

## Synthesis of 4-*O*-Methylcedrusin. Selective Protection of Catechols with Diphenyl Carbonate

Stefaan M. O. Van Dyck, Guy L. F. Lemière\*, Tim H. M. Jonckers and Roger Dommisse

Department of Chemistry, Laboratory of Natural Product Synthesis for Chemotherapy, University of Antwerp (RUCA), Groenenborgerlaan 171, 2020 Antwerpen, Belgium

Tel.: ++32 3 2180226, Fax: ++32 3 2180233, E-mail: [lemiere@ruca.ua.ac.be](mailto:lemiere@ruca.ua.ac.be)

\*Author to whom correspondence should be addressed.

Received: 1 November 1999 / Accepted: 19 January 2000 / Published: 18 February 2000

---

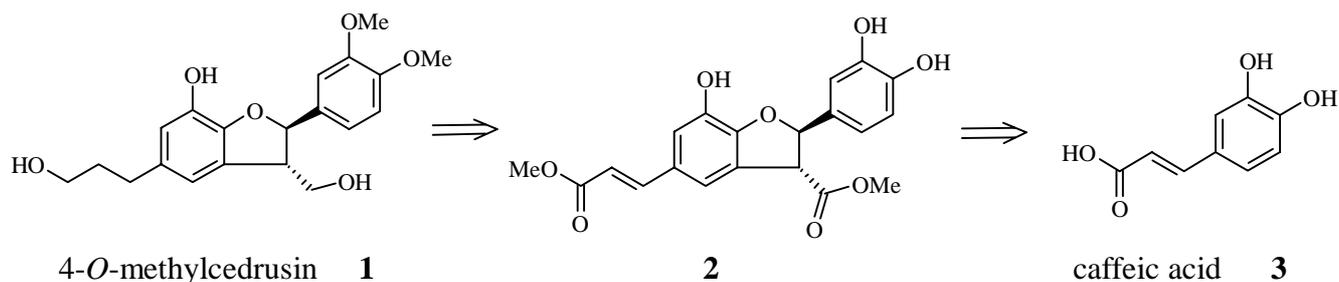
**Abstract:** 4-*O*-Methylcedrusin, a minor component in ‘sangre de drago’, has been synthesized using a strategy of successive protection and deprotection reactions under very mild conditions. The key step of this synthesis is a selective protection of a catechol group as a cyclic carbonate in the presence of an isolated phenol group.

**Keywords:** Carbonates, lignans, phenolics, protecting groups, natural products.

---

### Introduction

The red viscous latex ‘sangre de drago’ or dragon’s blood, obtained by slashing the bark of various *Croton* species (Euphorbiaceae), is used in South-American popular medicine for several purposes including wound healing [1]. Recently the anticancer activity of the dihydrobenzofuran-type neolignan extracted from this latex and of some analogues has been demonstrated [2]. 4-*O*-Methylcedrusin is a minor component found in sangre de drago [3]. We now wish to report the first synthesis of racemic [4] 4-*O*-methylcedrusin from caffeic acid (Scheme 1).



Scheme 1.

