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Total synthesis of 3,5-*O*-dicaffeoylquinic acid and its derivatives

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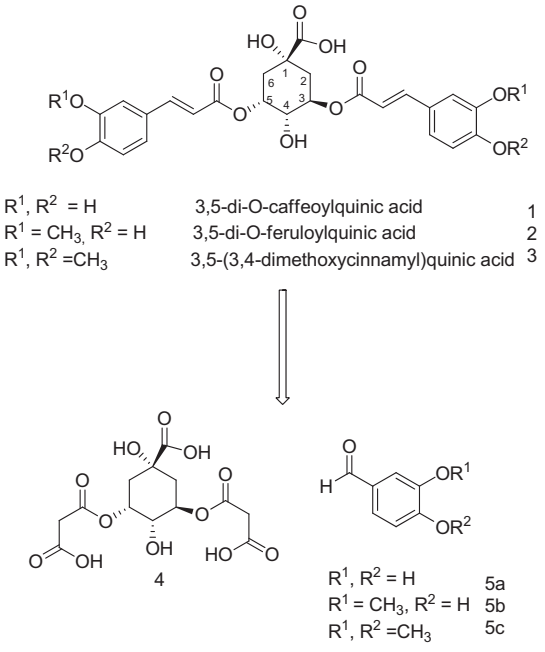
ABSTRACT

We report the first total synthesis of 3,5-*O*-dicaffeoylquinic acid and its derivatives, 3,5-*O*-diferuloylquinic acid and 3,5-(3,4-dimethoxycinnamyl)quinic acid, in a nine-step sequence. The key step involves Knoevenagel condensations between vanillin, 3,4-dimethoxybenzaldehyde or 4-hydroxy-3-methoxybenzaldehyde and the dimalonate ester of quinic acid.

Dicaffeoylquinic acids (DCQAs) are constituents of coffee, and artichoke extracts. DCQAs possess a wide range of pharmacological properties including antiviral, antioxidant, antibacterial and antihistamic.[1–5] Their metabolism has never been studied in detail, however there is evidence that caffeoylquinic esters in general are hydrolysed to caffeic acid which is subsequently further metabolised.[6] In rats, 1,5-dicaffeoylquinic acid has been shown to be metabolised into glucuronide conjugates.[7] However, the exact nature of these conjugates remains unclear in the absence of fully characterised standard compounds. It is likely that similar metabolism occurs for the isomeric 3,5-*O*-dicaffeoylquinic acid.

DCQAs are formed by esterification of hydroxycinnamic acids with quinic acid.[1] There has been significant interest in the synthesis and metabolism of DCQAs and their derivatives. In 2001, Sefkow et al.[8] described the synthesis of 1-, 4-, and 5-caffeoylquinic acids based on the esterification of quinic acid by cinnamic acid derivatives. This methodology required the protection of both precursors until the final step of the synthesis. Recently Smarrito et al.[9] developed a new method for the synthesis of 5-*O*-feruloylquinic acid and 5-*O*-feruloylquinic methyl ester in which the (*E*)-double bond was formed in the final step of the synthesis using a Knoevenagel condensation reaction. The advantage of this method was that neither the aldehyde nor the quinic acid fragment required protection for the final step of the synthesis.

Herein, we have applied the Knoevenagel method to achieve the first total synthesis of 3,5-*O*-dicaffeoylquinic acid (**1**), 3,5-*O*-diferuloylquinic acid (**2**) and 3,5-(3,4-dimethoxycinnamyl)quinic acid (**3**) (Scheme 1), such that they were available as pure compounds for



Scheme 1.

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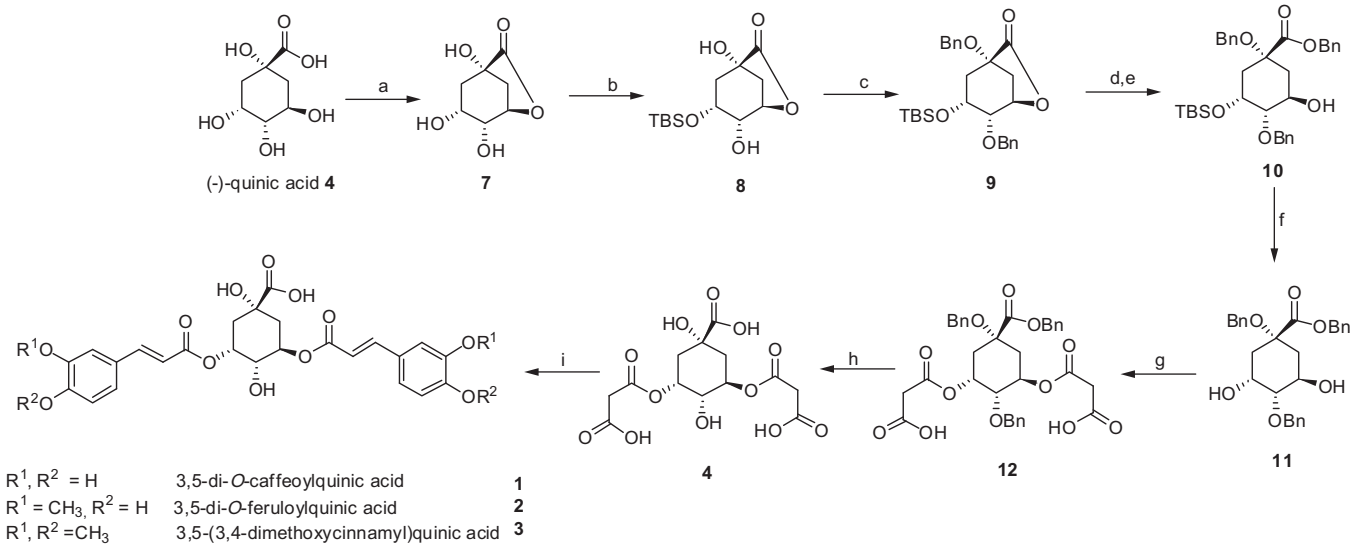

