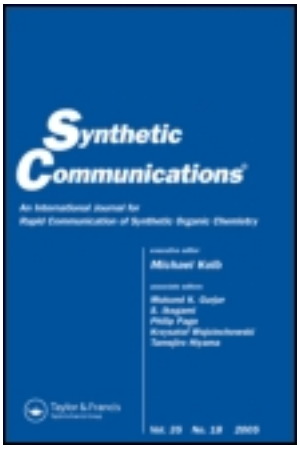

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of New Avenalumic Carboxamide Derivatives in the Ferulic Series

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Published online: 20 Oct 2008.

To cite this article: Marc-Antoine Bazin , Lala El Kihel , Marie Jouanne , Jean-Charles Lancelot & Sylvain Rault (2008) Synthesis of New Avenalumic Carboxamide Derivatives in the Ferulic Series, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:22, 3947-3959, DOI: 10.1080/00397910802238817

To link to this article: http://dx.doi.org/10.1080/00397910802238817

Synthetic Communications®, 38: 3947–3959, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802238817

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Synthesis of New Avenalumic Carboxamide Derivatives in the Ferulic Series

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Abstract: A seven-step synthesis of (2*E*,4*E*)-5-[4-hydroxy-3-methoxyphenyl]-penta-2,4-dienoic acid from ferulic acid was developed. The use of a natural by-product found in rice bran as a raw material provided the ferulic acid vinylogous in an overall high yield. This compound will be useful for the preparation of a wide variety of avenalumic carboxamide derivatives.

Keywords: Avenalumic acids, avenanthramides, ferulic acid, Horner–Emmons olefination

Avenanthramides are a group of natural compounds occurring in oat groats and hulls (*Avena sativa* L.). They consist of conjugated forms containing various hydroxy/methoxy-substituted cinnamic or phenylpentadienoic acids linked to an anthranilic acid (Fig. 1).[1,2]

In the cinnamic series (n=1), avenanthramides have been characterized as antioxidants in vitro in several studies.[3] Fungal infection and treatment with various elicitors induced their production in oat leaves, and they were thus also classified in the phytoalexins family.[4]

In the avenalumic series (n=2), avenanthramides are considered as *trans*-ethylenic homologs of the previous series. In 1991, Collins

Received May 20, 2008.
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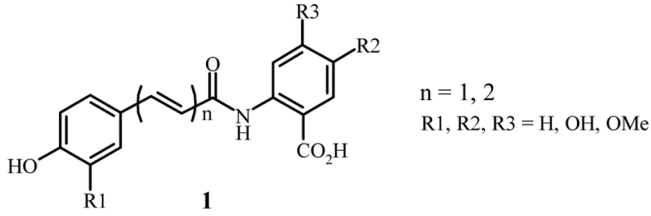


Figure 1. General structure of avenanthramides.

identified and characterized avenalumic acid **2** and *N*-anthranilic carboxamides **3** derivated from **2** (Fig. 2).[5]

In contrast with avenanthramides in the cinnamic series, avenalumic carboxamide derivative chemistry is not well known, and the antioxidant capacity and the UV absorbant potential of **2** and **3** were only suggested.[5] Indeed, these compounds have not been the subject of extended studies. This lack of knowledge prompted us to investigate an efficient synthesis of this type of compound, and we publish herein the first results of our synthetic studies.

Besides, (2*E*,4*E*)-5-arylpenta-2,4-dienamides have been of great interest because many biologically active avenalumic carboxamide derivatives such as piperine analogs,[6] antiallergic agents,[7] platelet-activating factor (PAF) inhibitors,[8] 5-lipoxygenase inhibitors,[9] ultraviolet (UV) absorbers,[10] or cell proliferation modulators[11] have been developed.

The increasing interest in such bioactive (2*E*,4*E*)-5-arylpenta-2,4-dienamides and our focus on cinnamic acids chemistry[12] and the synthesis of ferulic acid derivatives[13] led us to undertake the preparation of ferulic acid vinylogous **11** starting from ferulic acid **4**. Ferulic acid is an extremely abundant hydroxycinnamic acid in the plant cell wall (mainly in cereals such as rice bran, oats, and wheat).[14] Agricultural by-products such as rice bran oil are commonly used for manufacturing ferulic acid.[15] Ferulic acid itself exhibits a wide range of biological actions including antioxidant,[16] anti-inflammatory,[17] and anticancer[18]

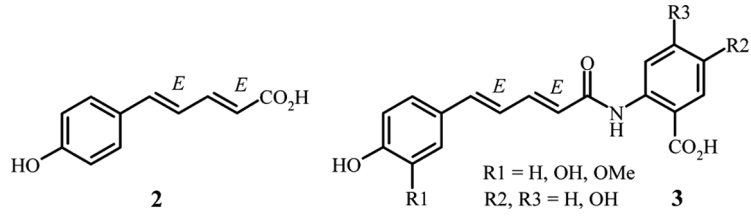


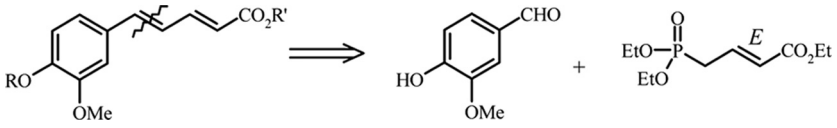
Figure 2. Structures of avenalumic acid **2** and avenalumic carboxamide derivatives **3**.

activities and is now widely used in the food and cosmetic industries.[19] Because these activities are shown to be moderate, pharmacomodulations of ferulic acid may improve them.