## Results and Discussion

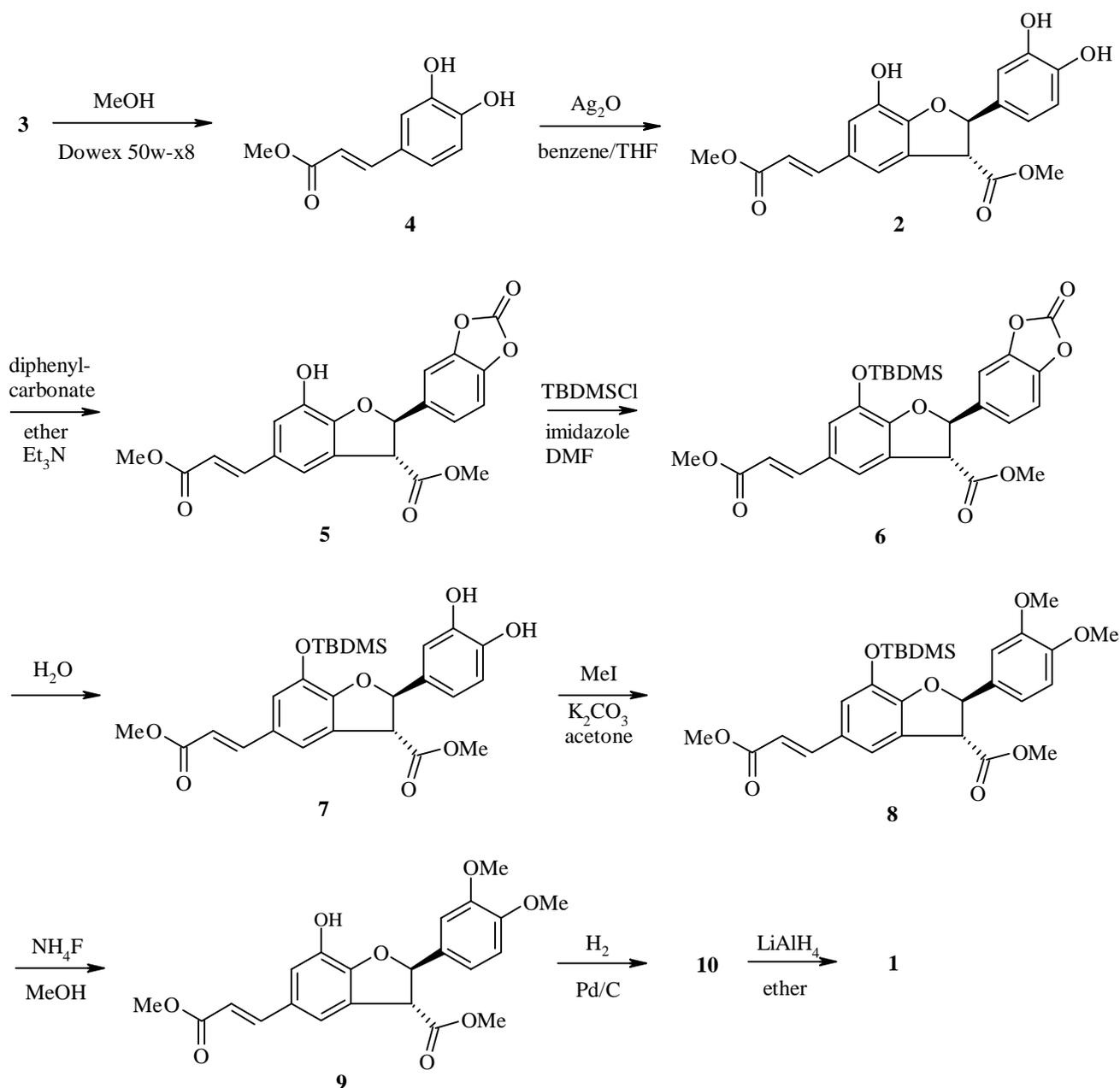
The dihydrobenzofuran skeleton of this type of neolignan is often obtained by an oxidative coupling of cinnamate esters using silver oxide [5] or horseradish peroxidase [6]. Therefore caffeic acid was esterified in methanol using Dowex 50w-X-8<sup>®</sup> as a heterogenous acidic catalyst giving methyl caffeate in quantitative yield. The ester was then oxidized with silver oxide in benzene/THF at room temperature resulting in the formation of (**2**).

Since only the two catecholic hydroxyl groups in product (**2**) have to be methylated we looked for a method to selectively protect a catechol in the presence of an isolated phenol group. After the protection of the phenol group and deprotection of the catechol moiety the methylation can be performed. In this strategy one should also consider that product (**2**) is base as well as acid sensitive. Since some widely used catechol protecting groups such as acetals, cyclic boronates and cyclic sulfates [7] sometimes require rather drastic conditions for their formation or removal they did not appear to be useful for our synthesis. We preferred the cyclic carbonate protecting group because it can easily be introduced and removed. Although this group is often used in sugar chemistry [8], it has been used only to a very limited extent for catechols since these carbonates are very sensitive to hydrolysis [7]. Also no information about the selectivity of this group towards catechols could be found in the literature. Therefore the protection conditions were examined in a test reaction on a mixture of the model compounds 4-cyanophenol and catechol. The reaction products were analyzed by GC and showed a selectivity of over 95% towards the catechol indicating the usefulness of the cyclic carbonate as a selective protecting group.