Scheme 2. Reagents and conditions: (a) *p*-TsOH, toluene, DMF, reflux, 12 h, 99%; (b) imidazole, DMF, TBSCl, 0 °C for 30 min and 1 h at rt 83%; (c) NaH, DMF, 0 °C, 30 min, then BnBr, DMF, 60 °C, 12 h, 60%; (d) NaOH, THF–H_2O (4:1), rt, 40 min, 93%; (e) Cs_2CO_3, MeOH–H_2O, rt, 20 min, then BnBr, DMF, rt, 12 h, 95%; (f) HF-pyridine, THF, 0 °C to rt, 12 h, 93%; (g) Meldrum's acid, toluene, 60 °C, 4 h, 79%; (h) $Pd(OH)_2$, H_2, MeOH, rt, 36 h, 94%; (i) **5a**–**c**, DMAP, piperidine (cat.), DMF, rt, 8 d, **1** (68%), **2** (72%), **3** (81%).

metabolism studies. This method involved the double condensation of a bis-malonic acid ester (**4**) with two equivalents of the appropriate benzaldehyde **5** followed by decarboxylative dehydration.

The synthesis of **1** and its derivatives commenced with the preparation of bicyclic trihydroxy lactone **7** from commercially available (−)-quinic acid (**6**) (Scheme 2). The selective protection (C-3) of **7** as the TBS ether **8** was achieved in good yield.[10] The remaining free hydroxy groups (C-1 and C-4), were then subjected to benzyl ether protection to provide **9** in 60% yield.[11] Hydrolysis of **9** with NaOH in THF–H_2O at room temperature, followed by esterification of the resulting carboxylate by treatment with Cs_2CO_3 and benzyl bromide afforded the benzyl ester **10** in 55% yield over the two steps.[12] Removal of the TBS protecting group was achieved using HF-pyridine in THF at 0 °C and furnished diol **11** in a good (93%) yield.[13] Diol **11** was then subjected to a double acylation by treatment with 2.2 equiv of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in toluene at 60 °C. This gave diester **12** in 79% yield.[14] Cleavage of the benzyl protecting groups was achieved in 94% yield by hydrogenolysis [$Pd(OH)_2$, MeOH] to give the deprotected diester **4** as the immediate precursor to three dicaffeoylquinic acids. The final step of the syntheses involved a double Knoevenagel condensation without any protecting groups. Accordingly, treatment of **4** with aldehydes **5a**–**c**, DMAP and piperidine in anhydrous DMF afforded the target compounds in moderate to good yields [3,5-DCQA (**1**)[15] (68%), 3,5-diferuloylquinic acid (**2**)[16] (72%) and 3,5-(3,4-dimethoxycinnamyl)quinic acid (**3**)[17] yield (81%)].

In conclusion, the development of a protocol for the synthesis of 3,5-DCQA (**1**), 3,5-diferuloylquinic acid (**2**) and 3,5-(3,4-dimethoxycinnamyl)quinic acid (**3**) is described, exploiting a Knoevenagel strategy. This protocol should be amenable to a wide range of symmetrical difunctionalised derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.127.

