Electronic Supplementary Material (ESI) for RSC Advances.

Electronic Supporting Information

Upgrading Malic Acid to Bio-based Benzoates *via* a Diels–Alder-Initiated Sequence with the Methyl Coumalate Platform

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I. Experimental Procedures and Spectroscopic Data of Compounds

General Procedures. All starting materials and solvents were purchased from Sigma-Aldrich and used without further purification. All reactions were carried out in flame-dried glassware under argon with dry solvents under anhydrous conditions. All yields refer to isolated products either by column chromatography or by recrystallization. Thin-layer chromatography (TLC) data was obtained with 0.20 mm silica gel plates using UV light as a visualizing agent and potassium permanganate with heat as the developing agent. Silica gel 60A, particle size 0.032 – 0.063 mm, was used for flash column chromatography. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ on a Varian MR-400 or Bruker Avance III 600 MHz spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual protonated chloroform peak ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm) as an internal reference. High-resolution mass spectra (HRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization) or APCI (atmospheric-pressure chemical ionization) or EI (electron ionization) on an Agilent 6890 GC/MS.

General Procedures for the Preparation of Coumalic Acid (4)

Procedure with Sulfuric Acid:

To a solution of *DL*-malic acid (5g, 37.29 mmol) in dichloroethane (75 mL) was added concentrated sulfuric acid (9.94 mL, 186.45 mmol) and heated to 100 °C for 16 h. After cooling to RT, the red solution was poured onto ice and stirred for 30 min. The mixture was extracted with ethyl acetate (3x) and the combined organic extracts were washed with ice-cold water (3x), dried over $MgSO_4$, and concentrated *in vacuo* to give a 16:1 mixture of coumalic acid and fumaric acid (**5**).

Procedure with Acetic Acid and Trifluoroacetic Acid:

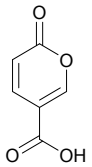
To a solution of *DL*-malic acid (0.268 g, 2 mmol) in concentrated sulfuric acid (10 mL) was added solvent (10 mL) and additive (10 vol %) if needed as described in Table 1. The solution was heated to the specified temperature for 16 h, cooled to rt and poured onto ice. The mixture was extracted with ethyl acetate (3x) and the combined organic layers were washed with ice-cold water (3x), dried over $MgSO_4$, filtered and concentrated to give the crude products.

General Procedure for Sulfonic Acids:

To a solution of *DL*-malic acid (0.268 g, 2 mmol) in dichloroethane (10 mL) was added sulfonic acid (5 equiv) and the solution was heated to 100 °C for 16 h. After cooling to RT, the solution was poured onto ice (50 g) and stirred 30 min. The mixture was extracted with EtOAc (25 mL x 3) and the combined organic extracts were washed with ice-cold water (25 mL x 3), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products.

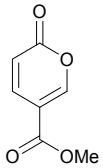
Procedure for para-toluenesulfonic acid:

A mixture of *L*-malic acid and *para*-toluenesulfonic acid was heated to 120 °C with stirring, which resulted in melting of both solids into a red, viscous solution. After 16 h, the mixture was cooled to RT and quenched with H_2O, extracted with ethyl acetate and washed with brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give fumaric acid (**5**) as a tan solid in 71% yield.



4

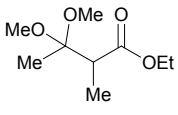
Coumalic acid (**4**): Prepared using the previously described general procedures from malic acid, most successfully by using sulfuric acid (80%) and trifluoroacetic acid (86%). Light yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.42 (dd, J = 0.9, 2.4 Hz, 1H), 7.86 (dd, *J* = 2.7, 9.9 Hz, 1H), 6.36 (dd, *J* = 1.2, 9.6 Hz, 1H).



6

Methyl coumalate (**6**): To a solution of *DL*-malic acid (1g, 7.46 mmol) in dichloroethane (10 mL, ~1 M) was added H_2SO_4 (1.99 mL, 37.29 mmol) slowly at 0 °C. The mixture was warmed to RT then heated to 100 °C for 16 h. After cooling to rt, methanol (1.51 mL, 37.29 mmol) was added and the solution was heated to 80 °C for 8 h. After cooling, the reaction was carefully quenched with water and a saturated solution of sodium bicarbonate at 0 °C. The solution was extracted with EtOAc, washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product which was purified via flash column chromatography (5:1-1:1 hexanes:EtOAc) to give **6** as a yellow solid in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (dd, *J* = 1.2, 2.7 Hz, 1H), 7.79 (dd, *J* = 2.4, 9.6 Hz, 1H), 6.35 (dd, *J* = 0.9, 9.9 Hz, 1H), 3.91 (s, 3H).

