A Convenient Synthesis of the *Echinacea*-Derived Immunostimulator and HIV-1 Integrase Inhibitor (−)-(2*R*,3*R*)-Chicoric Acid

by **Anne-Marie Lamidey**, **Lionel Fernon**, **Laurent Pouységu**, **Charlotte Delattre**, **Stéphane Quideau***

Laboratoire de Chimie des Substances Végétales, Centre de Recherche en Chimie Moléculaire, Université Bordeaux 1, 351 cours de la Libération, F-33405 Talence Cedex (e-mail: s.quideau@lcsv.u-bordeaux1.fr; fax: (33)556846439)

and

Patrick Pardon

Institut du Pin, Université Bordeaux 1, 351 cours de la Libération, F-33405 Talence Cedex

The *Echinacea*-derived immunostimulator and HIV-1 integrase inhibitor (−)-chicoric acid (=2,3-bis{[3-(3,4-dihydroxyphenyl)-1-oxoprop-2-enyl]oxy}butanedioic acid; **1a**) was conveniently prepared *via* a silane-promoted Pd-mediated chemoselective hydrogenolysis of its perbenzylated derivative **12a**, which was generated from an efficient and reliable carbodiimide-mediated coupling reaction between the caffeic acid dibenzyl ether derivative **7** and commercially available (+)-dibenzyl L-tartrate (**9a**). The other naturally occurring dextrorotatory chicoric acid (**1b**) can be similarly prepared.

Introduction. – *Echinacea purpurea* (L.) MOENSCH is one of the most potent herbs that support the immune system. Extracts from this purple cone-flower plant were the best selling herbal products in natural food stores in the USA in 1997 [1]. These extracts exhibit skin cicatrizing properties, appear to lessen the severity of the flu and respiratory diseases such as rhinitis and pneumonia, are active against psoriasis, eczema, and candidosis, and display anti-inflammatory, antifungal, antibacterial, antiparasitical, antitumor, and antiviral activities [2]. Reports on their immunostimulating properties have been particularly important in making *Echinacea* species a major source of the immunotropic preparations on the medicinal plant market [2c–e][3][4]. It has, for example, been observed that granulocyte and macrophage secretions of certain cytokines such as interleukine-1, IFN-α, and TNF-α are increased upon treatment with *Echinacea* sp. extracts [2d].

Such therapeutically-relevant activities have engendered numerous investigations of the chemical composition of *Echinacea* species [1][2e][2f][4a][5]. Immunostimulatory and antiviral properties are generally attributed to phenylpropanoid metabolites and, in particular, to caffeoyl derivatives, which have been identified as units bearing pharmacophores common to potent *in vitro* inhibitors of HIV-1 integrase (*vide infra*) [6]. Chicoric acid (**1**) belongs to this class of phenylpropanoid metabolites. In view of recent literature reports in which (−)-chicoric acid (**1a**, (2*R*,3*R*)-*O*-dicaffeoyltartaric acid) is considered unnatural [7], it is important to recall that the two optically active stereoisomers are naturally occurring. In contrast to the dextrorotatory compound **1b** found in *Cichorium* species [8], the chicoric acid present in *Echinacea* species is its

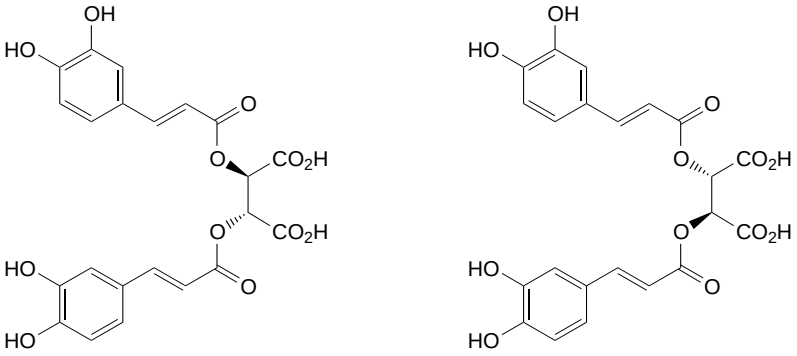


Fig. 1. L-*Chicoric acid* (**1a**) *from* Echinacea purpurea *and* D-*chicoric acid* (**1b**) *from* Cichorium intybus *and* endivia

