

# A novel efficient and versatile route to the synthesis of 5-*O*-feruloylquinic acids

Candice Menozzi Smarrito, Caroline Munari, Fabien Robert and Denis Barron\*

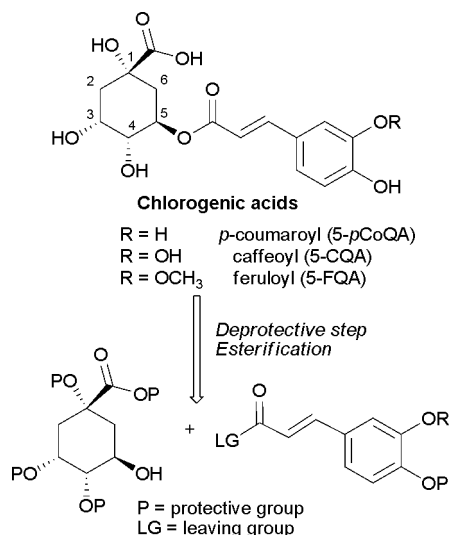
Received 11th December 2007, Accepted 29th January 2008

First published as an Advance Article on the web 12th February 2008

DOI: 10.1039/b719132d

A novel synthesis of 5-*O*-feruloylquinic acid, a polyphenolic compound found in coffee beans, and its methyl ester derivative has been optimized. The sequence involves 6 steps and is compatible with the preparation of potential human metabolites of these compounds. The key reaction is a Knoevenagel condensation of 4-hydroxy-3-methoxy-benzaldehyde and a malonate ester of quinic acid.

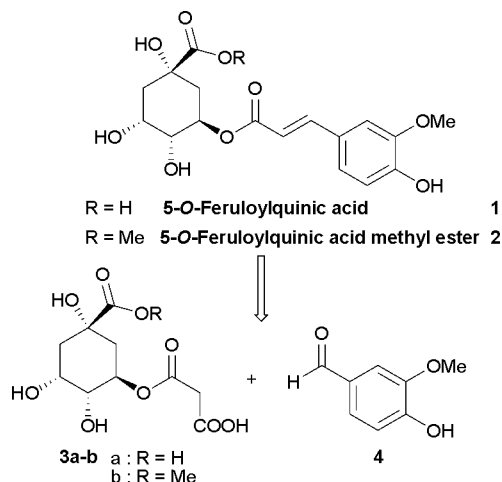
Chlorogenic acids are natural polyphenolic compounds containing quinic acid and *trans*-cinnamic acid units. The main subgroup is formed by the 5-mono-esters of caffeic (5-CQA), *p*-coumaric (5-*p*CoQA) and ferulic acid (5-FQA) (Scheme 1), present in coffee beans, potatoes and many fruits and vegetables.<sup>1</sup> Chlorogenic acids possess many biological properties such as antibacterial, antioxidant, antimutagenic, antitumor and antiviral activities.<sup>2,3</sup> Consequently there is a lot of interest in the chemistry of chlorogenic acids and their potential human metabolites. The previously reported syntheses of chlorogenic acids and their derivatives were based on the esterification of quinic acid by a cinnamic acid derivative (Scheme 1).<sup>4</sup> However, the regioselective esterification requires suitable protection of both precursors, and the final deprotection step could be delicate. In fact, the chlorogenic acid skeleton may be sensitive to hydrogenative, basic or strong acidic conditions under which some double bond reduction, isomerisation (transesterification) and/or ester cleavage reactions can take place.



Scheme 1

Herein we describe a new flexible approach towards chlorogenic acids and its first application to the synthesis of 5-*O*-feruloylquinic acid **1** and its methyl ester derivative **2**.