General Procedures for the Preparation of Ketals

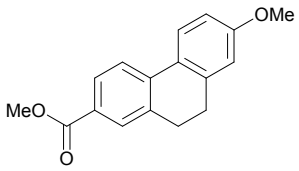


11f

Ethyl 3,3-dimethoxy-2-methylbutanoate (**11f**): The conditions for the preparation of ketal **11f** were also used for the preparation of ketals **11d** and **11g** and were adapted from Wenkert et al.[1] To a solution of ethyl 2-methylacetoacetate (5.0 mL, 35.34 mmol) in methanol (10 mL) at room temperature was added trimethyl orthoformate (5.0 mL, 45.94 mmol) and sulfuric acid (0.77 mL of a 0.40M solution in methanol). The solution was refluxed for 12 hours, after which the solution was concentrated *in vacuo* and cooled in an ice

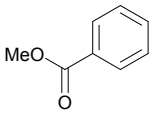
bath. The cold solution was poured into an aqueous KOH solution (0.05M, 0.098 g, 1.75 mmol) and extracted with ethyl acetate (2 x 50 mL) and washed with brine (50 mL). The solution was concentrated *in vacuo* to afford **11f** (5.48 g) as an orange crude liquid, which was used without further purification.

General Procedure for the Diels-Alder Reaction of Methyl Coumalate



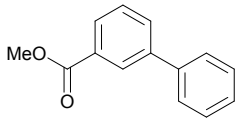
10b

Methyl 7-methoxy-9,10-dihydrophenanthrene-2-carboxylate (**10b**): The synthesis of **10b** is representative, with the exception of **10a** where 1.5 equivalents of butyl vinyl ether was sufficient to effect the desired domino reaction. To a sealable 25-mL pressure vessel was successively added methyl coumalate (0.154 g, 1.0 mmol), toluene (2 mL), and dienophile **7a** (0.33 mL, 3.0 mmol) under argon. The solution was heated to 200 ^{o}C and stirred for 16 h. Upon completion of the reaction, the sealable pressure vessel was cooled to room temperature. The solution was transferred to another flask, while rinsing with ethyl acetate, after which the solution was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:20) to afford **10b** (0.09 g, 34% yield) as a pale yellow liquid. **10b**: R_f = 0.74 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.93 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.88 (d, *J* = 1.4 Hz, 1H), 7.71 (dd, *J* = 8.4, 2.9 Hz, 2H), 6.86 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, *J* = 2.6 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 2.88 (t, *J* = 8.5 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 160.0, 139.9, 139.2, 136.5, 129.4, 128.5, 127.9, 126.6, 125.9, 123.0, 113.7, 112.8, 55.5, 52.2, 29.4, 29.0 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{17}O_3$ $[M + H]^+$ 269.1172, found 269.1180.



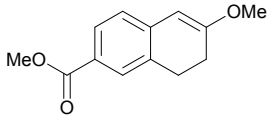
10a

Methyl Benzoate (**10a**): Yellow liquid (0.121 g, 89% yield); R_f = 0.92 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.04 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 3.91 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.2, 133.0, 130.2 (2C), 129.6 (2C), 128.4, 52.2 ppm; HRMS (APCI-TOF) calcd for $C_8H_9O_2$ [*M* + H]$^+$ 137.0597, found 137.0594.



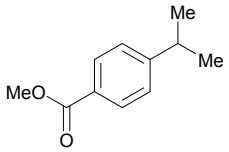
10c

Methyl [1,1'-biphenyl]-3-carboxylate (**10c**): Pale yellow liquid (0.108 g, 51% yield); R_f = 0.74 (silica gel, EtOAc:hexanes 1:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.29 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 3.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 141.6, 140.3, 131.7, 130.8, 129.0 (3C), 128.5, 128.4, 127.9, 127.3 (2C), 52.4 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{13}O_2$ [*M* + H]$^+$ 213.0910, found 213.0908.



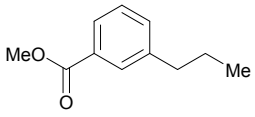
10d

Methyl 6-methoxy-7,8-dihydronaphthalene-2-carboxylate (**10d**): Yellow solid (0.156 g, 72% yield); R_f = 0.80 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.78 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.74 (s, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 5.59 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 2.92 (t, *J* = 8.2 Hz, 2H), 2.43 (t, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 163.1, 140.8, 131.9, 128.4, 128.2, 125.9, 124.6, 96.3, 55.2, 52.0, 28.4, 27.5 ppm; HRMS (ESI-TOF) calcd for $C_{13}H_{15}O_3$ [*M* + H]$^+$ 219.0943, found 219.1016.



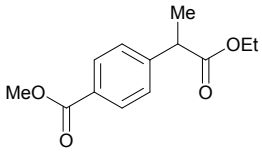
12c

Methyl 4-isopropylbenzoate (**12c**): Yellow oil (0.072 g, 40% yield); R_f = 0.86 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.96 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.90 (s, 3H), 3.00 – 2.92 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 154.4, 129.8, 127.9, 126.6, 52.1, 34.4, 23.8 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{15}O_2$ [*M* + H]$^+$ 179.1067, found 179.1062.