levorotatory antipode **1a** (*Fig. 1*) [5a]. It notably occurs as a major constituent of *Echinacea purpurea* roots and aerial parts [5a][5c], and it has been identified as a key element in the *in vitro* stimulation of human polymorphonuclear granulocytes phagocytosis [3b][3c]. (−)-Chicoric acid (**1a**) is also one of the most potent *Echinacea*-derived caffeoyl-based inhibitors of hyaluronidase activity with a 50% inhibitory concentration value of 0.42 mM [9]. This dicaffeoyl-tartaric acid is also considered a promising lead to new anti-HIV agents. It blocks HIV-1 replication in syncitia cell-based assays at a 50% effective concentration value of 2 μg/ml with a toxic concentration more than 100-fold greater [10a]. This cytoprotective effect of **1a** is quite remarkable in view of other catechol derivatives that exhibit appalling cytotoxicity levels commonly blamed on facile oxidation to reactive quinone species [6b][10b]. (−)-Chicoric acid (**1a**) selectively inhibits HIV integrase at concentrations ranging from 0.06 to 0.15 μg/ml [10], and displays a significant *in vitro* synergism as an integrase inhibitor candidate for triple combination therapy against HIV infection [10f].

Our investigations into the utilization of natural phenols and catechols as immunomodulatory agents in biological systems obviously led us to consider **1a** as a candidate. (−)-Chicoric acid (**1a**) is commercially available through extraction from its natural sources, but it remains relatively expensive. We, thus, preferred to rely on an in-house synthesis of the compound. To our knowledge, only three syntheses of chicoric acids have been reported [7][8][10a]. The three procedures are based on acylation of various tartrates with differently protected caffeoyl chlorides and suffer from either a lack of reproducibility or the use of rather expensive starting tartrate derivatives. Here, we wish to report on a rapid alternative method for the synthesis of **1a**, as well as of its dextrorotatory enantiomer (+)-**1b**.

Results and Discussion. – The cause for low yields and lack of reproducibility of the first two syntheses of **1a**/**1b** is likely the utilization of the highly unstable caffeoyl chloride carbonate derivative **2** (*Fig. 2*). This derivative is used in standard nucleophilic

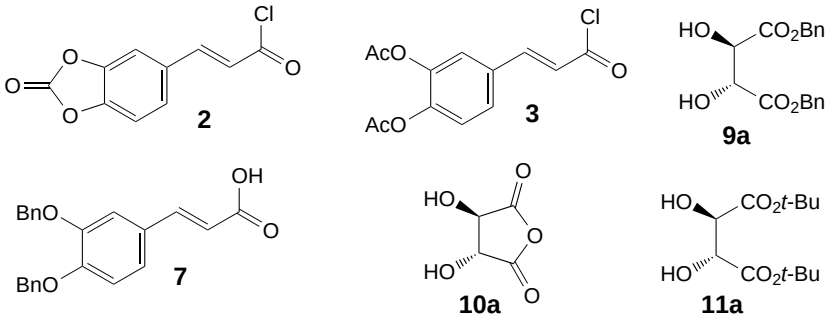


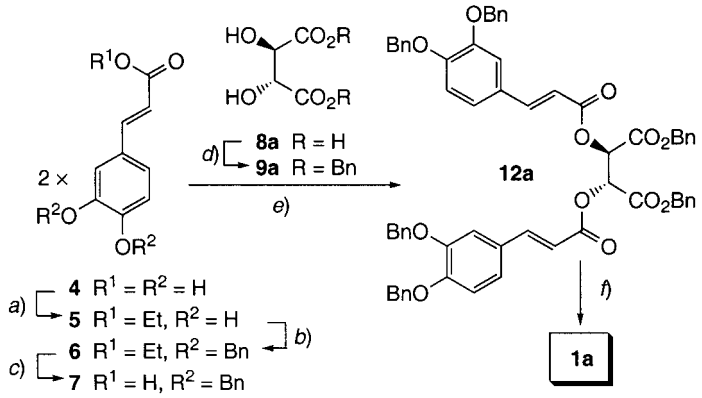
Fig. 2. *Intermediates in the synthesis of chicoric acids*

