Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

First diastereoselective synthesis of methyl caffeoyl- and feruloyl-*muco*-quinates

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Supplementary information

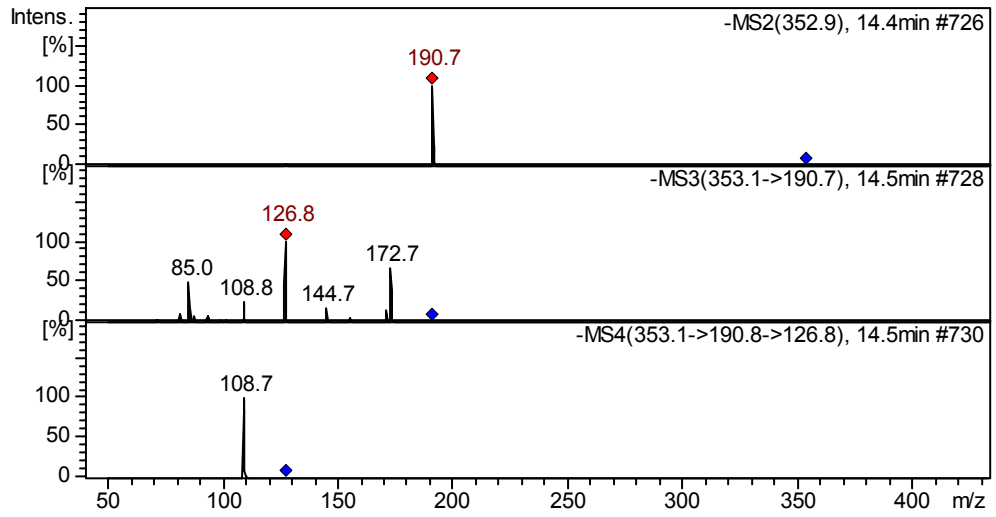


Figure 1: MS^4 Spectra of *muco*-3-CQA.

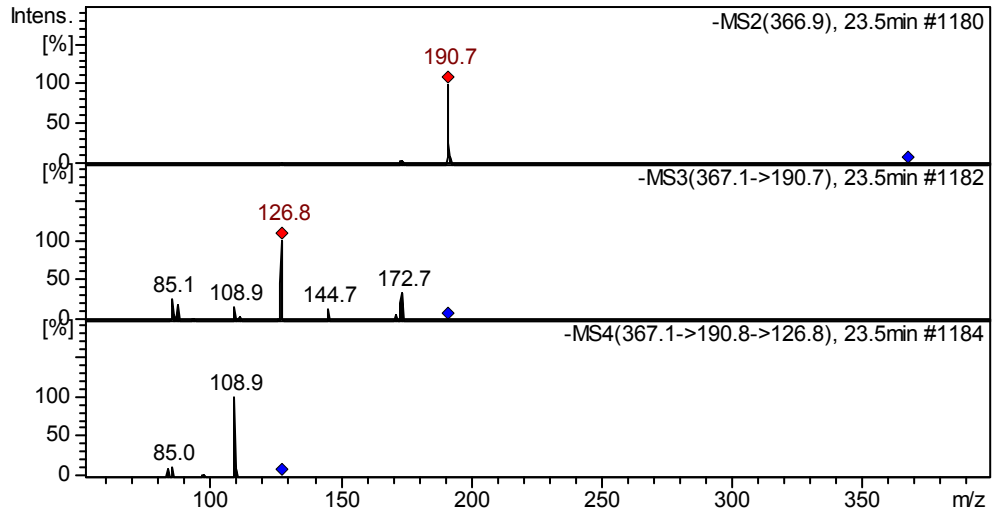


Figure 2: MS^4 Spectra of *muco*-3-FQA.

Synthesis of 3-caffeoyl-*muco*-quinic acid and 3-feruloyl-*muco*-quinic acid 30 and 31

Synthesis of methyl 3-*O*-(4-*O*-allyl)-feruloyl-TMB-*muco*-quinate. To a solution of methyl TMB-*muco*-quinate (1 g, 3.12 mmol) and 4-(dimethyl amino)-pyridine (DMAP) (77 mg, 0.63 mmol) in DCM (50 mL) were added pyridine (10 mL) and acid chloride (4.68 mmol) at room temperature. The reaction mixture was refluxed for 24 h and acidified with a 1 M HCl solution to pH = 3. The layers were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 30-50%) to give methyl 3-*O*-(4-*O*-allyl)-feruloyl-TMB-*muco*-quinate as a pale yellow powder (1.60 g, 96%), mp 101-103 ^{o}C; ν_{max}/cm^{-1} (KBr) 3423br, 3080w, 2992, 2951, 1749s, 1713s, 1631vs, 1597vs, 1264s, 1139; δ_H ($CDCl_3$): 1.24 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.86 (1H, dd, *J* 13.0, 11.4, 6-*H*H), 1.89 (1H, ddd, *J* 12.5, 5, 2.2, 2-*H*H), 1.97 (1H, t, *J* 12.5, 6-H*H*), 2.25 (1H, ddd, *J* 12.8, 5.0, 2.3, 2-H*H*), 3.20 (3H, S, $COCH_3$), 3.28 (3H, s, $COCH_3$), 3.75 (1H, t, *J* 10.1, 4-H), 3.75 (3H, s, $COOCH_3$), 3.87 (3H,