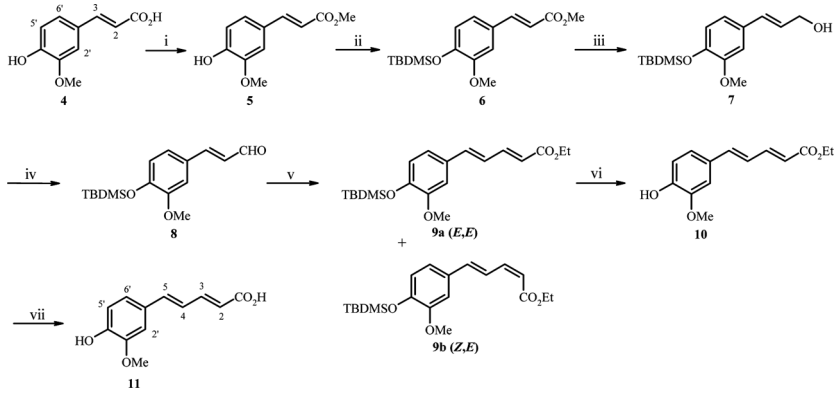
To our knowledge, only one method of the preparation of (2*E*,4*E*)-5-[4-hydroxy-3-methoxyphenyl]penta-2,4-dienoic acid **11** has been reported. It needs the use of both an expensive cinnamaldehyde and the benzene as solvent.[11] In terms of strategy, the Horner–Wadsworth–Emmons reaction using (2*E*)-triethylphosphonocrotonate and vanillin could be used (Scheme 1). Nevertheless, this reaction needs the use of the single *E*-isomer, which is difficult to isolate from the commercial ethyl bromocrotonate isomer mixture.

Because of these difficulties, we searched for a better way, and we now report a multistep stereoselective synthesis of the (2*E*,4*E*)-5-[4-hydroxy-3-methoxyphenyl]penta-2,4-dienoic acid from ferulic acid in a high overall yield and the application of this methodology to prepare *N*-anthranilic carboxamides. The key step of the sequence is the stereoselective carbon–carbon double-bond formation. *E*-Selective Horner–Emmons olefination involving a cinnamaldehyde intermediate has been carried out, as described by some authors.[20] Reduction of alkyl cinnamates is a common strategy for converting cinnamic acids into aldehydes.[21] The Horner–Emmons reaction needs the protection of the phenol function. This group must be a suitable protective group for subsequent reduction and oxidation steps. After several attempts using benzyl, acetyl, or tetrahydropyrannyl protective groups, we found that the *tert*-butyldimethylsilyl ether was the best one.

As depicted in Scheme 2, the phenolic group of methyl ferulate **5** was protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) to afford compound **6** in quantitative yield. Reduction of this cinnamate with diisobutylaluminium hydride (DIBAL-H) gave the coniferyl alcohol **7**, which was oxidized with MnO_2 to provide (*O*-TBDMS) coniferaldehyde **8**. Condensation of this aldehyde with triethylphosphonoacetate at room temperature gave the expected (2*E*,4*E*) diene **9a** in a very good yield (97%). The presence (1%) of the (2*Z*,4*E*) isomer **9b** can be detected by Thin-Layer Chromatography (TLC), and the two isomers were easily separated using silica-gel column chromatography.



Scheme 1. Possible retrosynthetic pathway of alkyl (2*E*,4*E*)-5-arylpenta-2,4-dienoate.

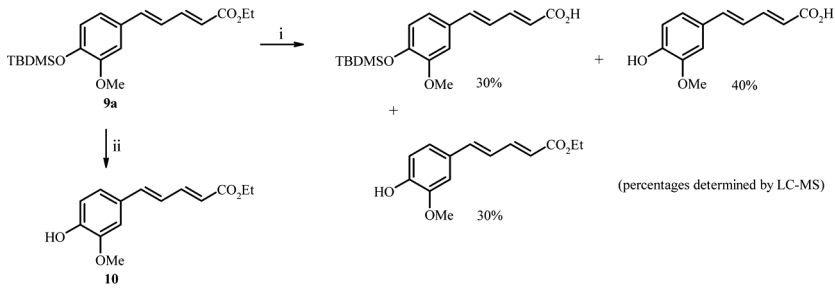


Scheme 2. Reagents and conditions: i) MeOH, H_2SO_4, reflux, 24 h, 97%; ii) TBDMSCL, imidazole, DMF, rt, 2 h, 99%; iii) DIBAL-H, THF, – 10 °C to rt, 6 h, 93%; iv) MnO_2, CH_2Cl_2, rt, 24 h, 89%; v) triethylphosphonoacetate, NaH; DMF, 0 °C to rt, 1 h, 97% (**9a**) and 1% (**9b**); vi) TBAF, AcOH, THF, 0 °C, 30 min, 93%; vii) 15% aqueous KOH, MeOH, reflux 4 h, 90%.