The procedure described in the literature for the introduction of a cyclic carbonate was greatly simplified [9]. Product (**2**) and diphenyl carbonate, both dissolved in diethyl ether, were stirred at room temperature with a catalytic amount of triethylamine. The carbonate (**5**) precipitated from the solution allowing an easy work-up. The formation of the cyclic carbonate was clearly visible in the IR spectra. Product (**5**) had a characteristic (C=O) absorption at 1831 cm<sup>-1</sup>. Further, the very broad hydroxyl absorption band of product (**2**) changes into a much sharper signal at 3358 cm<sup>-1</sup> after the carbonate formation.

Protection of the remaining phenol group was achieved through the reaction of (**5**) with tert-butyldimethylchlorosilane (TBDMSCl) and imidazole in dry DMF. The cyclic carbonate protecting

group could immediately be removed by addition of a small amount of water to this reaction mixture. Hydrolysis was complete within 3 hours [10] giving deprotected product (7). Subsequently the catechol unit is methylated with methyl iodide and  $K_2CO_3$  in acetone giving product (8). The TBDMS protecting group was then removed by refluxing (8) with an excess of ammonium fluoride in methanol. The use of a polar protic solvent for the fluoride ions was decisive for the success of the deprotection. In non-polar solvents the fluoride ion is too basic to be compatible with our products. The double bond in the side chain was reduced with  $H_2$  on Pd/C (10) and the ester functions were reduced with  $LiAlH_4$  leading to the desired 4-O-methylcedrusin (1).



Scheme 2.

## Conclusion

Summarising we can say that 4-*O*-methylcedrusin has been synthesized in a straightforward way from caffeic acid using a strategy of successive selective protection and deprotection reactions. A new synthetic method for the selective protection of a catechol as a cyclic carbonate was introduced. The low stability of the catechol carbonates towards hydrolysis was turned into an advantage by incorporating the deprotection of the catechol in a convenient one-pot synthesis. The incorporation of this cyclic carbonate as a protective group is expected to be useful in the syntheses of other sensitive polyphenolic natural products.

*Acknowledgements:* We wish to thank Joos Verreydt and Jos Aerts for their technical assistance. Tim Jonckers would like to thank the 'Vlaams instituut ter bevordering van het wetenschappelijk technologisch onderzoek in de industrie (IWT)' for a scholarship.

## Experimental

### General

Melting points were determined on a Büchi B-545 melting point apparatus.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were measured on a Varian Unity 400 spectrometer. Additional HETCOR and long-range HETCOR measurements to verify the proposed assignments were performed on the same spectrometer. DCI mass spectra were obtained on a Ribermag R-10-10B mass spectrometer. Infrared spectra were obtained from a Bruker Vector 22 infrared spectrometer. Column chromatography was performed on Merck silicagel 60, 0.040-0.063 mm, 230-400 mesh ASTM. Precoated silica gel plates (kieselgel 60, F<sub>254</sub>, 0.2 mm) were used for TLC analysis. All products and reagents were purchased from Acros.

### Methyl caffeate (4)

It was prepared from a mixture of caffeic acid (4 g) and Dowex 50 W x 8 200-400<sup>®</sup> (0.4 g) in 25 cm<sup>3</sup> of absolute methanol. After heating under reflux for 1 night the mixture was filtered and evaporated under reduced pressure to afford the product as a solid (100%) which was used without further purification.

Amorphous, mp 158°C;  $^1\text{H}$  NMR (acetone-*d*<sub>6</sub>)  $\delta$  8.3 (s, 2 H, 3-OH, 4-OH) 7.53 (d, *J* = 15.87 Hz, 1 H, H-7) 7.15 (d, *J* = 2.14 Hz, 1 H, H-2) 7.03 (dd, *J* = 8.09, 2.14 Hz, H-6) 6.86 (d, *J* = 8.09 Hz, 1 H, H-5) 6.27 (d, *J* = 16.02 Hz, 1 H, H-8) 3.70 (s, 3 H, 9-OCH<sub>3</sub>);  $^{13}\text{C}$  NMR (acetone-*d*<sub>6</sub>)  $\delta$  167.82 (C-9) 148.75 (C-4) 146.33 (C-3) 145.68 (C-7) 127.75 (C-1) 122.51 (C-6) 116.43 (C-5) 115.28 (C-2) 115.21 (C-8) 51.45 (9-OCH<sub>3</sub>); DCI-MS (NH<sub>3</sub>): *m/z* = 195 (MH<sup>+</sup>).