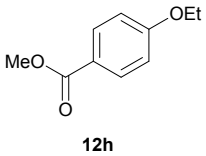
12d

Methyl 3-propylbenzoate (**12d**): Yellow liquid (0.077 g, 43% yield); R_f = 0.64 (silica gel, EtOAc:hexanes 1:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.85 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 3.91 (s, 3H), 2.63 (t, *J* = 8.0 Hz, 2H), 1.66 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 143.1, 133.3, 130.2, 129.7, 128.4, 127.1, 52.2, 37.9, 24.6, 13.9 ppm; HRMS (EI-GC/MS) calcd for $C_{11}H_{14}O_2$ [*M* + H]$^+$ 178.0994, found 178.0793.



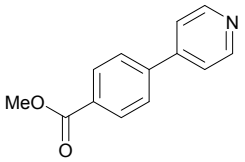
12f

Methyl 4-(1-ethoxy-1-oxopropan-2-yl)benzoate (**12f**): White oil (0.179 g, 76% yield); R_f = 0.81 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.99 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.18 – 4.07 (m, 2H), 3.91 (s, 3H), 3.76 (q, *J* = 7.2 Hz, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0, 167.0, 145.9, 130.1 (2C), 129.1, 127.7 (2C), 61.1, 52.2, 45.7, 18.6, 14.2 ppm; HRMS (ESI-TOF) calcd for $C_{13}H_{16}O_4$ [*M* + H]$^+$ 237.1121, found 237.1116.



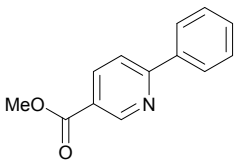
12h

Methyl 4-ethoxybenzoate (**12ah**): Yellow oil (0.086 g, 48% yield); R_f = 0.82 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.98 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0, 162.9, 131.7 (2C), 122.5, 114.1 (2C), 63.8, 52.0, 14.8 ppm; HRMS (APCI-TOF) calcd for $C_{10}H_{13}O_3$ [*M* + H]$^+$ 181.0859, found 181.0854.



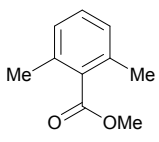
14d

Methyl 4-(pyridin-4-yl)benzoate (**14d**): White solid (0.048 g, 23% yield); R_f = 0.26 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 8.70 (d, *J* = 6.1 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 6.1 Hz, 2H), 3.95 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.7, 150.6 (2C), 147.4, 142.6, 130.8, 130.5 (2C), 127.2 (2C), 121.9 (2C), 52.5 ppm; HRMS (ESI-TOF) calcd for $C_{13}H_{12}NO_2$ [*M* + H]$^+$ 214.0863, found 214.0861.



14e

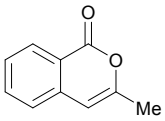
Methyl 6-phenylnicotinate (**14e**): Tan solid (0.038 g, 18% yield); R_f = 0.75 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.28 (d, *J* = 1.6 Hz, 1H), 8.35 (dd, *J* = 8.3, 1.9 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.50 (q, *J* = 8.6 Hz, 3H), 3.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 161.1, 151.1, 138.4, 138.0, 130.1, 129.1 (2C), 127.5 (2C), 124.3, 120.0, 52.5 ppm; HRMS (APCI-TOF) calcd for $C_{13}H_{12}NO_2$ [*M* + H]$^+$ 214.0863, found 214.0860.



16a

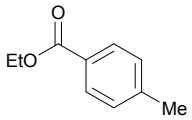
Methyl 2,6-dimethylbenzoate (**16a**): Yellow liquid (0.089 g, 54% yield); R_f = 0.91 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.19 (t, *J* =

7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 2H), 3.91 (s, 3H), 2.31 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 170.6, 135.1 (2C), 133.9, 129.5, 127.7 (2C), 52.0, 19.8 (2C) ppm; HRMS (APCI-TOF) calcd for $C_{10}H_{13}O_2$ [M + H]$^+$ 165.0910, found 165.0908.



16b

3-Methyl-1H-isochromen-1-one (**16b**): Yellow solid (0.072 g, 45% brsm); R_f = 0.55 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.67 (d, J = 9.5 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.36 (d, J = 9.5 Hz, 1H), 2.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.3, 154.3, 143.5, 143.3, 127.7, 125.7, 117.2, 116.6, 115.6, 21.9 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_9O_2$ [M + H]$^+$ 161.0597, found 161.0597.



16c

Ethyl 4-methylbenzoate (**16b**): Yellow liquid (0.069 g, 42%); R_f = 0.87 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.94 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8, 143.5, 129.7, 129.6, 129.1, 129.1, 127.8, 60.8, 21.8, 14.4 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_{12}O_2$ [M + H]$^+$ 164.0837, found 164.0786.

II. Reference

1. Adapted from Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Guo, M.; Guan, Y.; Wenkert, E. *Helv. Chim. Acta* **2005**, *88*, 330-338.