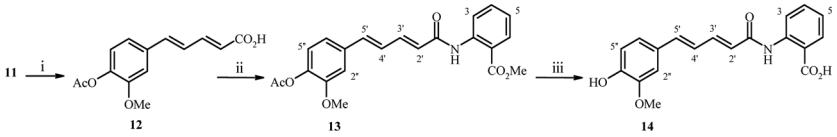
The latter **9b** was readily identified by the cis $J_{H2\text{-}H3}$ value of 11.2 Hz in the ^1H NMR spectrum, whereas the trans $J_{H2\text{-}H3}$ value for **9a** was 15.4 Hz. After selective cleavage of the silyl group with tetrabutylammonium fluoride (TBAF), the ester **10** was saponified using aqueous potassium hydride (KOH) solution in MeOH, and the desired acid **11** was obtained in 84% yield (two steps).

It can be noticed that alkaline hydrolysis of **9a** was attempted, but this reaction gave a complex mixture of partially *O*-deprotected esters and acids (Scheme 3).

The second part of our work consisted in synthesizing an *N*-anthranilic carboxamide derivative. The strategy involved the carboxylic acid



Scheme 3. Reagents and conditions: i) 15% aqueous KOH, EtOH, reflux, 4 h; ii) TBAF, AcOH, THF, 0 °C, 30 min, 93%.



Scheme 4. Reagents and conditions: i) Ac_2O, DMAP, pyridine, rt, 18 h, 92%; ii a) ethyl chloroformate, Et_3N, CH_3CN, 0 °C, 2 h, ii b) methyl anthranilate, CH_3CN, reflux, 4 h, 65%; iii) LiOH monohydrate, H_2O, 60 °C, 4 h, 60%.

activation using an anhydride intermediate. As shown in Scheme 4, protection of the phenol with acetic anhydride afforded acid **12**, which was treated with ethyl chloroformate in the presence of triethylamine to give the corresponding mixed anhydride, whose amidation with methyl anthranilate provided the carboxamide **13** in 65% yield. Removal of the acetyl group and ester hydrolysis were achieved using lithium hydroxide monohydrate and afforded the dienamide **14** in a good yield (60%).

In conclusion, we have developed a strategy starting from ferulic acid for the synthesis of useful avenalumic carboxamide derivatives. The stereocontrolled seven-step synthesis of the ferulic acid vinylogous was successfully achieved in a high overall yield (64%) thanks to an appropriate phenol protective group. This acid allowed the easy preparation of *N*-anthranilic carboxamides with potent antioxidant and UV absorption properties.

EXPERIMENTAL

Reagents and materials were obtained from commercial suppliers and were used without further purification. The reactions were monitored by TLC on Kieselgel-G (Merck Si 254 F) layers (0.25 mm thick). Column chromatography was carried out using silica gel 60 (0.063–0.2 mm) (Merck). Melting points were determined on a Kofler block. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. EI mass spectra were recorded on a Jeol-GCmate (GC-MS system) spectrometer. ESI mass spectra were recorded on a LC/MS Waters alliance. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ or DMSO-d_6 respectively at 400 MHz (Jeol Lambda 400 spectrometer) and at 100 MHz. Chemical shifts are reported relative to TMS; *J* values are given in hertz. ^{13}C NMR spectra are ^{1}H-decoupled. Chemical shifts (*) could be interchanged. Elemental analyses were performed at the Institut de Recherche en Chimie Organique Fine (Rouen).

Methyl Ferulate (5)

Five drops of conc. H_2SO_4 were added to a stirred solution of ferulic acid (30.0 g, 154.5 mmol) in MeOH (200 mL). The mixture was refluxed for 24 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (500 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×100 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate: 7/3) to give compound **5** (31.2 g, 97% yield) as white crystals. Mp 68 °C; IR (KBr): 3399 (O–H), 1698 (C=O ester), 1634, 1603, 1513, 1434, 1371, 1266, 1160, 1123, 1031, 981, 861, 817, 604, 570 cm^{-1}; ^1H NMR ($CDCl_3$): 3.80 (s, 3H, $-CO_2Me$), 3.93 (s, 3H, –OMe), 5.86 (s, 1H, –OH), 6.29 (d, J_{2-3}=15.9 Hz, 1H, H_2), 6.92 (d, $J_{5'-6'}$=8.3 Hz, 1H, $H_{5'}$), 7.02 (d, $J_{2'-6'}$=1.7 Hz, 1H, $H_{2'}$), 7.07 (dd, $J_{6'-5'}$=8.3 Hz and $J_{6'-2'}$=1.7 Hz, 1H, $H_{6'}$), 7.62 (d, J_{3-2}=15.9 Hz, 1H, H_3) ppm; ^{13}C NMR ($CDCl_3$): 51.6 ($-CO_2\underline{Me}$), 55.9 (–OMe), 109.3, 114.7, 115.2, 123.0, 127.0, 144.9, 146.7, 147.9, 167.7 ($-CO_2Me$) ppm; MS (ESI): $[M+H]^+$ 209; HRMS (EI) m/z [M^+] calcd. for $C_{11}H_{12}O_4$: 208.0736, found: 208.0732.