addition-elimination reactions with either (+)-(2*R*,3*R*)-dibenzyl L-tartrate (**9a**) or its D-enantiomer (−)-**9b**, followed by sequential base- and acid-deprotecting hydrolyses to furnish **1a** or **1b**, respectively [10a]. In the synthesis of *Scarpati* and *Oriente* [8], the caffeoyl chloride **2** and (+)-(2*R*,3*R*)-L-tartaric acid (**8a**) or its enantiomer **8b** are mixed together and neatly heated above 100° to afford **1a** or **1b**, presumably *via* the tartaric anhydrides **10a** and **10b**, respectively. The method recently described by *Zhao* and *Burke* [7], instead, relies on the use of the caffeoyl chloride diacetate derivative **3** for acylating (+)-(2*R*,3*R*)-di(*tert*-butyl) L-tartrate (**11a**) or its enantiomer **11b**. A two-step acid-mediated deprotecting sequence then furnished the desired chicoric acids.

We surmised that a convenient single-type protecting-group approach could also be devised by relying on a carbodiimide-mediated acylation between Bn-protected coupling partners. An ultimate debenzylation step should, then, furnish the chicoric acids. The only caveat in this route lies in the extent of chemoselectivity at which the debenzylation must be performed without affecting the sensitive ester linkages and the reducible C=C bonds of the product(s). The synthesis started from commercially available caffeic acid (**4**), which was esterified with EtOH in the presence of AcCl, benzylated with BnBr and K_2CO_3 in refluxing EtOH, and saponified with KOH in refluxing EtOH, to furnish the dibenzyl ether derivative **7** in 80% overall yield (*Scheme*). Both dibenzyl tartrate enantiomers **9a**/**9b** are commercially available and inexpensive, or can easily be prepared in yields exceeding 90% from their corresponding tartaric acid isomer (**8a**/**8b**) [11].

The carbodiimide-based biscaffeoylation of **9a**/**9b** with **7** was first attempted with dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 according to the method of *Neises* and *Steglich* [12]. Difficulties in removing the substituted urea by-product prompted us to use 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) [13] instead of DCC. The perbenzylated chicoric acid derivatives **12a**/**12b** were thus obtained in yields of 95 and 80%, respectively. An extensive investigation was carried out to identify appropriate debenzylation conditions. Metal-catalyzed hydrogenolysis (poisoned Pd, *W-2 Raney*-Ni), *Lewis* acid-mediated cleavage ($FeCl_3$ or $BF_3 \cdot Et_2O$/EtSH) and transfer hydrogenation with various hydrogen donors (cyclohexene, cyclohexa-1,4-diene, HCOOH, ammonium formate) were all unsuccessful.

Scheme. *A Convenient Synthesis of (−)-Chicoric Acid* (**1a**)



a) EtOH, AcCl, r.t., 2 d; 95%. *b*) BnBr, K_2CO_3, EtOH, reflux, 20 h; 98%. *c*) KOH, EtOH, reflux, 20 h; 85%. *d*) BnOH, 200° [11a] (dibenzyl tartrate **9a** is commercially available). *e*) EDCI, DMAP, CH_2Cl_2, r.t., 1 d; 95%. *f*) $Pd(OAc)_2$, Et_3SiH, Et_3N, CH_2Cl_2, r.t. (58 → 92%). The synthesis of (+)-chicoric acid (**1b**) can be similarly accomplished from commercially available dibenzyl tartrate **9b**.

