by the addition of TMSOTf (0.81 mL, 4.449 mmol) and TfOH (13 µL, 0.1483 mmol). The resulting mixture was stirred under reflux (open vessel) at 85 °C while irradiating at 100 W for 2 hours in a microwave reactor. Once completed, the reaction mixture was quenched by the addition of methanol (2 mL) and adsorbed to silica. Purification using silica-gel column chromatography eluting with 15/85 ethyl acetate/*n*-hexane, v/v, afforded chrysophanol (**4**) as a yellow solid (726.3 mg, 2.857 mmol, 96%). R_f = 0.57, in 15/85 ethyl acetate/*n*-hexane, v/v. m.p: FTIR (cm^{-1}): 3455, 2914, 1706, 1644, 1617, 1574, 1402, 1361, 1231. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.13 (s, 1H, C8-OH), 12.02 (s, 1H, C1-OH), 7.82 (d, *J* = 7.50 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.29 (d, *J* = 8.37 Hz, 1H), 7.10 (s, 1H), 2.47 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.7, 182.2, 162.9, 162.6, 149.5, 137.1, 133.8, 133.4, 124.7, 124.5, 121.5, 120.1, 116.0, 113.9, 22.4 ($\underline{C}H_3$). HRMS (TOF-ESI): Calculated for $C_{15}H_{10}O_4$, [M+H], 255.0652 found, 255.0650. The spectroscopic data is consistent with reported literature.

Aloesaponarin II (5)[43]

To a 50 mL high pressure glass tube charged with a stirrer bar and 10 mL dichloroethane, was added 3-hydroxy-2-(4-hydroxy-2-methylbenzoyl)benzoic acid (**21**; 476.3 mg, 1.747 mmol), followed by the addition of TMSOTf (0.48 mL, 2.621 mmol) and TfOH (7.2 µL, 0.087 mmol). The resulting mixture was stirred under reflux (open vessel) at 85 °C while irradiating at 100 W for 2 hours in a microwave reactor. Once completed, the reaction mixture was quenched by the addition of methanol (2.1 mL) and adsorbed to silica. Purification using silica-gel column chromatography eluting with 30/70 ethyl acetate/*n*-hexane, v/v, gave aloesaponarin II (**5**) as a yellow solid (358.5 mg, 1.402 mmol, 81%). R_f = 0.21, in 30/70 ethyl acetate/*n*-hexane, v/v. FTIR (cm^{-1}): 3110, 2906, 1781, 1716, 1691, 1644, 1520, 1432, 1374, 940. ^{1}H NMR (400 MHz, $CDCl_3$): 12.98 (s, C8-OH), 7.50 (t, *J* = 7.9 Hz, H-7), 7.47 (dd, *J* = 2.69 Hz, 1H, H-4), 7.14 (dd, *J* = 7.9, *J* = 1.6 Hz, H-6), 6.73 (d, *J* = 2.5 Hz, H-1), 6.17 (d, *J* = 2.4 Hz, H-3), 2.51 (C<u>H</u>$_3$). ^{13}C NMR (101 MHz, CDCl$_3$): 185.7 (C10), 184.4 (C9), 162.2 (C3), 161.7 (C8), 145.5 (C1), 133.9 (C14), 133.4 (C13), 128.7 (C7), 124.0 (C2), 119.0 (C5), 118.3 (C11), 117.3 (C4), 111.7 (C12), 24.0 (C<u>H</u>$_3$). HRMS (TOF-ESI): Calculated for $C_{15}H_{10}O_4$, [M+H], 255.0652 found, 255.0651. The spectroscopic data is consistent with reported literature.

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Supplementary Material

Supplementary information has been provided in a separate file.