Methyl (2*E*)-3-[4-[[*Tert*-butyldimethylsilyl]oxy]-3-methoxyphenyl]-prop-2-enoate (6)

Imidazole (24.5 g, 359.9 mmol) was added to a stirred solution of compound **5** (30.0 g, 144.1 mmol) and *tert*-butyldimethylsilyl chloride (26.1 g, 173.2 mmol) in DMF (100 mL). The solution was stirred at room temperature for 2 h. Water (200 mL) was added, and the mixture was extracted with diethyl ether (4×150 mL). The organic layer was washed with brine (200 mL) and water (200 mL) successively, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate: 9/1) to give compound **6** (45.8 g, 99% yield) as white needles. Mp 65 °C; IR (KBr): 1711 (C=O ester), 1643, 1599, 1512, 1471, 1423, 1342, 1288, 1163, 1127, 1032, 994, 912, 843, 781, 722, 693, 653, 607, 556, 495 cm^{-1}; ^1H NMR ($CDCl_3$): 0.17 [s, 6H, $(CH_3)_2$-Si], 0.99 [s, 9H, $(CH_3)_3C$–Si], 3.79 (s, 3H, –OMe), 3.83 (s, 3H, $-CO_2Me$), 6.30 (d, J_{2-3}=16.0 Hz, 1H, H_2), 6.84 (d, $J_{5'-6'}$=8.5 Hz, 1H, $H_{5'}$), 6.99–7.03 (m, 2H, $H_{2'}$, and $H_{6'}$), 7.62 (d, J_{3-2}=16.0 Hz, 1H, H_3) ppm; ^{13}C NMR ($CDCl_3$): −4.6 [$(\underline{C}H_3)_2$–Si], 18.5 [$(CH_3)_3\underline{C}$–Si], 25.7 [$(\underline{C}H_3)_3$ C–Si], 51.6 ($-CO_2Me$), 55.5 (–OMe), 110.9, 115.5, 121.1, 122.2, 128.3, 145.0, 147.6, 151.2, 167.7 ($-CO_2Me$) ppm; MS (ESI): $[M+H]^+$ 323; HRMS (EI) m/z [M^+] calcd. for $C_{17}H_{26}O_4Si$: 322.1600, found: 322.1597.

(2*E*)-3-[4-[[*Tert*-butyldimethylsilyl]oxy]-3-methoxyphenyl] prop-2-en-1-ol (7)

DIBAL-H (1 M in THF, 340 mL, 340.0 mmol) was added dropwise over 30 min to a solution of compound **6** (21.9 g, 67.9 mmol) in THF (300 mL) at −10 °C under argon. The solution was stirred at room temperature for 6 h. Water (100 mL) was carefully added dropwise at 0 °C. The mixture was acidified to pH=5 with a 2 M HCl aqueous solution. The phases were separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate: 9/1) to give compound **7** (18.6 g, 93% yield) as a colorless oil. IR (KBr): 3350 (O–H), 1654, 1600, 1577, 1513, 1464, 1417, 1362, 1281, 1255, 1160, 1126, 1092, 1037, 965, 900, 840, 804, 782, 703, 661, 623 cm^{-1}; ^1H NMR ($CDCl_3$): 0.15 [s, 6H, $(CH_3)_2$–Si], 0.99 [s, 9H, $(CH_3)_3$ C–Si], 3.82 (s, 3H, –OMe), 4.30 (d, J_{1-2}=5.9 Hz, 2H, –C$\underline{H_2}$OH), 6.24 (dt, J_{2-3}=15.7 Hz and J_{2-1}=5.9 Hz, 1H, H_2), 6.54 (d, J_{3-2}=15.7 Hz, 1H, H_3), 6.79 (d, $J_{5'-6'}$=8.1 Hz, 1H, $H_{5'}$), 6.85 (dd, $J_{6'-5'}$=8.1 Hz and $J_{6'-2'}$=2.1 Hz, 1H, $H_{6'}$), 6.91 (d, $J_{2'-6'}$=2.1 Hz, 1H, $H_{2'}$) ppm; ^{13}C NMR ($CDCl_3$): − 4.8 [($\underline{C}H_3)_2$–Si], 18.3 [$(CH_3)_3\underline{C}$–Si], 25.6 [($\underline{C}H_3)_3$C–Si], 55.2 (–OMe), 63.3 (C1), 109.8, 119.4, 120.7, 126.5, 130.6, 130.8, 144.7, 150.8 ppm; MS (EI, 70 eV) *m/z* (%): 294 (30) [M^+], 237 (100) [M^+ –*t*-Bu], 222 (41), 209 (45), 194 (36), 179 (26), 166 (20), 119 (31), 117 (32). HRMS (EI) m/z [M^+] calcd. for $C_{16}H_{26}O_3Si$: 294.1651, found: 294.1648.