Removal of the six Bn groups of **12a** was finally accomplished in one step *via* a silane-promoted Pd-mediated hydrogenolysis. The reaction conditions were adapted from the method of *Coleman* and *Shah* [14]. The amount of each reactant, *i.e.*, Et_3SiH, $Pd(OAc)_2$, and Et_3N, and their order of addition at the onset of the reaction were found to be extremely critical to ensure an efficient and chemoselective debenzylation. Substoichiometric amounts of $Pd(OAc)_2$ were sufficient to mediate the required multiple removal of Bn groups. Treatment of **12a** with 0.80 equiv. of $Pd(OAc)_2$ for 72 h furnished **1a** in 58% yield. It is remarkable that mixing of all reactants prior to the addition of the starting material **12a** appeared detrimental to the desired chemoselective reaction; in all cases, incomplete debenzylation and significant C=C bond hydrogenation were observed. Higher yields of **1a** (up to 92%) were obtained by first mixing $Pd(OAc)_2/Et_3N$ with the starting material in a CH_2Cl_2 solution to which excess Et_3SiH was added dropwise (4 equiv. per Bn group). The best result was obtained by performing the reaction at a concentration of 30 mM perbenzylated chicoric acid **12a**. Purification of **1a** can be conveniently carried out by semipreparative reversed-phase HPLC to a minimum purity level of 90%. The same conditions afforded (+)-chicoric acid (**1b**) in 66% yield from the corresponding perbenzylated derivative **12b**.

Conclusions. – This convenient synthesis of chicoric acid and, in particular, of its immuno-enhancing and anti-HIV levorotatory enantiomer, should prove itself valuable in future studies aimed at elucidating and exploiting the biological activity of these caffeic acid based natural products. This synthetic source of chicoric acids will be useful when undertaking bioavailability studies for medicinal applications. Chromatographic standardization of *Echinacea*-based phytopharmaceutical commercial preparations could also make use of these synthetic compounds.

The support of *Biolandes*, the *Délégation Régionale à la Recherche et à la Technologie pour l'Aquitaine* (FEDER Grant No. Z0131), and the *Conseil Régional d'Aquitaine* (Grant No. 990209003) is gratefully acknowledged. The authors also wish to thank *Gaëlle-Anne Cremer* (ENS Chimie, Rennes) and *Patricia Castel* (Institut du Pin, Bordeaux 1) for their contributions to this work.

Experimental Part

General. CH_2Cl_2 was purified by distillation from CaH_2 under Ar immediately before use. Moisture and O_2-sensitive reactions were carried out in flame-dried glassware under Ar. Evaporations were conducted under reduced pressure at temp. below 45° unless otherwise noted. Column chromatography (CC) was carried out under positive N_2 pressure with 40–63 μm silica gel (*Merck*) and the indicated solvents. M.p.: uncorrected. NMR Spectra of samples in the indicated solvent were recorded at 200 or 250 MHz on *Bruker* instruments. ^{13}C-multiplicities were determined by DEPT135 experiments. Electron impact (EI) and liquid secondary-ion (LSI), and low- and high-resolution (HR) MS analyses were obtained from the mass spectrometry laboratory at the CESAMO, Université Bordeaux 1. Combustion analyses were performed by *Laboratoires Wolff*, Clichy, France.

High-Performance Liquid Chromatography (HPLC). Semi-prep. HPLC purification of **1a** was performed on a *Waters Delta Prep 3000* pump system with a *C-18 Lichrospher* column (25 × 250 mm, 5 μm). The mobile phase was MeCN/H_2O–HCO_2H 99.5 : 0.5 and isocratic elution 18 : 82 was applied at a flow rate of 20 ml/min. Column effluent was monitored by UV detection at 280 nm with a *LKB 2158 Uvicord SD* UV/VIS detector. HPLC Analysis of eluted fractions was carried out on a *Thermo* system with a *C-18 Lichrospher* column (4.6 × 250 mm, 5 μm) with *P4000* pumps and UV detection was performed at 330 and 280 nm with a *UV2000* detector. The mobile phase was MeCN/H_2O–HCO_2H 99.5 : 0.5 and gradient elution (0–50 min: 12 to 40% MeCN) was applied at a flow rate of 0.8 ml/min.