*Methyl (E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate (2)*

It was prepared according to the method of Lemière *et al.* [11], using 1.905 g (9.8 mmol) of methyl caffeate, 0.826 g (3.5 mmol) of silver(I)oxide, 40 cm<sup>3</sup> of anhydrous benzene and 20 cm<sup>3</sup> of anhydrous acetone. The product was purified by column chromatography (column 30 cm x 3.8 cm, silica gel 60, 0.040-0.063 mm) with ethyl acetate/heptane 1/1 as the eluent. After evaporation and lyophilisation a white foam is obtained (33%); amorphous mp 159°C.

<sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 8.05 (s, 2 H, 3-OH, 4-OH) 7.57 (d, J = 16.02 Hz, 1 H, H-7') 7.14 (s, 1 H, H-6') 6.90 (d, J = 1.95 Hz, 1 H, H-2) 6.84 (d, J = 8.24 Hz, 1 H, H-5) 6.79 (dd, J = 8.24, 1.98 Hz, 1 H, H-6) 6.33 (d, J = 16.02 Hz, 1 H, H-8') 5.97 (d, J = 8.33 Hz, 1 H, H-7) 4.35 (d, J = 8.33 Hz, 1 H, H-8) 3.79 (s, 3 H, 9'-OCH<sub>3</sub>) 3.71 (s, 3 H, 9-OCH<sub>3</sub>) 3.38 (s, 1 H, 3'-OH); <sup>13</sup>C NMR (acetone-d<sub>6</sub>) δ 171.69 (C-9) 167.79 (C-9') 150.07 (C-3') 146.33 (C-4) 146.09 (C-3) 145.42 (C-7') 142.53 (C-4') 132.70 (C-1) 129.40 (C-1') 127.33 (C-5') 118.70 (C-6) 117.76 (C-2') 117.33 (C-6') 116.16 (C-5) 116.05 (C-8') 113.93 (C-2) 87.88 (C-7) 56.29 (C-8) 52.95 (9-OCH<sub>3</sub>) 51.55 (9'-OCH<sub>3</sub>) [12]; DCI-MS (NH<sub>3</sub>): m/z = 387 (MH<sup>+</sup>); *Anal.* Calcd for C<sub>20</sub>H<sub>18</sub>O<sub>8</sub>: C, 62.17; H, 4.70. Found: C, 62.08; H, 4.64.

*Methyl (E)-3-[2-(2-oxo-1,3-benzodioxol-5-yl)-7-hydroxy-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate (5)*

It was prepared by stirring 800 mg of coupling product (2), 440 mg of diphenyl carbonate and 3 drops of triethyl amine in 30 cm<sup>3</sup> of diethyl ether for 2 days. The product precipitated from the mixture and was filtered and washed with a minimal amount of diethyl ether. After lyophilisation the carbonate was obtained in 60% yield as a white powder (mp 175°C). Product (2) could be recovered from the filtrate in 30% yield.