(2*E*)-3-[4-[[*Tert*-butyldimethylsilyl]oxy]-3-methoxyphenyl] acrylaldehyde (8)

To a solution of compound **7** (15.9 g, 54.0 mmol) in CH_2Cl_2 (200 mL), MnO_2 (70.4 g, 810.1 mmol) was added, and the solution was then stirred at room temperature for 24 h. The mixture was filtered through celite, washing by EtOAc. The filtrate was concentrated to give compound **8** (14.1 g, 89% yield) as a white solid. Mp 79 °C; IR (KBr): 1670 (C=O aldehyde), 1621, 1596, 1511, 1464, 1424, 1283, 1164, 1129, 1034, 984, 906, 837, 783 cm^{-1}; ^1H NMR ($CDCl_3$): 0.18 [s, 6H, $(CH_3)_2$ –Si], 1.00 [s, 9H, $(CH_3)_3$ C-Si], 3.85 (s, 3H, –OMe), 6.60 (dd, J_{2-3}=15.9 Hz and $J_{2\text{-Hald}}$=7.8 Hz, 1H, H_2), 6.88 (d, $J_{5'-6'}$=8.0 Hz, 1H, $H_{5'}$), 7.05–7.09 (m, 2H, $H_{2'}$ and $H_{6'}$), 7.40 (d, J_{3-2}=15.9 Hz, 1H, H_3), 9.66 (d, $J_{\text{Hald-2}}$=7.8 Hz, Hz, 1H, H_{ald}) ppm; ^{13}C NMR ($CDCl_3$): − 4.5 [($\underline{C}H_3)_2$–Si], 18.4 [$(CH_3)_3$ $\underline{C}$–Si], 25.6 [($\underline{C}H_3)_3$ C–Si], 55.3 (–OMe), 111.0, 121.2, 123.1, 126.7, 127.9, 148.6, 151.4, 153.1, 193.7 (C1) ppm; MS (ESI): $[M + H]^+$

293; HRMS (EI) m/z [M^+] calcd. for $C_{16}H_{24}O_3$ Si: 292.1495, found: 292.1500.

Ethyl (2*E*,4*E*)-5-[4-[[*Tert*-butyldimethylsilyl]oxy]-3-methoxyphenyl]-penta-2,4-dienoate (9a) and Ethyl (2*Z*,4*E*)-5-[4-[[*Tert*-butyldimethylsilyl]-oxy]-3-methoxyphenyl]penta-2,4-dienoate (9b)

NaH (2.1 g, 89.1 mmol) was added in a small amount to a solution of compound **8** (13.0 g, 44.5 mmol) and triethyl phosphonoacetate (11.0 g, 49.0 mmol) in DMF (100 mL) at 0 °C. The solution was then stirred at room temperature for 1 h. Ice water (200 mL) was added to the solution, and the mixture was extracted with diethyl ether (4×100 mL). The organic layer was washed with water (100 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate: 95/5) to give compound **9a** (15.60 g, 97% yield) as a colorless solid and compound **9b** (0.16 g, 1% yield) as a colorless oil.

Compound **9a**: Mp 48 °C; IR (KBr): 1710 (C=O ester), 1625, 1594, 1511, 1464, 1418, 1367, 1313, 1285, 1264, 1174, 1132, 1038, 998, 905, 841, 806, 783, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.16 [s, 6H, $(CH_3)_2$–Si], 0.99 [s, 9H, $(CH_3)_3$ C–Si], 1.31 (t, J=7.1 Hz, 3H, –$OCH_2\underline{CH_3}$), 3.84 (s, 3H, –OMe), 4.22 (q, J=7.1 Hz, 2H, –$OC\underline{H_2}CH_3$), 5.94 (d, J_{2-3}=15.4 Hz, 1H, H_2), 6.73 (dd, J_{4-5}=15.6 Hz and J_{4-3}=10.6 Hz, 1H, H_4), 6.81–6.85 (m, 2H, H_5 and $H_{5'}$), 6.93–6.96 (m, 2H, $H_{2'}$ and $H_{6'}$), 7.43 (dd, J_{3-2}=15.4 Hz and J_{3-4}=10.6 Hz, 1H, H_3) ppm; ^{13}C NMR ($CDCl_3$): −4.6 [$(\underline{C}H_3)_2$–Si], 14.3 (–OCH_2 $\underline{C}H_3$), 18.5 [$(CH_3)_3\underline{C}$–Si], 25.7 [$(\underline{C}H_3)_3$C–Si], 55.5 (–OMe), 60.2 (–$O\underline{C}H_2CH_3$), 110.2, 120.2, 121.0, 121.1, 124.4, 130.0, 140.5, 144.9, 146.4, 151.2, 167.3 (C1) ppm; MS (ESI): $[M+H]^+$ 363. Anal. calcd. for $C_{20}H_{30}O_4Si$: C, 66.26; H, 8.34. Found: C, 66.47; H, 8.69.

