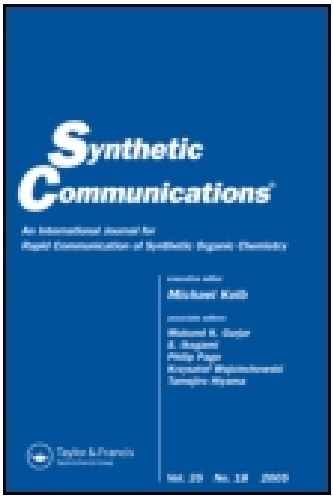

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Facile Syntheses of (2R,3R)-(-)- and (2S,3S)-(+)-Chicoric Acids

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FACILE SYNTHESES OF (2R,3R)-(-)- AND (2S,3S)-(+)-CHICORIC ACIDS

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ABSTRACT: Practical and efficient syntheses of (2R, 3R)-(-)- and (2S, 3S)-(+)-chicoric acids are reported, which may be amenable to analogue preparation.

(+)-Chicoric acid ((2S,3S)-2,3-bis[[3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]oxy]butanedioic acid, **1**) is a bis-catechol derivative of (-)-tartaric acid which was first isolated from chicory plants in 1958.[1] Recently, interest in chicoric acid has heightened due to the reported ability of the unnatural (2R,3R)-(-)-chicoric acid (**2**) to both inhibit HIV-1 integrase in extracellular enzyme preparations and to exhibit protective effects in HIV-infected cells.[2,3] In a continuation of our studies to prepare HIV integrase inhibitors[4] we desired to synthesize both enantiomers of chicoric acid as well as various analogues. The original synthesis of chicoric acid[1] was achieved in low yield utilizing the highly unstable acid chloride **3**. A more recent synthesis for which no experimental details were provided, also employed this intermediate.[3] Because our attempts at reproducing both of these procedures proved troublesome, we sought an alternate strategy which was straight forward and did not rely on **3**. We therefore report herein a new synthesis of both natural chicoric acid **1** and its antipode **2** in high yield using stable, readily obtainable intermediates. This approach should be amenable to the preparation of chicoric acid analogues.

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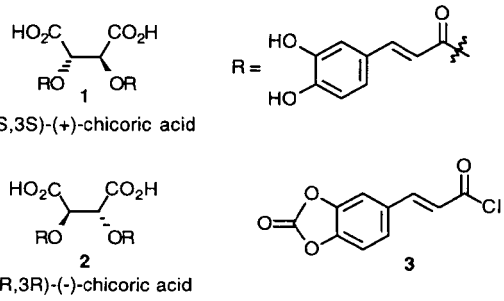
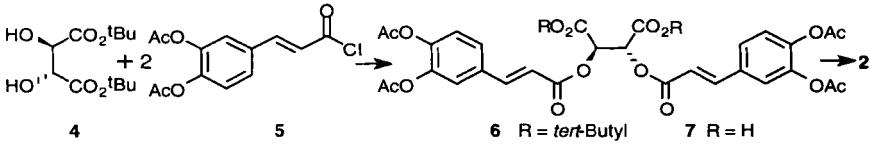


In attempting to reproduce the recently reported synthesis of L-chicoric acid[3] we found that both the preparation and isolation of two key reactants, acid chloride **3** and L-tartaric acid bis-diphenyl ester, to be difficult. In fact, we could not obtain the desired final product in useable quantity. Therefore, alternate protection strategies were employed for both tartaric acid and the dihydroxycinnamic acid components. In the case of tartaric acid, the bis-(*tert*-butyl) ester was chosen, since the ester functionality can be removed under mild acidic conditions, and more importantly, the material is commercially available. For dihydroxycinnamic acid, the acid chloride **5**, bearing acetyl phenolic protection, was utilized since it was easily prepared and isolated.[5] Acylation of **4** with **5** in pyridine provided fully protected intermediate **6** as a crystalline solid in nearly quantitative yield. Removal of protecting groups was then achieved in a two-step process initiated by TFA-mediated hydrolysis of *tert*-butyl esters to yield free diacid **7**. Treatment with 3 N HCl in acetone then provided desired (-)-chicoric acid **2** as a crystalline solid in greater than 80% overall yield from starting commercially available tartrate **4**. The practicality and high yield of this method make it attractive. Furthermore, it should be amenable to the preparation of a wide range of chicoric acid analogues which may have potential value as HIV integrase inhibitors.