References

1. Ramchuran, S. O.; O'Brien, F.; Dube, N.; Ramdas, V. *Curr. Opin. Green Sustain. Chem*. **2023**, *41*, 100832. https://doi.org/10.1016/j.cogsc.2023.100832
2. Queneau, Y.; Han, B. Innov. **2022**, *3,* 100184. https://doi.org/10.1016/j.xinn.2021.100184
3. Lizundia, E.; Luzi, F.; Puglia, D. *Green Chem*. **2022**, *24*, 5429. https://doi.org/10.1039/d2gc01668k
4. Ufitikirezi, J. D.; Filip, M.; Ghorbani, M.; Zoubek, T.; Olšan, P.; Bumbálek, R.; Strob, M.; Bartoš, P.; Umurungi, S. N.; Murindangabo, Y. T.; Heřmánek, A.; Tupý, O.; Havelka, Z.; Stehlík, R.; Černý, P.; Smutný, L. Sustainability **2024**, *16*, 3617. https://doi.org/10.3390/su16093617
5. Wang, P.; Wei, J.; Hua, X.; Dong, G.; Dziedzic, K.; Wahab, A.; Efferth, T.; Sun, W.; Ma, P. *J. Cell. Physiol.* **2024**, *239*, 31063. https://doi.org/10.1002/jcp.31063
6. Mazouria, S. El; Aanniza, T.; Touhtouha, J.; Kandoussia, I.; Hakmia, M.; Belyamanib, L.; Ibrahimia, A.; Ouadghiria, M. *Int. J. Appl. Biol. Pharm. Technol*. **2021**, *12*, 338. https://doi.org/10.26502/ijabpt.202104
7. Avery, M. L.; Tillman, E. A.; Humphrey, J. S.; Cummings, J. L.; York, D. L.; Davis Jr, J. E. *Crop Prot*. **2000**, *19*, 225. https://doi.org/10.1016/S0261-2194(00)00012-0
8. Osman, C. P.; Ismail, N. H.; Widyawaruyanti, A.; Imran, S.; Tumewu, L.; Choo, C. Y.; Ideris, S. *Lett. Drug Des. Discov*. **2019**, 353. https://doi.org/10.2174/1570180815666180607085102
9. Gautrot, J. E.; Hodge, P.; Cupertino, D.; Helliwell, M. *New J. Chem*. **2007**, *31*, 1585. https://doi.org/10.1039/b701257h
10. Chang, P.; Lee, K. H. *J. Nat. Prod.* **1985**, *48*, 948. https://doi.org/10.1021/np50042a011

11. Chien, S. C.; Wu, Y. C.; Chen, Z. W.; Yang, W. C. *Evid. Based Complement. Altern. Med*. **2015**, 357357. https://doi.org/10.1155/2015/357357
12. Henamayee, S.; Banik, K.; Sailo, B. L.; Shabnam, B.; Harsha, C.; Srilakshmi, S.; VGM, N.; Baek, S. H.; Ahn, K. S.; Kunnumakkara, A. B. *Mol.* **2020**, *25*, 2278. https://doi.org/10.3390/molecules25102278
13. Qun, T.; Zhou, T.; Hao, J.; Wang, C.; Zhang, K.; Xu, J.; Wang, X.; Zhou, W. *RSC Med. Chem*. **2023**, *14*, 1446. https://doi.org/10.1039/d3md00116d
14. Gartman, J. A.; Tambar, U. K. *Tetrahedron*, **2022**, *105*, 132501. https://doi.org/10.1016/j.tet.2021.132501.
15. Chakiri, A. B.; Hodge, P. *R. Soc. Open Sci*. **2017**, *4*, 170451. https://doi.org/10.1098/rsos.170451.
16. El-Sayrafi, S.; Rayyan, S. *Mol.* **2001**, 279. https://doi.org/10.3390/60300279.
17. Kaper, H.; Antonietti, M.; Goettmann, F. *Tetrahedron Lett*. **2008**, *49*, 4546. https://doi.org/10.1016/j.tetlet.2008.05.027.
18. Anand, N.; Upadhyaya, K.; Ajay, A.; Mahar, R.; Shukla, S. K.; Kumar, B.; Tripathi, R. P. *J. Org. Chem.* **2013**, *78*, 4685. https://doi.org/10.1021/jo302589t.
19. Roy, J.; Mal, T.; Jana, S.; Mal, D. *Beilstein J. Org. Chem*. **2016**, *12*, 531. https://doi.org/10.3762/bjoc.12.52.
20. Mal, D.; Ray, S.; Sharma, I. *J. Org. Chem*. **2007**, *72*, 4981. https://doi.org/10.1021/jo062271j.
21. Sawano, T.; Toyoshima, Y.; Takeuchi, R. *Inorganics* **2019**, *7*, 138. https://doi.org/10.3390/inorganics7110138.
22. Madje, B. R.; Shelke, K. F.; Sapkal, S. B.; Kakade, G. K.; Shingare, M. S. *Green Chem. Lett. Rev*. **2010**, *3*, 269. https://doi.org/10.1080/17518251003776877
23. Puigjaner, L.; Pérez-Fortes, M.; Somoza-Tornos, A.; Espuña, A. *Front. Energy Res.* **2021**, *9*, 780533. https://doi.org/10.3389/fenrg.2021.780533.
24. Megía, P. J.; Vizcaíno, A. J.; Calles, J. A.; Carrero, A. *Energy Fuels* **2021**, *35*, 16403. https://doi.org/10.1021/acs.energyfuels.1c02501
25. Levi, P. G.; Cullen, J. M. *Environ. Sci. Technol*. **2018**, *52*, 1725. https://doi.org/10.1021/acs.est.7b04573
26. Caillol, S. *Eur. Polym. J.* **2023**, *193*, 112096. https://doi.org/10.1016/j.eurpolymj.2023.112096
27. Taiwo, E. A. In Advances in Petrochemicals; Patel, V. Ed.; IntechOpen: Rijeka, 2015; 1. https://doi.org/10.5772/61096
28. Talbiersky, J.; Polaczek, J.; Ramamoorty, R.; Shishlov, O. *Oil Gas Eur. Mag.* **2009**, *35*, 33.
29. dos Santos, M.; de, M. *J. Braz. Chem. Soc.* **1999**, *10*, 13. https://doi.org/10.1590/s0103-50531999000100003
30. Ngwira, K. J.; Kühlborn, J.; Mgani, Q.; Koning, C. B.; Opatz, T. *Eur. J. Org. Chem.* **2019**, *2019*, 4478. https://doi.org/10.1002/ejoc.201900743
31. Jagot, F.; Minnie, I.; Rahman, A.; Ntsimango, S.; Ngwira, K. J.; de Koning, C. B., F. M. *SynOpen* **2022**, *6*, 58. https://doi.org/10.1055/s-0040-1719903
32. Ullmann, F.; Schmidt, W. *Eur. J. Inorg Chem*. **1919**, *52*, 2098.