Compound **9b**: IR (KBr): 1712 (C=O ester), 1621, 1593, 1510, 1464, 1285, 1255, 1177, 1128, 1036, 998, 905, 840, 808, 783, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.16 [s, 6H, $(CH_3)_2$–Si], 0.99 [s, 9H, $(CH_3)_3$ C–Si], 1.33 (t, J=7.1 Hz, 3H, –$OCH_2\underline{C}H_3$), 3.84 (s, 3H, –OMe), 4.22 (q, J=7.1 Hz, 2H, –$OC\underline{H_2}CH_3$), 5.66 (d, J_{2-3}=11.2 Hz, 1H, H_2), 6.69–6.85 (m, 3H, H_4, H_5 and $H_{5'}$), 6.97 (dd, $J_{6'-5'}$=8.3 Hz and $J_{6'-2'}$=2.0 Hz, 1H, $H_{6'}$), 7.05 (d, $J_{2'-6'}$=2.0 Hz, 1H, $H_{2'}$), 8.01 (dd, J_{3-4}=11.5 Hz and J_{3-2}=11.2 Hz, 1H, H_3) ppm; ^{13}C NMR ($CDCl_3$): −4.6 [$(CH_3)_2$–Si], 14.3 (–OCH_2 $\underline{C}H_3$), 18.5 [$(CH_3)_3\underline{C}$–Si], 25.7 [$(\underline{C}H_3)_3$ C–Si], 55.4 (–OMe), 59.9 (–$O\underline{C}H_2CH_3$), 110.0, 116.1, 121.0, 121.5, 123.1, 124.4, 130.3, 141.5, 145.3, 151.1, 166.8 (C1) ppm; MS (ESI): $[M+H]^+$ 363, $[M+MeCN+H]^+$ 402. Anal. calcd. for $C_{20}H_{30}O_4$ Si: C, 66.26; H, 8.34. Found: C, 66.19; H, 8.14.

Ethyl (2*E*,4*E*)-5-[4-Hydroxy-3-methoxyphenyl]penta-2,4-dienoate (10)

To a solution of compound **9a** (15.0 g, 41.4 mmol) in THF (100 mL), glacial acetic acid (8 mL) was added at 0 °C under argon. TBAF (1 M in THF, 82.7 mL, 82.7 mmol) was then added dropwise, and the mixture was stirred at the same temperature for 1 h. THF was evaporated under reduced pressure. The mixture was acidified to pH=5 with a 0.5 M HCl aqueous solution. The aqueous layer was extracted with diethyl ether (4 × 100 mL). The organic layer was washed with water (50 mL) and brine (50 mL) successively, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate: 8/2) to give compound **10** (9.6 g, 93% yield) as a pale yellow solid. Mp 90 °C; IR (KBr): 3430 (O–H), 1684 (C=O ester), 1624, 1587, 1512, 1336, 1259, 1208, 1185, 1137, 1031, 1017, 1004, 864, 806 cm^{-1}; ^1H NMR ($CDCl_3$): 1.31 (t, J=7.1 Hz, 3H, –$OCH_2C\underline{H}_3$), 3.93 (s, 3H, –OMe), 4.22 (q, J=7.1 Hz, 2H, –$OC\underline{H}_2CH_3$), 5.78 (br s, 1H, OH), 5.94 (d, J_{2-3}=15.2 Hz, 1H, H_2), 6.72 (dd, J_{4-5}=15.3 Hz and J_{4-3}=10.7 Hz, 1H, H_4), 6.82 (d, J_{5-4}=15.3 Hz, 1H, H_5), 6.89 (d, $J_{5'-6'}$=8.1 Hz, 1H, $H_{5'}$), 6.97 (d, $J_{2'-6'}$=1.7 Hz, 1H, $H_{2'}$), 6.99 (dd, $J_{6'-5'}$=8.1 Hz and $J_{6'-2'}$=1.7 Hz, 1H, $H_{6'}$), 7.43 (dd, J_{3-2}=15.2 Hz and J_{3-4}=10.7 Hz, 1H, H_3) ppm; ^{13}C NMR ($CDCl_3$): 14.3 (–$OCH_2\underline{C}H_3$), 56.0 (–OMe), 60.3 (–$O\underline{C}H_2CH_3$), 108.7, 114.7, 120.1, 121.7, 124.1, 128.7, 140.5, 144.9, 146.8, 146.9, 167.3 (C1) ppm; MS (ESI): $[M–H]^-$ 247. Anal. calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.39; H, 6.76.