s, C_{Ar}-OCH_3), 4.09 (1H, ddd, *J* 11.4, 5.0, 1.8, 3-H), 4.60 (2H, d, *J* 2.3, C_{Ar}-OCH_2), 5.27 (2H, m, CH*H*=CH), 5.38 (1H, ddd, *J* 12.8, 2.5, 1.4, C*H*H=CH), 6.1 (1H, m, CH_2=C*H*), 6.23 (1H, d, *J* 16.0, C_{Ar}-CH=C*H*), 6.82 (1H, d, J 8.7, C_{Ar}*H*), 7.04 (2H, m, C_{Ar}*H*), 7.57 (1H, d, J 16.0, C_{Ar}-C*H*); δ_C ($CDCl_3$): 17.7 (CH_3), 17.8 (CH_3), 37.5 (C-2), 38.9 (C-6), 47.8 (CO*C*H_3), 48.0 (CO*C*H_3), 53.2 (COO*C*H_3), 56.0 (Ar-O*C*H_3), 65.6 (C-3), 69.3 (C-5), 69.8 (C_{Ar}-O*C*H_2), 73.3 (C-4), 73.5 (C-1), 99.6 (*C*OCH_3), 99.7 (*C*OCH_3), 110.2 (C_{Ar}), 112.9 (C_{Ar}), 115.8 (*C*H-COO), 118.4 (*C*H_2=CH), 122.5 (C_{Ar}), 127.6 (C_{Ar}-CH), 132.8 (CH_2=*C*H), 144.9 (C_{Ar}-*C*H), 149.6 (C_{Ar}-OCH_3), 150.2 (C_{Ar}-OCH_2), 166.3 (CH-*C*OO), 175.2 (*C*OOCH_3); HRMS (ESI+): Exact mass calculated for $C_{27}H_{36}O_{11}Na$ $[M+Na^+]^+$, 559.2155. Found 559.2154.

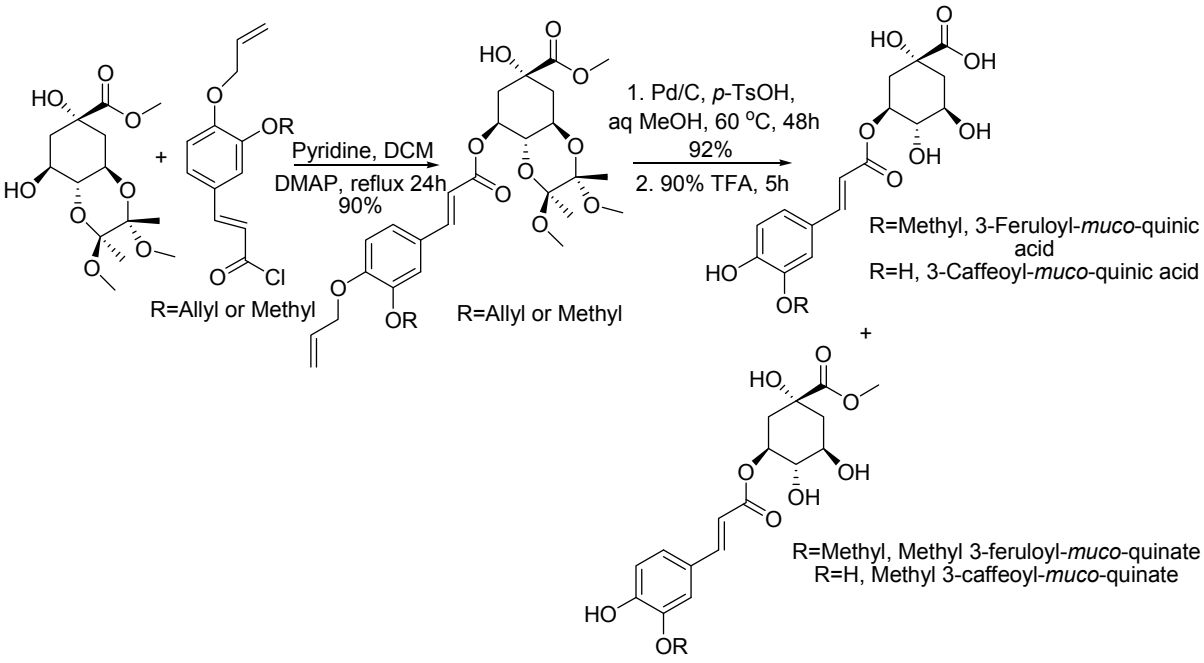
Synthesis of 3-*O*-feruloyl-*muco*-quinic acid (31). To a solution of methyl 3-*O*-(4-*O*-allyl)-feruloyl-TMB-*muco*-quinate (537 mg, 1 mmol), and *p*-TsOH (20 mg, 0.105 mmol) in methanol-water (9:1, 30 mL) was added 10% Pd/C (195 mg) at room temperature. The reaction mixture was heated at 60 ^oC for 48 h, cooled to room temperature, filtered and methanol was removed in vacuo. Aqueous reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 60-80%) to give methyl 3-*O*-feruloyl-TMB-*muco*-quinate pale yellow powder (471 mg, 95%). Methyl 3-*O*-feruloyl-TMB-*muco*-quinate (471 mg, 0.95 mmol) was dissolved in a TFA (90% aq. solution, 20 mL) at 0 ^oC and the solution was stirred for 5 h at room temperature. The solvents were removed in vacuo to afford the target compound which was analyzed by HPLC-MS.