Ethyl 3-(3,4-Dihydroxyphenyl)prop-2-enoate (*Ethyl Caffeoate*; **5**). To an ice-cold soln. of *caffeic acid* **4** (5.0 g, 27.8 mmol) in abs. EtOH (140 ml) was added dropwise freshly distilled AcCl (13.8 ml, 194.5 mmol). The mixture was stirred at r.t. for 2 d, and then evaporated. The solid residue was dissolved in 100 ml of H_2O, and extracted with AcOEt (3 × 50 ml). The org. layer was washed with sat. aq. $NaHCO_3$ soln. (2 × 20 ml) and brine (2 × 20 ml), dried (Na_2SO_4), filtered, and evaporated. Crystallization of the solid residue from AcOEt/hexanes 1 : 4 furnished **5** (5.48 g, 95%). Amber-colored crystals. M.p. 148–149°. IR (KBr) 3460, 1680. ^{1}H-NMR ((D$_6$)acetone, 250 MHz): 1.26 (*t*, *J* = 7.0, 3 H); 4.18 (*q*, *J* = 7.0, 2 H); 6.27 (*d*, *J* = 15.9, 1 H); 6.87 (*d*, *J* = 8.2, 1 H); 7.04 (*dd*, *J* = 2.1, 8.2, 1 H); 7.16 (*d*, *J* = 2.1, 1 H); 7.54 (*d*, *J* = 15.9, 1 H); 8.33 (br. *s*, 2 H). ^{13}C-NMR ((D$_6$)acetone, 62.9 MHz): 166.6; 147.8; 145.4; 144.7; 126.8; 121.7; 115.6; 114.9; 114.4; 59.7; 13.9. EI-MS: 209 (10, $[M+1]^+$), 208 (82, M^+), 180 (18), 163 (100).

Ethyl 3-[3,4-Bis(benzyloxy)phenyl]prop-2-enoate (**6**) [15]. Under stirring, to a soln. of **5** (3.7 g, 17.8 mmol) in abs. EtOH (100 ml), powdered K_2CO_3 (5.2 g, 37.5 mmol) and BnBr (4.65 ml, 39.2 mmol) were added, and the mixture was refluxed overnight. EtOH was then evaporated, and the residue was dissolved in AcOEt (50 ml). This org. layer was washed with 1M H_3PO_4 (15 ml) and brine (2 × 15 ml), and dried (Na_2SO_4). Evaporation of the solvent afforded a yellowish solid, which was purified by recrystallization from EtOH to give **6** (6.76 g, 98%). Off-white powder. M.p. 81–82°. IR (KBr) 1696. ^{1}H-NMR ($CDCl_3$, 250 MHz): 1.34 (*t*, *J* = 7.0, 3 H); 4.26 (*q*, *J* = 7.0, 2 H); 5.18 (*s*, 2 H); 5.20 (*s*, 2 H); 6.26 (*d*, *J* = 15.9, 1 H); 6.92 (*d*, *J* = 8.2, 1 H); 7.05–7.49 (*m*, 12 H); 7.59 (*d*, *J* = 15.9, 1 H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): 167.1; 150.9; 148.9; 144.3; 136.8; 136.7; 128.5; 127.9; 127.2; 127.1; 122.7; 116.1; 114.2; 113.6; 71.2; 70.9; 60.3; 14.3. EI-MS: 389 (4, $[M+1]^+$), 388 (14, M^+), 297 (9), 91 (100).