References and Notes

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15. Selected analytical data for (1_{Sn},3*R*,4_{Sn},5*R*)-3,5-*O*-dicaffeoylquinic acid (**1**):[18] $[\alpha]_D^{25}$ +76 (*c* 0.1, MeOH) δ_H (500 MHz, DMSO-d_6) 9.59 (2H, s),9.16 (2H, s, 1-H), 7.47 (1H, d, *J* = 16.0 Hz), 7.46 (1H, d, *J* = 16.0 Hz), 7.04 (1H, d, *J* = 1.8 Hz), 7.05 (1H, d, *J* = 1.8 Hz), 7.00 (1H, dd, *J* = 8.1, 1.8 Hz), 6.99 (1H, dd, *J* = 8.1, 1.8 Hz), 6.77 (2H, d, *J* = 8.1 Hz,), 6.20 (1H, d, *J* = 16.0 Hz,), 6.19 (1H, d, *J* = 16.0 Hz), 5.25 (1H, td, *J* = 8.4, 3.9 Hz), 4.95 (1H, s), 4.59 (1H, d, *J* = 4.3 Hz), 4.1–10 (1H, m), 3.6–58 (1H, m), 2.3–26 (3H, m), 1.9–88 (1H, m); δ_c (75.46 MHz, DMSO-d_6) 172.9, 166.4, 165.7, 148.9, 148.8, 146.0, 145.9, 145.6, 126.0, 125.9, 121.8. 121.7, 116.2, 115.2, 114.6, 79.5, 71.2, 70.3, 67.8, 36.1, 34.5; *m*/*z* (ES^-) 515 [$(M-H)^-$, 100%]; HRMS: Calcd. for $C_{25}H_{23}O_{12}$ 515.1190, found 515.1190.
16. Selected analytical data for (1_{Sn},3*R*,4_{Sn},5*R*)-3,5-di-*O*-feruloylquinic acid (**2**).[18] $[\alpha]_D^{25}$ +39 (*c* 0.5, MeOH); υ_{max}(film)/cm^{-1} 3460, 1592, 1513, 1270, 1158; δ_H (500 MHz, DMSO-d_6) 9.63 (1H, s), 9.62 (1H, s), 7.54 (1H, d, *J* = 16.0 Hz), 7.53 (1H, d, *J* = 16.0 Hz), 7.32 (1H, d, *J* = 1.8 Hz), 7.30 (1H, d, *J* = 1.8 Hz), 7.11 (1H, dd, *J* = 8.1, 1.8 Hz), 7.08 (1H, dd, *J* = 8.1, 1.8 Hz), 6.80 (2H, d, *J* = 8.1 Hz), 6.45 (1H, d, *J* = 16.0 Hz), 6.39 (1H, d, *J* = 16.0 Hz), 5.24 (1H, ddd, *J* = 3.5, 3.5, 4.1 Hz), 4.95

(1H, d, J = 4.4 Hz), 4.1–07 (1H, m), 3.83 (3H, s), 3.82 (3H, s) 3.6–58 (1H, m), 2.3–25 (3H, m), 1.9–87 (1H, m); δ_c (75.4 MHz, DMSO-d_6) 172.5, 166.0, 165.4, 149.3, 149.2, 147.9, 147.8, 145.4, 145.0, 125.5, 123.3, 123.1, 115.4, 114.6, 111.1, 110.8, 79.1, 70.9, 69.8, 67.4, 55.6, 35.7, 34.0; m/z (ES^-) 543 [$(M-H)^-$], 100%]; HRMS (ES^-) [Found: $(M-H)^-$, 543.1500, $C_{27}H_{27}O_{12}$ requires 543.1503].

17. Selected analytical data for (1$_{Sn}$,3R,4$_{Sn}$,5R)-3,5-(3,4-dimethoxycinnamyl)quinic acid (**3**).[18] $[\alpha]_D^{25}$ +52 (c 0.18, MeOH); ν_{max}(thin film)/cm^{-1} 3054, 1707, 1631, 1263; δ_H (500 MHz, DMSO-d_6) 7.38 (1H, d, J = 16.0 Hz), 7.37 (1H, d, J = 16.0 Hz), 7.15 (1H, d, J = 1.8 Hz), 7.13 (1H, d, J = 1.8 Hz), 7.04 (1H, dd, J = 8.1, 1.8 Hz), 7.01 (1H, dd, J = 8.1, 1.8 Hz), 6.82 (2H, d, J = 8.1), 6.33 (1H, d, J = 16.0 Hz), 6.27 (1H, d, J = 16.0 Hz), 5.0–01 (1H, m), 4.70 (1H, d, J = 4.4 Hz), 3.9–82 (1H, m), 3.62 (3H, s), 3.61 (3H, s), 3.59 (6H, s), 3.4–37 (1H, m), 2.0–07 (2H, m), 1.7–67 (2H, m); δ_c (75.4 MHz, DMSO-d_6) 173.0, 166.4, 165.8, 151.4, 149.4, 145.4, 145.1, 127.3, 123.6, 123.4, 116.2, 112.0, 110.7, 110.5, 79.9, 71.5, 70.5, 68.0, 56.0, 36.3, 34.5; m/z (ES^+) 595 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 595.1791, $C_{29}H_{32}O_{12}Na$ requires 595.1793].

18. Nomenclature as in: Eliel, E. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3551.