Synthesis of methyl 3-*O*-(3,4-di-*O*-allyl)-caffeoyl-TMB-*muco*-quinate. To a solution of methyl TMB-*muco*-quinate (1 g, 3.12 mmol) and DMAP (77 mg, 0.63 mmol) in DCM (50 mL) were added pyridine (10 mL) and acid chloride **7** (1.30 g, 4.68 mmol) at room

temperature. The reaction mixture was refluxed for 36 h and acidified with a 1 M HCl solution to pH = 3. The layers were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 20-40%) to give methyl 3-*O*-(3,4-di-*O*-allyl)-caffeoyl-TMB-*muco*-quinate as a pale yellow powder (1.66 g, 95%), mp 82-84 ^oC; ν_{max}/cm^{-1} (KBr) 3423, 2951, 2992, 3080, 1749, 1713, 1631, 1597, 1511, 1264, 1139, 1076; δ_H ($CDCl_3$): 1.28 (6H, s, CH_3), 1.85 (2H, m, 6-*H*H, 2-*H*H), 1.99 (1H, t, *J* 12.4, 6-H*H*), 2.23 (1H, m, 2-H*H*), 3.16 (1H, m, 2-H*H*), 3.24 (6H, s, $COCH_3$), 3.31 (3H, s, $COOCH_3$), 3.77 (1H, t, *J* 10, 4-H), 4.10 (1H, ddd, *J* 14.2, 12.3, 5, 3-H), 4.6 (4H, m, C_{Ar}-OCH_2), 5.29 (2H, d, *J* 9.62, CH*H*=CH), 5.43 (2H, d, *J* 16.9, C*H*H=CH), 6.06 (2H, m, CH_2=C*H*), 6.21 (1H, d, *J* 16, C_{Ar}-CH=C*H*), 6.85 (1H, d, J 8.7, $C_{Ar}H$), 7.04 (2H, m, $C_{Ar}H$), 7.56 (1H, d, J 16, C_{Ar}-C*H*); δ_C ($CDCl_3$): 17.7 (CH_3), 17.8 (CH_3), 37.5 (C-2), 38.7 (C-6), 47.7 (CO*C*H_3), 47.9 (CO*C*H_3), 53.2 (COO*C*H_3), 65.5 (C-3), 69.2 (C-5), 69.7 (C_{Ar}-O*C*H_2), 70.0(C_{Ar}-O*C*H_2), 73.2 (C-4), 73.46 (C-1), 99.6 (*C*OCH_3), 99.9 (*C*OCH_3), 112.9 (C_{Ar}), 113.5 (C_{Ar}), 115.9 (*C*H-COO), 117.9 (*C*H_2=CH), 117.9 (*C*H_2=CH), 122.4 (C_{Ar}), 127.6 (C_{Ar}-CH), 132.9 (CH_2=*C*H), 133.2 (CH_2=*C*H), 144.8 (C_{Ar}-*C*H), 148.6 (C_{Ar}-OCH_2), 150.7 (C_{Ar}-OCH_2), 166.2 (CH-*C*OO), 175.3 (*C*OOCH_3); HRMS (ESI+): Exact mass calculated for $C_{29}H_{38}O_{11}Na$ $[M+Na^+]^+$, 585.2155. Found 559.2154.

Synthesis of 3-*O*-caffeoyl-*muco*-quinic acid (30). To a solution of methyl 3-*O*-(3,4-di-*O*-allyl)-caffeoyl-TMB-*muco*-quinate (562 mg, 1 mmol), and *p*-TsOH (40 mg, 0.21 mmol) in methanol-water (9:1, 30 mL) was added 10% Pd/C (390 mg) at room temperature. The reaction mixture was heated at 60 ^oC for 48 h, cooled to room temperature, filtered and methanol was removed in vacuo. The aqueous reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 60-90%) to give methyl 3-*O*-caffeoyl-TMB-*muco*-

quinate as a pale yellow powder (461 mg, 93%). Methyl 3-*O*-caffeoyl-TMB-*muco*-quinate (461 mg, 0.93 mmol) was dissolved in a TFA solution (90% aq. solution, 20 mL) at 0 ^{o}C and the solution was stirred for 5 h at room temperature. The solvents were removed in vacuo to afford the target compound which was analyzed by HPLC-MS



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