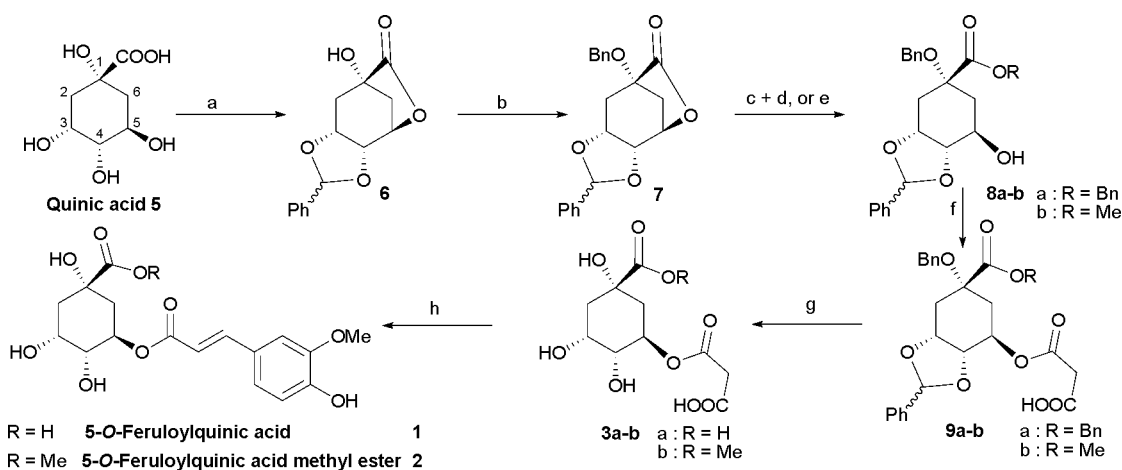
In our convergent approach to 5-*O*-feruloylquinic acid **1** and 5-*O*-feruloylquinic acid methyl ester **2**, the (*E*)-double bond will be formed in the last step by the condensation of the aldehyde **4** and malonates **3a–b** derived from quinic acid (Scheme 2). Advantageously, this Knoevenagel reaction did not require the protection of the phenol **4** and the malonyl quinic fragments **3a–b**. Using this approach, the desired hydroxycinnamoyl quinic acid was directly obtained with no deprotection step, thus eliminating any additional reaction on the sensitive FQA skeleton.



Scheme 2

The synthesis of malonates **3a–b** was readily achieved starting from commercially available quinic acid **5** (Scheme 3). The latter was first dehydrated and protected to the benzylidene quinide derivative **6** (92%) by heating it to reflux in toluene with benzaldehyde and a catalytic amount of *p*-toluenesulfonic acid.<sup>5</sup> Protection of the free 1-hydroxyl group in **6** under standard benzylation conditions (NaH, BnBr, DMF)<sup>6</sup> provided the lactone **7** in 87% yield. Saponification using NaOH in THF–H<sub>2</sub>O at room temperature, followed by esterification of the resulting carboxylate by treatment with Cs<sub>2</sub>CO<sub>3</sub> (0.5 eq.) and benzyl bromide,<sup>7</sup> afforded benzyl ester **8a** in 94% yield over the two steps. The methyl ester **8b** was directly prepared by treatment of the lactone **7** with MeONa in MeOH (94%).<sup>5</sup> The 5-alcohol functions of **8a–b** were then esterified by refluxing in toluene with commercially available 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid),<sup>8</sup> to lead to the corresponding malonates **9a–b** in 92% and 79% yields, respectively. Removal of all protective groups was then performed in one step using hydrogenative conditions (Pd/C 5%, MeOH/H<sub>2</sub>O), to give the quinic acid fragments **3a–b** (70% and

Nestlé Research Center, Vers Chez Les Blanc, 1000, Lausanne 26, Switzerland. E-mail: denis.barron@rdls.nestle.com; Fax: (+41) 021 785 8554; Tel: (+41) 021 785 9497