3-[3,4-Bis(benzyloxy)phenyl]prop-2-enoic Acid (**7**). Under stirring, to a 1M ethanolic KOH soln. (12 ml), a soln. of **6** (2.9 g, 7.5 mmol) in EtOH (15 ml) was added, and the mixture was heated under reflux overnight. After evaporation of the EtOH, the residue was dissolved in 15 ml of H_2O and extracted with AcOEt (2 × 30 ml). The aq. layer was then acidified by adding 10% HCl, extracted with AcOEt (3 × 30 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a white solid, which was recrystallized from AcOEt/hexanes to afford **7** (2.29 g, 85%). Off-white powder. M.p. 190–192°. IR (KBr) 2576, 2508, 1692, 1670. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 5.18 (*s*, 2 H); 5.20 (*s*, 2 H); 6.44 (*d*, *J* = 15.9, 1 H); 7.06 (*d*, *J* = 8.5, 1 H); 7.18 (*d*, *J* = 1.6, 1 H); 7.21–7.55 (*m*, 12 H); 12.27 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO, 62.9 MHz): 168.1; 150.3; 148.5; 144.2; 137.3; 137.1; 128.6; 128.0; 127.8; 127.7; 127.6; 123.1; 117.2; 114.0; 113.0; 70.2; 70.0. EI-MS: 361 (2, $[M+1]^+$), 360 (10, M^+), 269 (6), 91 (100).

*Dibenzyl (−)-(2*R*,3*R*)-2,3-Bis[3-[2,3-bis(3,4-dibenzyloxy)phenyl]prop-2-enoyloxy]-*L*-tartrate* (**12a**). Under stirring, to a suspension of **7** (1.20 g, 3.33 mmol) in dry CH_2Cl_2 (8 ml), DMAP (406 mg, 3.33 mmol), a soln. of **9a** (500 mg, 1.51 mmol) in dry CH_2Cl_2 (3 ml), and EDCI (1.27 g, 6.66 mmol) were added successively. The

resulting pale yellow soln. was stirred at r.t. for 1 d, then it was diluted in AcOEt (30 ml) and water (5 ml). Extraction with AcOEt (2 × 15 ml), followed by washings with 1M H_3PO_4 (5 ml) and brine (3 × 5 ml), led to an org. layer, which was dried (Na_2SO_4). Evaporation of the solvent afforded a solid residue, which was submitted to CC (hexanes/AcOEt 3:2) to give **12a** (1.46 g, 95%). Yellow foam. M.p. 45–47°. $[\alpha]_D^{22} = -80.8$ ($c = 1.93$, $CHCl_3$). IR (KBr) 1770, 1726. ^{1}H-NMR ($CDCl_3$, 250 MHz): 5.12–5.30 (*m*, 12 H); 5.94 (*s*, 2 H); 6.23 (*d*, *J* = 15.9, 2 H); 6.93–7.52 (*m*, 36 H); 7.59 (*d*, *J* = 15.9, 2 H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): 165.8; 165.5; 151.4; 148.9; 146.6; 136.7; 136.6; 134.7; 128.5; 128.4; 127.9; 127.4; 127.2; 127.1; 123.4; 114.0; 113.8; 113.6; 71.2; 70.8; 67.7. LSI-MS: 1037 (9, $[M + Na]^+$), 1015 (6, $[M + 1]^+$), 1014 (7, M^+), 343 (100). Anal. calc. for $C_{64}H_{54}O_{12}$: C 75.71, H 5.37; found: C 75.88, H 5.44.

*Dibenzyl (+)-(2*S*,3*S*)-2,3-Bis{3-[2,3-bis(benzyloxy)phenyl]prop-2-enoyloxy}-*D*-tartrate* (**12b**). Compounds **7** and **9b** were coupled according to the same procedure as described for **12a** to furnish **12b** as a yellow foam (80% yield). M.p. 46–47°. $[\alpha]_D^{22} = +70.4$ ($c = 1.46$, $CHCl_3$); all other spectroscopic data were identical to those reported for **12a**.