https://doi.org/10.1002/cber.19190521020

33. Ogawa, A.; Curran, D. P. *J. Org. Chem*. **1997**, *62*, 450. https://doi.org/10.1021/jo9620324.
34. Vekariya, R. H.; Aubé, J. *Org. Lett*. **2016**, *18*, 3534. https://doi.org/10.1021/acs.orglett.6b01460
35. Nambela, L.; Haule, L.; Mgani, Q. *Cleaner. Chem. Eng.* **2022**, *3*, 100056. https://doi.org/10.1016/j.clce.2022.100056
36. Kisula, L.; Mdachi, S. J. M.; de Koning, C. B.; Mgani, Q. A. *Tanzan. J. Sci.* **2015**, *41*, 27.
37. Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17. https://doi.org/10.1021/op9900683

Czopek, A.; Partyka, A.; Bucki, A.; Pawłowski, M.; Kołaczkowski, M.; Siwek, A.; Głuch-Lutwin, M.; Koczurkiewicz, P.; Pękala, E.; Jaromin, A.; Tyliszczak, B.; Wesołowska, A.; Zagórska, A. *Mol*. **2020**, *25*, 3868. https://doi.org/10.3390/molecules25173868

39. Satpute, M. S.; Gangan, V. D.; Shastri, I. *Int. J. Sci. Res. Sci. Technol.* **2018**, *4*, 369. https://doi.org/10.31788/RJC.2019.1235167
40. Ji, F.; Huang, H.; Li, M.; Guo, Y.; Song, C.; Chang, J. *Synthesis* **2018**, *50*, 3921. https://doi.org/10.1055/s-0037-1610185
41. Yin, W.; Pan, X.; Leng, W.; Chen, J.; He, H. *Green Chem*. **2019**, *21*, 4614. https://doi.org/10.1039/c9gc01965k
42. Kundu, S.; Mandal, S.; Thirupathi, B. *J. Org. Chem*. **2025**, *90*, 2472. https://doi.org/10.1021/acs.joc.4c03041
43. Cameron, D. W.; Feutrill, G. I.; Griffiths, P. G.; Hodder, D. J. *J. Chem. Soc., Chem. Commun.* **1978**, 688. https://doi.org/10.1039/C39780000688