**Scheme 3** Reagents and conditions: a) PhCHO, *p*-TsOH, toluene, reflux, 16 h, 92%; b) NaH, DMF, 0 °C, 30 min then BnBr, DMF, rt, 12 h, 87%; c) NaOH, THF–H<sub>2</sub>O, rt, 40 min, quant.; d) Cs<sub>2</sub>CO<sub>3</sub>, MeOH–H<sub>2</sub>O, rt, 20 min then BnBr, DMF, rt, 8 h, **8a** 94%; e) NaOMe, MeOH, rt, 1 h, **8b** 94%; f) Meldrum's acid, toluene, reflux, 3 h 30 min, **9a** 92%, **9b** 79%; g) H<sub>2</sub>, Pd/C 5%, MeOH–H<sub>2</sub>O, rt, 40 h, **3a** 70%, **3b** quant.; h) vanillin **4**, DMAP, piperidine, DMF, rt, 7 days, **1** 40%, **2** 75%

quantitative, respectively). Finally, DMAP-catalysed Knoevenagel condensation was achieved on vanillin **4** and malonates **3a–b**, using the mild conditions developed by List *et al.* (rt, 7 days).<sup>9</sup> This afforded 5-*O*-feruloylquinic acid<sup>10</sup> **1** (40%) and 5-*O*-feruloylquinic acid methyl ester<sup>11</sup> **2** (75%). The analytical data (<sup>1</sup>H and <sup>13</sup>C NMR) of synthetic 5-*O*-feruloylquinic acid **1** were in good agreement with the reported data for the natural product.<sup>12</sup>

In conclusion, starting from quinic acid and vanillin, the syntheses of 5-*O*-feruloylquinic acid and 5-*O*-feruloylquinic acid methyl ester were achieved in 19% and 44% overall yields, respectively. This new efficient route to chlorogenic acids could be applied in the future to the synthesis of potential human metabolites of these compounds (sulfo- and glucuro-conjugates), which are not compatible with the deprotection step conditions used in the previous reported syntheses. Work on the synthesis of these conjugates is in progress in our laboratory and the details will be published in a forthcoming paper.