(−)-2,3-Bis{[3-(3,4-dihydroxyphenyl)-1-oxoprop-2-enyl]oxy}butanedioic Acid (*(−)-Chicoric Acid*; **1a**). To $Pd(OAc)_2$ (334 mg, 1.49 mmol) maintained under Ar, a soln. of Et_3N (207 µl, 1.49 mmol) in dry CH_2Cl_2 (10 ml) was added. The mixture was stirred at r.t. for 5 min, then **12a** (630 mg, 0.62 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise. The resulting brown soln. was stirred at r.t. for 5 min, and Et_3SiH (2.37 ml, 14.90 mmol) was then added slowly; the mixture immediately became dark, and it was stirred for 24 h at r.t. Complete debenzylation was confirmed by ^{1}H-NMR analysis of an aliquot in (D_6)acetone. Addition of MeOH (3 ml), followed by filtration and evaporation of the filtrate, afforded a yellow oil, which was diluted with AcOEt (30 ml) and H_2O (5 ml). After separation, the aq. phase was extracted with AcOEt (10 ml), and the combined extracts were washed with 1M H_3PO_4 and brine until pH 7. Drying (Na_2SO_4), and evaporation gave an oily residue, which was diluted again in AcOEt (2 ml). Addition of hexanes (40 ml) afforded a precipitate that was filtered off and dried under vacuum to give **1a** (271 mg, 92%) as an amorphous off-white solid. This solid was purified by semi-prep. HPLC to afford **1a** with a purity level of 90% as determined by UV analysis. $[\alpha]_D^{22} = -242.7$ ($c = 0.89$, MeOH) ([8]: $[\alpha]_D^{25} = -384.2$ ($c = 1.075$, MeOH)). IR (KBr) 3406, 1707. ^{1}H-NMR ((D_6)acetone, 250 MHz): 5.94 (*s*, 2 H); 6.44 (*d*, *J* = 15.8, 2 H); 6.93 (*d*, *J* = 8.2, 2 H); 7.16 (*dd*, *J* = 2.1, 8.2, 2 H); 7.27 (*d*, *J* = 2.1, 2 H); 7.70 (*d*, *J* = 15.8, 2 H). ^{13}C-NMR ((D_6)acetone, 62.9 MHz): 167.6; 166.3; 149.1; 147.6; 146.3; 127.2; 122.9; 116.3; 115.4; 113.8; 71.6. LSI-MS: 497 (35, $[M + Na]^+$), 475 (7, $[M + 1]^+$), 474 (9, M^+).

(+)-Chicoric Acid (**1b**). The same procedure as that described above for **1a** furnished **1b** from **12b** as an amorphous off-white solid (66% yield). $[\alpha]_D^{22} = +214.6$ ($c = 0.63$, MeOH) ([8]: $[\alpha]_D^{22} = +340.0$ ($c = 1.075$, MeOH)). All other spectroscopic data were identical to those reported for **1a**.

REFERENCES

[1] R. Bauer, in 'Immunomodulatory Agents from Plants', Ed. H. Wagner, Birkhäuser Verlag, Basel, Switzerland, 1999, p. 41–88.

[2] a) O. Hoheisel, M. Sandberg, S. Bertram, M. Bulitta, M. Schäfer, *Eur. J. Clin. Res.* **1997**, *9*, 261; b) R. M. Facino, M. Carini, G. Aldini, L. Saibene, P. Pietta, P. Mauri, *Planta Med*. **1995**, *61*, 510; c) M. J. Parnham, *Pharmazeutische Z*. **1996**, *141*, 4282; d) L. Girre, *Phytotherapy* **1995**, *43*, 3; e) P. Goetz, *Revue de Phytothérapie Pratique* **1989**, *3*, 14; f) A. Cheminat, R. Zawatzky, H. Becker, R. Brouillard, *Phytochemistry* **1988**, *27*, 2787; g) H. Funke, *Z. Phytotherapy* **1983**, *4*, 650.

[3] a) R. Fleischhacker, *Dtsch. Apoth. Z.* **1998**, *138*, 1850; b) R. Bauer, P. Remiger, K. Jurcic, H. Wagner, *Z. Phytotherapy* **1989**, *10*, 43; c) R. Bauer, K. Jurcic, J. Puhlmann, H. Wagner, *Arzneim.-Forsch*. **1988**, *38*, 276; d) H. Wagner, *Z. Phytother*. **1986**, *7*, 91; e) H. Wagner, A. Proksch, *Z. Angew. Phytother*. **1981**, *2*, 166.