(2*E*,4*E*)-5-[4-Hydroxy-3-methoxyphenyl]penta-2,4-dienoic Acid (11)

Aqueous KOH (15%, 75 mL) was added to a solution of compound **10** (8.0 g, 32.3 mmol) in MeOH (75 mL). The mixture was refluxed for 4 h. MeOH was evaporated under reduced pressure, and the aqueous solution was acidified to pH=4 with a 2 M HCl aqueous solution. The aqueous layer was extracted with ethyl acetate (2×150 mL). The organic layer was washed with water (100 mL), dried over $MgSO_4$, and concentrated. Recrystallization from MeOH/H_2O (1:1) gave compound **11** (6.4 g, 90% yield) as a yellow solid. Mp 199 °C; IR (KBr): 3525 (O–H), 3457 (O–H carboxylic acid), 1681 (C=O carboxylic acid), 1587, 1514, 1429, 1336, 1311, 1267, 1209, 1164, 1125, 1022, 994, 926, 853, 819, 761, 699, 606, 549 cm^{-1}; ^1H NMR (DMSO-d_6): 3.80 (s, 3H, –OMe), 5.89 (d, J_{2-3}=15.0 Hz, 1H, H_2), 6.76 (d, $J_{6'-5'}$=8.1 Hz, 1H, $H_{6'}$), 6.92–6.98 (m, 3H, H_4, H_5 and $H_{5'}$), 7.15 (s, 1H, $H_{2'}$), 7.30 (ddd, J_{3-2}=15.1 Hz, J_{3-4}=6.9 Hz and J_{3-5}=3.0 Hz, 1H, H_3), 9.76 (brs, 1H, OH phenol), 12.12 (brs, 1H, OH acid) ppm; ^{13}C NMR (DMSO-d_6): 56.0 (–OMe), 110.6,

115.9, 120.4, 121.9, 124.0, 128.1, 141.1, 145.7, 148.2 (2 C), 168.3 (Cl) ppm; MS (ESI): $[M–H]^-$ 219. Anal. calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.57; H, 5.53.

(2*E*,4*E*)-5-[4-Acetyloxy-3-methoxyphenyl]penta-2,4-dienoic Acid (12)

To a solution of compound **11** (5.0 g, 22.7 mmol) in pyridine (50 mL), DMAP (0.1 g, 1.1 mmol) and acetic anhydride (2.4 mL, 25.0 mmol) were added successively at room temperature. The solution was then stirred for 18 h. The solution was acidified to pH=3 with a 1 M HCl aqueous solution. The aqueous layer was extracted with ethyl acetate (3×150 mL). The organic layer was washed successively with brine and water and dried over $MgSO_4$. Concentration in vacuo afforded compound **12** (5.5 g, 92% yield) as a beige solid. Mp 210 °C; IR (KBr): 3436 (O–H), 1766 (C=O ester), 1674 (C=O carboxylic acid), 1612, 1511, 1423, 1313, 1268, 1208, 1125, 1032, 996, 909, 861, 824, 699 cm^{-1}; ^1H NMR ($CDCl_3$): 2.33 (s, 3H, –OCOC$\underline{H}_3$), 3.88 (s, 3H, –OMe), 6.01 (d, J_{2-3}=15.2 Hz, 1H, H_2), 6.84 (dd, J_{4-5}=15.5 Hz and J_{4-3}=10.1 Hz, 1H, H_4), 6.92 (d, J_{5-4}=15.5 Hz, 1H, H_5), 7.03 (d, $J_{5'-6'}$=8.1 Hz, 1H, $H_{5'}$), 7.06–7.09 (m, 2H, $H_{2'}$ and $H_{6'}$), 7.52 (dd, J_{3-2}=15.2 Hz and J_{3-4}=10.1 Hz, 1H, H_3) ppm; ^{13}C NMR (DMSO-d_6): 20.4 (–OCO$\underline{C}H_3$), 55.9 (–OMe), 110.7, 120.1, 122.3, 123.2, 127.0, 135.0, 139.3, 139.9, 144.3, 151.1, 167.6 (–O$\underline{C}$OCH$_3$), 168.5 (C1) ppm; MS (ESI): $[M–H]^-$ 261; HRMS (EI) m/z $[M^+]$ calcd. for $C_{14}H_{14}O_5$: 262.0841, found: 262.0838. Anal. calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.22; H, 4.95.

Methyl 2-({(2*E*,4*E*)-5-[4-Acetyloxy-3-methoxyphenyl]penta-2,4-dienoyl}amino)benzoate (13)

Triethylamine (2.1 mL, 15.3 mmol) was added to a solution of compound **12** (4.0 g, 15.3 mmol) in acetonitrile (50 mL) at 0 °C. The mixture was then stirred for 1 h at 0 °C. Ethyl chloroformate (1.5 mL, 15.3 mmol) was added dropwise, and the solution was stirred for 1 h at the same temperature. The white precipitate was filtered and washed with acetonitrile (10 mL), and the filtrate was concentrated. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (2 × 150 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a yellowish solid. The crude product was used in the next step without purification. To a solution of crude anhydride (15.3 mmol) in acetonitrile (75 mL), methyl anthranilate (2.0 mL, 15.3 mmol) was added, and the solution was then refluxed for 4 h. The solvent was removed under reduced pressure. Water (100 mL)