Representative Experimental Procedure

A solution of commercially available (+)-di-tert-butyl L-tartrate **4** in anhydrous pyridine (3 mL to 1 mmol of **4**) was treated with the solution of 2.5

equivalent of freshly prepared 3,4-diacetyl caffeoyl acid chloride[5] **5** in toluene (5 mL to 1 mmol of **4**) at room temperature overnight. After removal of pyridine, the residue was dissolved in toluene and evaporated under reduced pressure. Two subsequent additions and evaporations of toluene eliminated residual pyridine. The resulting material was passed through silica gel (EtOAc:hexane 1:1) then crystallized from EtOAc:hexane to provide **6** as a white solid[6] (97% yield). Compound **6** was treated with TFA (20 equivalents) in dichloromethane (v/v =1:3) at room temperature overnight, then either crystallized (acetone:hexane) to provide **7** as a white solid[7] (96%), or directly taken to dryness and hydrolyzed with 3 N HCl (10 mL to 1 mmol of **6**) in acetone (v/v = 1:3) under reflux (3 h). After cooling to room temperature, the solution was diluted with EtOAc (5 volumes), washed with brine and dried over anhydrous sodium sulfate. Solvent was removed and residue crystallized from H_2O to provide (2R,3R)-(-)-chicoric acid[8] **2** (90% yield). Enantiomeric natural (2S,3S)-chicoric acid[9] was obtained in an identical fashion starting from commercially available (-)-di-*tert*-butyl D-tartrate.

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References and Notes

1. Scarpati, M. L.; Oriente, G. *Tetrahedron* **1958,** *4*, 43-48.
2. Robinson, W. E., Jr.; Cordeiro, M.; Abdel-Malek, S.; Jia, Q.; Chow, S. A.; Reinecke, M. G.; Mitchell, W. M. *Mol. Pharm.* **1996,** *50*, 846-855.
3. Robinson, W. E., Jr.; Reinecke, M. G.; Abdel-Malek, S.; Jia, Q.; Chow, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996,** *93*, 6326-6331. (No experimental details were provided for the synthesis of L-chicoric acid.)
4. Zhao, H.; Neamati, N.; Mazumder, A.; Sunder, S.; Pommier, Y.; Terrence R. Burke, Jr. *J. Med. Chem.* **1997,** *40*, 1186-1194.
5. Compound **5** has been previously prepared (for example: Haslam, E.; Makinson, G. K.; Naumann, M. O.; Cunningham, J. *J. Chem. Soc.* **1964**, 2137.) It is easily synthesized on large scale by treatment of 3,4-dihydroxycinnamic acid with acetic anhydride (10 equivalents) in pyridine (v/v = 5:1) in the dark

overnight at room temperature. Upon removal of solvent, residue is crystallized from EtOAc:hexane to provide diacetyl caffeic acid as a white solid. Reflux (3 h) with thionyl chloride (5 equivalents) in benzene (v/v = 8:1) provides **5** upon removal of solvent.

6. Mp 153-155 °C; $[\alpha]^{25}_D$ -146° ($CHCl_3$, c 0.51); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73 (d, *J* = 16.0 Hz, 2H), 7.44-7.36 (m, 4H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 2H), 5.79 (s, 2H), 2.30 (s, 6H), 2.28 (s, 6H), 1.41 (s, 18 H); FABMS *m/z* 756 $(MH)^+$. Anal. calcd. for $C_{38}H_{42}O_{16}$: C, 60.47; H, 5.61. Found: C, 60.38; H, 5.65.
7. Mp 186-188 °C; $[\alpha]^{25}_D$ -159° (MeOH, c 0.16); ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.81 (d, *J* = 1.8 Hz, 2H), 7.76-7.70 (m, 4H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 16.2 Hz, 2H), 5.74 (s, 2H), 2.28 (s, 12H); FABMS *m/z* 644 $(MH)^+$. Anal. calcd. for $C_{30}H_{26}O_{16}$: C, 56.08; H, 4.08. Found: C, 55.82; H, 4.17.
8. Mp 204-206 °C; $[\alpha]^{25}_D$ -333° (MeOH, c 0.10; lit.[1] -384.2° (MeOH, c 1.075)); ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.69 (s, 2H), 9.16 (s, 2H), 7.55 (d, *J* = 15.8 Hz, 2H), 7.09-7.07 (m, 4H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.36 (d, *J* = 15.9 Hz, 2H), 5.67 (s, 2H); FABMS *m/z* 475 $(MH)^+$. Anal. calcd. for $C_{22}H_{18}O_{12}\cdot{}^7/_4H_2O$: C, 52.23; H, 4.28. Found: C, 52.07; H, 4.33.
9. $[\alpha]^{25}_D$ +340° (MeOH, c 0.14). Other physical data were identical to that displayed by **2**.

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