[4] a) B. Nüsslein, M. Kurzmann, R. Bauer, W. Kreis, *J. Nat. Prod.* **2000**, *63*, 1615; b) D. Melchart, K. Linde, in 'Immunomodulatory Agents from Plants', Ed. H. Wagner, Birkhäuser Verlag, Basel, Switzerland, 1999, pp. 105–118; c) M. J. Parnham, in 'Immunomodulatory Agents from Plants', Ed. H. Wagner, Birkhäuser Verlag, Basel, Switzerland, 1999, pp. 119–135.

[5] a) H. Soicke, G. Al-Hassan, K. Görler, *Planta Med*. **1988**, *54*, 175; b) R. Bauer, P. Remiger, H. Wagner, *Dtsch. Apoth. Z.* **1988**, *128*, 174; c) H. Becker, W. C. Hsieh, *Z. Naturforsch., C* **1985**, *40*, 585.

[6] a) N. Neamati, H. Hong, S. Sunder, G. W. A. Milne, Y. Pommier, *Mol. Pharmacol.* **1997**, *52*, 1041; b) H. Zhao, N. Neamati, A. Mazumder, S. Sunder, Y. Pommier, T. R. Burke Jr., *J. Med. Chem*. **1997**, *40*, 1186; c) N. Mahmood, P. S. Moore, N. De Tommasi, F. De Simone, A. J. Hay, C. Pizza, *Antivial Chem. Chemother*. **1993**, *4*, 235.

[7] H. Zhao, J. T. R. Burke, *Synth. Commun*. **1998**, *28*, 737.
[8] M. L. Scarpati, G. Oriente, *Tetrahedron* **1958**, *4*, 43.
[9] R. M. Facino, M. Carini, G. Aldini, C. Marinello, E. Arlandini, L. Franzoi, M. Colombo, P. Pietta, P. Mauri, *Il Farmaco* **1993**, *48*, 1447.
[10] a) W. E. Robinson Jr., M. G. Reinecke, S. Abdel-Malek, Q. Jia, S. A. Chow, *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 6326; b) Z. Lin, N. Neamati, H. Zhao, Y. Kiryu, J. A. Turpin, C. Aberham, K. Strebel, K. Kohn, M. Witvrouw, C. Pannecouque, Z. Debyser, E. De Clercq, W. G. Rice, Y. Pommier, T. R. Burke Jr., *J. Med. Chem*. **2000**, *42*, 1401; c) W. E. Robinson Jr., M. Cordeiro, S. Abdel-Malek, Q. Jia, S. A. Chow, M. G. Reinecke, W. M. Mitchell, *Mol. Pharmacol*. **1996**, *50*, 846; d) B. McDougall, P. J. King, B. W. Wu, Z. Hostomsky, M. G. Reinecke, W. E. Robinson Jr., *Antimicrob. Agents Chemother*. **1998**, *42*, 140; e) P. J. King, W. E. Robinson Jr., *J. Virol*. **1998**, *72*, 8420; f) W. E. Robinson Jr., *Antiviral Res.* **1998**, *39*, 101.
[11] a) Y. Hu, K. A. Yamada, D. K. Chalmers, D. P. Annavajjula, D. F. Covey, *J. Am. Chem. Soc.* **1996**, *118*, 4550; b) J. E. Bishop, J. F. O'Connel, H. Rapoport, *J. Org. Chem*. **1991**, *56*, 5079; c) R. Wagner, J. W. Tilley, K. Lovey, *Synthesis* **1990**, 785.
[12] B. Neises, W. Steglich, *Angew. Chem., Int. Ed*. **1978**, *17*, 522.
[13] N. Flaih, C. Pham-Huy, H. Galons, *Tetrahedron Lett*. **1999**, *40*, 3697.
[14] R. S. Coleman, J. A. Shah, *Synthesis* **1999**, 1399.
[15] J. R. McElhanon, M.-J. Wu, M. Escobar, U. Chaudhry, C.-L. Hu, D. V. McGrath, *J. Org. Chem*. **1997**, *62*, 908.

Received March 21, 2002