<sup>1</sup>H NMR (1,4-dioxane-d<sub>8</sub>) δ 8.00 (s, 1 H, 3'-OH) 7.62 (d, J = 15.87 Hz, 1 H, H-7') 7.52 (s, 1 H, H-2) 7.36 (s, 2 H, H-5, H-6) 7.17 (s, 1 H, H-2') 7.12 (s, 1 H, H-6') 6.38 (d, J = 15.87 Hz, 1 H, H-8') 6.21 (d, J = 7.76 Hz, 1 H, H-7) 4.39 (d, J = 7.93 Hz, 1 H, H-8) 3.84 (s, 3 H, 9'-OCH<sub>3</sub>) 3.75 (s, 3 H, 9-OCH<sub>3</sub>); <sup>13</sup>C NMR (1,4-dioxane-d<sub>8</sub>) δ 171.91 (C-9) 168.28 (C-9') 152.41 (C-4') 150.00 (3-OCOO) 145.76 (C-7') 145.66 (C-3) 145.36 (C-4) 143.16 (C-3') 138.94 (C-1) 131.16 (C-1') 127.14 (C-5') 123.87 (C-6) 118.39 (C-6') 118.10 (C-2') 117.54 (C-8') 111.52 (C-5) 119.62 (C-2) 87.81 (C-7) 57.35 (C-8) 53.76 (9-OCH<sub>3</sub>) 52.27 (9'-OCH<sub>3</sub>) [12]; DCI-MS (NH<sub>3</sub>): m/z = 413 (MH<sup>+</sup>), m/z = 430 (MNH<sub>4</sub><sup>+</sup>); IR (KBr) cm<sup>-1</sup>: 1831 (C=O), 3358 (OH); *Anal.* Calcd for C<sub>21</sub>H<sub>16</sub>O<sub>9</sub>: C, 61.17; H, 3.91. Found: C, 60.77; H, 4.02.

*Methyl (E)-3-[2-(2-oxo-1,3-benzodioxol-5-yl)-7-(tert-butyldimethylsilyloxy)-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate (6)*

It was prepared by stirring 570 mg of carbonate (5) with 230 mg TBDMSCl and 282 mg of imida-

zole in 15 cm<sup>3</sup> of anhydrous DMF for 8 hours. The reaction product was not isolated but the protecting carbonate group was immediately hydrolyzed with a little water (see below).

DCI-MS (NH<sub>3</sub>) of the crude reaction mixture: m/z = 527 (MH<sup>+</sup>), m/z = 539 (MNH<sub>4</sub><sup>+</sup>)

*Methyl (E)-3-[2-(3,4-dihydroxyphenyl)-7-(tert-butyl dimethylsilyloxy)-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate (7)*

It was prepared by adding 0.3 cm<sup>3</sup> of water to the previous reaction mixture. This mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (column 30 cm x 3.8 cm, silica gel 60, 0.040-0.063 mm) with ethyl acetate/heptane 3/5 as the eluent. After evaporation and lyophilisation a slightly brown tinted oil is obtained in 64% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.58 (d, J = 15.87 Hz, 1H, H-7') 7.12 (s, 1 H, H-6') 6.95 (s, 1 H, H-2') 6.89 (d, J = 1.98 Hz, 1 H, H-2) 6.84 (d, J = 8.09 Hz, 1 H, H-5) 6.80 (dd, J = 8.09, 1.98 Hz, 1 H, H-6) 6.25 (d, J = 15.87 Hz, 1 H, H-8') 6.01 (d, J = 7.63 Hz, 1 H, H-7) 4.23 (d, J = 8.33 Hz, 1 H, H-8) 3.82 (s, 3 H, 9'-OCH<sub>3</sub>) 3.79 (s, 3 H, 9-OCH<sub>3</sub>) 0.96 (s, 9 H, H-12) 0.18 (s, 3H, H-10a) 0.19 (s, 3H, H-10b); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 170.98 (C-9) 168.01 (C-9') 152.21 (C-4') 144.94 (C-7') 144.00 (C-3) 143.91 (C-4) 140.15 (C-3') 133.03 (C-1) 128.48 (C-1') 126.24 (C-5') 121.68 (C-6) 118.64 (C-6') 118.31 (C-2') 115.53 (C-8') 115.32 (C-5) 113.02 (C-2) 86.37 (C-7) 55.84 (C-8) 52.84 (9-OCH<sub>3</sub>) 51.69 (9'-OCH<sub>3</sub>) 25.66 (C-12) 18.36 (C-11) -4.41 (C-10a)\* -4.46 (C-10b)\* (\* may be reversed) [12]; DCI-MS (NH<sub>3</sub>): m/z = 501 (MH<sup>+</sup>), m/z = 518 (MNH<sub>4</sub><sup>+</sup>); *Anal.* Calcd for C<sub>26</sub>H<sub>32</sub>O<sub>8</sub>Si: C, 62.38; H, 6.44. Found: C, 62.48; H, 6.49.