## Notes and references

- 1 (a) P. A. Kroon and G. Williamson, *J. Sci. Food Agric.*, 1999, **79**, 355–361; (b) M. N. Clifford, *J. Sci. Food Agric.*, 1999, **79**, 362–372; (c) M. N. Clifford, The nature of chlorogenic acids. Are they advantageous compounds in coffee?, *17ème Colloque Scientifique International sur le Café*, ed. ASIC, 1997, pp. 79–88.
- 2 (a) *Phytochemistry Dictionary*, ed. J. B. Harborne and H. Baxter, Taylor & Francis, London, 1993, p. 1745; (b) A. A. P. Almeida, A. Farah, D. A. M. Silva, E. A. Nunan and M. B. A. Gloria, *J. Agric. Food Chem.*, 2006, **54**, 8738–8743.
- 3 (a) H. Iwashashi, Y. Negoro, A. Ikeda, H. Morishita and R. Kido, *Biochem. J.*, 1986, **239**, 641–646; (b) M. Ohnishi, H. Morishita, H. Iwashashi, S. Toda, Y. Shirataki, M. Kimura and R. Kido, *Phytochemistry*, 1994, **36**, 579–583; (c) C. Castelluccio, G. Pagana, N. Melikan, G. P. Bolwell, J. Prodham, J. Sampson and C. Rice-Evans, *FEBS Lett.*, 1995, **368**, 188–192; (d) Y. Kono, S. Kashine, T. Yoneyama, Y. Sakamoto, Y. Matsui and H. Shibata, *Biosci., Biotechnol., Biochem.*, 1998, **62**, 22–27.
- 4 (a) K. Ishikawa, Y. Sakurai, T. Ariyama, S. Yoshioka, T. Shiraki, H. Horikoshi, H. Kuwano, T. Kinoshita and M. Boriboon, *Sankyo Kenkyusho Nempo*, 1991, **43**, 99–110; (b) H. Hemmerle, H.-J. Burger, P. Below, G. Schubert, R. Rippel, P. W. Schindler, E. Paulus and A. W. Herling, *J. Med. Chem.*, 1997, **40**, 137–145; (c) M. Sefkow, *Eur. J. Org. Chem.*, 2001, 1137–1141.
- 5 J. M. Harris, W. J. Watkins, A. R. Hawkins, J. R. Coggins and C. Abell, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2371–2377.
- 6 N. Kaila, W. S. Somers, B. E. Thomas, P. Thakker, K. Janz, S. DeBernardo, S. Tam, W. J. Moore, R. Yang, W. Wrona, P. W. Bedard, D. Crommie, J. C. Keith, D. H. H. Tsao, J. C. Alvarez, H. Ni, E. Marchese, J. T. Patton, J. L. Magnani and R. T. Camphausen, *J. Med. Chem.*, 2005, **48**, 4346–4357.
- 7 J.-L. Montchamp, J. Peng and J. W. Frost, *J. Org. Chem.*, 1994, **59**, 6999–7007.
- 8 Y. Ryu and I. Scott, *Tetrahedron Lett.*, 2003, **44**, 7499–7502.
- 9 B. List, A. Doehring, M. T. Hechavarria Fonseca, A. Job and R. Rios Torres, *Tetrahedron*, 2006, **62**, 476–482.
- 10 Data for compound **1**: white solid, [ $\alpha$ ]<sub>D</sub><sup>25</sup> = –19.64 (*c* = 1.12 g l<sup>–1</sup>, MeOH); <sup>1</sup>H NMR (360 MHz, MeOD-*d*<sub>4</sub>, TMS as reference)  $\delta$  7.63 (d, *J* = 15.9 Hz, 1H), 7.15 (d, *J* = 1.9 Hz, 1H), 7.04 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 5.38 (ddd, *J* = 11.3, 10.1, 5.0 Hz, 1H), 4.15 (q, *J* = 2.8 Hz, 1H), 3.87 (s, 3H, MeO), 3.69 (dd, *J* = 9.9, 3.1 Hz, 1H), 2.19–1.92 (m, 4H); <sup>13</sup>C NMR (90 MHz, MeOD-*d*<sub>4</sub>, TMS as reference)  $\delta$  182.4, 170.8, 153.8, 151.2, 148.4, 128.1, 125.8, 118.3, 116.4, 112.8, 79.1, 76.4, 74.4, 73.9, 57.7, 42.2, 40.4; EIMS (70 eV) *m/z* [*M* – 1]<sup>–</sup>: 367.09 (*M* – H), 191.05; EIMS (70 eV) *m/z* [*M* + 1]<sup>+</sup>: 177.05.
- 11 Data for compound **2**: white foam, [ $\alpha$ ]<sub>D</sub><sup>25</sup> = –31.25 (*c* = 1.12 g l<sup>–1</sup>, MeOH); <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>, TMS as reference)  $\delta$  7.62 (d, *J* = 15.9 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.28 (d, *J* = 15.9 Hz, 1H), 6.07 (s, OH), 5.38 (ddd, *J* = 11.6, 9.8, 4.8 Hz, 1H), 4.32 (s, OH), 4.24 (m, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.70 (m, 1H), 3.24 (d, *J* = 8.3 Hz, OH), 2.35 (ddd, *J* = 13.0, 4.7, 3.0 Hz, 1H), 2.25 (td, *J* = 14.8, 3.1 Hz, 1H), 2.09 (dd, *J* = 14.8, 3.2 Hz, 1H), 1.95 (dd, *J* = 12.9, 11.7, Hz, 1H); <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>, TMS as reference)  $\delta$  174.4, 167.6, 148.1, 146.8, 145.8, 126.7, 123.2, 114.8, 114.7, 109.4, 75.6, 73.9, 70.8, 70.6, 55.9, 53.2, 38.7, 36.8; EIMS (70 eV) *m/z* [*M* – 1]<sup>–</sup>: 381.10.
- 12 (a) K. Iwai, N. Kishimoto, Y. Karino, K. Mochida and T. Fujita, *J. Agric. Food Chem.*, 2004, **52**, 4893–4898; (b) E. J. Gentry, H. B. Jampani, A. Keshavarz-Shokri, M. D. Morton, D. V. Velde, H. Telikepalli and L. A. Mitscher, *J. Nat. Prod.*, 1998, **61**, 1187–1193.