was added, and the mixture was extracted with ethyl acetate (3×150 mL). The organic layer was washed with water (100 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 8:2) and recrystallized in MeOH to give compound **13** (3.9 g, 65% yield, two steps) as a pale yellow solid. Mp 149 °C; IR (KBr): 1761 (C=O acetyl), 1697 (C=O $-CO_2Me$), 1677 (C=O amide), 1612, 1587, 1530, 1511, 1446, 1261, 1201, 1129, 992, 757 cm^{-1}; ^1H NMR ($CDCl_3$): 2.32 (s, 3H, $-OCOCH_3$), 3.88* (s, 3H, –OMe), 3.95* (s, 3H, $-CO_2Me$), 6.22 (d, $J_{2'-3'}$=14.9 Hz, 1H, $H_{2'}$), 6.87–6.90 (m, 2H, $H_{4'}$ and $H_{5'}$), 7.02–7.11 (m, 4H, $H_{2'}$, $H_{5'}$, $H_{6'}$ and H_4*), 7.50 (ddd, $J_{3'-2'}$=14.9 Hz and $J_{3'-4'}$=7.8 Hz and $J_{3'-5'}$=2.2 Hz, 1H, $H_{3'}$), 7.57 (ddd, J_{5-6}=7.9 Hz and J_{5-4}=7.9 Hz and J_{5-3}=1.5 Hz, 1H, H_5*), 8.05 (dd, J_{3-4}=7.9 Hz and J_{3-5}=1.5 Hz, 1H, H_3), 8.84 (d, J_{6-5}=8.5 Hz, 1H, H_6), 11.30 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): 20.6 ($-OCO\underline{C}H_3$), 52.3 ($-CO_2\ \underline{C}H_3$), 55.8 (–OMe), 110.4, 114.8, 119.9, 120.4, 122.4, 123.1, 125.5, 126.6, 130.8, 134.7, 135.2, 139.1, 140.2, 141.8 (2 C), 151.2, 164.5 (C1′), 168.8* ($-O\underline{C}OCH_3$), 168.9* ($-\underline{C}O_2CH_3$) ppm; MS (ESI): $[M+H]^+$ 396; HRMS (EI) m/z $[M^+]$ calcd. for $C_{22}H_{21}NO_6$: 395.1369, found: 395.1360. Anal. calcd. for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.93; H, 5.35; N, 3.34.

2-({(2*E*,4*E*)-5-[4-Hydroxy-3-methoxyphenyl]penta-2,4-dienoyl}amino)benzoic Acid (14)

$LiOH \cdot H_2O$ (0.2 g, 20.2 mmol) was added to a suspension of compound **13** (2.0 g, 5.1 mmol) in water (75 mL). The solution was warmed for 4 h at 60 °C. The mixture was then cooled to room temperature and filtered. The solution was acidified to pH=1 with a 2 M HCl aqueous solution. The mixture was extracted with ethyl acetate (2×100 mL). The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The crude product was triturated with diethyl ether and filtered to give compound **14** (1.0 g, 60% yield) as a yellow solid. Mp 203 °C; IR (KBr): 3429 (O–H), 1686 (C=O acid), 1657 (C=O amide), 1606, 1586, 1514, 1452, 1375, 1278, 1250, 1209, 1137, 988, 760 cm^{-1}; ^1H NMR (DMSO-d_6): 3.81 (s, 3H, –OMe), 4.12 (br s, 1H, OH), 6.22 (d, $J_{2'-3'}$=14.7 Hz, 1H, $H_{2'}$), 6.77 (d, $J_{6''-5''}$=8.8 Hz, 1H, $H_{6''}$), 6.92–6.98 (m, 2H, $H_{5'}$ and $H_{5''}$), 7.04 (dd, $J_{4'-5'}$=15.6 Hz and $J_{4'-3'}$=10.8 Hz, 1H, $H_{4'}$), 7.12–7.16 (m, 1H, H_5), 7.18 (s, 1H, $H_{2''}$), 7.36 (dd, $J_{3'-2'}$=14.7 Hz and $J_{3'-4'}$=10.8 Hz, 1H, $H_{3'}$), 7.57–7.61 (m, 1H, H_4), 7.99 (d, J_{3-4}=7.8 Hz, 1H, H_3), 8.60 (d, J_{6-5}=6.8 Hz, 1H, H_6), 9.42 (s, 1H, NH), 11.44 (br s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6): 55.6 (–OMe), 110.3, 115.6, 116.4, 119.9, 121.3, 122.4, 123.5, 123.7, 127.7, 131.0, 133.8, 140.1,

141.0, 142.2, 147.8, 147.9, 163.9 (C1'), 169.5(–$\underline{C}O_2H$) ppm; MS (ESI): $[M+H]^+$ 340; HRMS (EI) m/z $[M^+]$ calcd. for $C_{19}H_{17}NO_5$: 339.1107, found: 339.1108. Anal. calcd. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.04; H, 4.87; N, 4.29.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from Laboratoires PCAS and the Conseil Régional de Basse-Normandie.

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