*Methyl (E)-3-[2-(3,4-dimethoxyphenyl)-7-(tert-butyl dimethylsilyloxy)-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate (8)*

It was prepared by heating a solution of 100 mg of product (7), 6 cm<sup>3</sup> of methyl iodide and 1 g of potassium carbonate in 20 cm<sup>3</sup> acetone under reflux for 16 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (column 30 cm x 3.8 cm, silica gel 60, 0.040-0.063 mm) with ethyl acetate/heptane 3/5 as the eluent. After evaporation and lyophilisation a colourless oil is obtained in 68% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.59 (d, J = 15.87 Hz, 1H, H-7') 7.18 (s, 1 H, H-6') 6.99 (s, 1 H, H-2') 6.94 (dd, J = 8.24, 1.98 Hz, 1 H, H-6) 6.91 (d, J = 1.83 Hz, 1 H, H-2) 6.85 (d, J = 8.24 Hz, 1 H, H-5) 6.26 (d, J = 15.87 Hz, 1 H, H-8') 6.09 (d, J = 8.09 Hz, 1 H, H-7) 4.28 (d, J = 8.09 Hz, 1 H, H-8) 3.87 (s, 3 H, 3-OCH<sub>3</sub>)\* 3.85 (s, 3 H, 4-OCH<sub>3</sub>)\* 3.83 (s, 3H, 9-OCH<sub>3</sub>) 3.78 (s, 3H, 9'-OCH<sub>3</sub>) 0.98 (s, 9 H, H-12) 0.19 (s, 6H, H-10); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 170.87 (C-9) 167.65 (C-9') 152.12 (C-3) 149.43 (C-4) 149.36 (C-4') 144.67 (C-7') 140.16 (C-3') 132.62 (C-1) 128.61 (C-1') 126.34 (C-5') 121.67 (C-6) 118.36 (C-6') 118.20 (C-2') 115.53 (C-8') 111.39 (C-5) 109.10 (C-2) 86.61 (C-7) 56.03 (3-OCH<sub>3</sub>) 56.00 (4-OCH<sub>3</sub>) 55.83 (C-8) 52.82 (9-OCH<sub>3</sub>) 51.56 (9'-OCH<sub>3</sub>) 25.67 (C-12) 18.37 (C-11) -4.39 (C-10) (\* may

be reversed) [12]; DCI-MS (NH<sub>3</sub>): m/z = 529 (MH<sup>+</sup>) m/z = 546 (MNH<sub>4</sub><sup>+</sup>); *Anal.* Calcd for C<sub>28</sub>H<sub>36</sub>O<sub>8</sub>Si: C, 63.61; H, 6.86. Found: C, 63.86; H, 6.94.

*Methyl (E)-3-[2-(3,4-dimethoxyphenyl)-7-hydroxy-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate (9)*

It was prepared by heating a reaction tube filled with a solution of 50 mg of product (8) and 20 mg of ammonium fluoride in 3 cm<sup>3</sup> of methanol for 45 minutes at 60°C. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (column 30 cm x 3.8 cm, silica gel 60, 0.040-0.063 mm) with ethyl acetate/heptane 3/5 as the eluent. After evaporation and lyophilisation a white solid (amorphous mp 143°C) is obtained in 82% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.61 (d, J = 15.87 Hz, 1H, H-7') 7.13 (s, 1 H, H-6') 7.07 (s, 1 H, H-2') 6.96 (dd, J = 8.24, 1.98 Hz, 1 H, H-6) 6.89 (d, J = 1.98 Hz, 1 H, H-2) 6.86 (d, J = 8.24 Hz, 1 H, H-5) 6.29 (d, J = 16.02 Hz, 1 H, H-8') 6.13 (d, J = 8.09 Hz, 1 H, H-7) 4.36 (d, J = 8.04 Hz, 1 H, H-8) 3.87 (s, 3 H, 3-OCH<sub>3</sub>)<sup>\*</sup> 3.86 (s, 3 H, 4-OCH<sub>3</sub>)<sup>\*</sup> 3.83 (s, 3H, 9-OCH<sub>3</sub>) 3.79 (s, 3H, 9'-OCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 170.62 (C-9) 167.64 (C-9') 149.77 (C-3) 149.58 (C-4) 148.33 (C-4') 144.57 (C-7') 140.53 (C-3') 131.84 (C-1) 129.21 (C-1') 125.59 (C-5') 118.81 (C-6) 117.51 (C-2') 116.03 (C-8') 116.13 (C-6') 111.53 (C-5) 109.36 (C-2) 87.73 (C-7) 56.12 (3-OCH<sub>3</sub>)<sup>\*</sup> 56.07 (4-OCH<sub>3</sub>)<sup>\*</sup> 55.77 (C-8) 52.91 (9-OCH<sub>3</sub>) 51.68 (9'-OCH<sub>3</sub>) (\* may be reversed) [12]; DCI-MS (NH<sub>3</sub>): m/z = 415 (MH<sup>+</sup>) m/z = 432 (MNH<sub>4</sub><sup>+</sup>); *Anal.* Calcd for C<sub>22</sub>H<sub>22</sub>O<sub>8</sub>: C, 63.76; H, 5.35. Found: C, 63.53; H, 5.36

*Methyl 3-[2-(3,4-dimethoxyphenyl)-7-hydroxy-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]propanoate (10)*

It was prepared from a mixture of 80 mg of product (9) and 100 mg of 5% Pd/C in 25 cm<sup>3</sup> of ethyl acetate. This mixture was shaken in a Parr apparatus for 30 minutes with hydrogen at 60 psi. Afterwards the catalyst was filtered off and the solvent was removed under reduced pressure giving a colourless oil in 90% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.92 (d, J = 1.98 Hz, 1 H, H-2) 6.86 (d, J = 8.08 Hz, 1 H, H-5), 6.80 (dd, J = 8.08, 1.98 Hz, 1 H, H-6) 6.68 (s, 1 H, H-2') 6.62 (s, 1 H, H-6') 5.97 (d, J = 7.48 Hz, 1 H, H-7) 4.36 (d, J = 7.48 Hz, 1 H, H-8) 3.87 (s, 3 H, 3-OCH<sub>3</sub>)<sup>\*</sup> 3.85 (s, 3 H, 4-OCH<sub>3</sub>)<sup>\*</sup> 3.83 (s, 3H, 9-OCH<sub>3</sub>) 3.79 (s, 3H, 9'-OCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.31 (C-9) 170.02 (C-9') 149.22 (C-3) 146.21 (C-4) 142.63 (C-3') 140.78 (C-4') 134.74 (C-1') 131.68 (C-1) 128.13 (C-5') 119.59 (C-6') 118.65 (C-2') 117.81 (C-6') 113.11 (C-5) 111.46 (C-2) 87.09 (C-7) 56.11 (3-OCH<sub>3</sub>)<sup>\*</sup> 56.06 (4-OCH<sub>3</sub>)<sup>\*</sup> 55.42 (C-8) 52.88 (9-OCH<sub>3</sub>) 51.67 (9'-OCH<sub>3</sub>) 34.88 (C-8') 31.44 (C-7') (\* may be reversed) [12]; DCI-MS (NH<sub>3</sub>): m/z = 417 (MH<sup>+</sup>) m/z = 434 (MNH<sub>4</sub><sup>+</sup>); *Anal.* Calcd for C<sub>22</sub>H<sub>24</sub>O<sub>8</sub>: C, 63.45; H, 5.81. Found: C, 63.37; H, 5.77

3-[2-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-7-hydroxy-2,3-dihydro-1-benzofuran-5-yl]propan-1-ol  
(1)

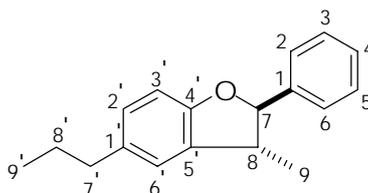
It was slowly prepared by adding a solution of 40 mg of product (10) in 5 cm<sup>3</sup> of anhydrous THF to a stirring suspension of 20 mg of LiAlH<sub>4</sub> in 15 cm<sup>3</sup> of anhydrous diethyl ether. After 2 hours concentrated HCl was added until a clear solution was obtained. This solution was extracted with ethyl acetate and the combined fractions were washed with water. The organic layer was dried on MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (column 30 cm x 3.8 cm, silica gel 60, 0.040-0.063 mm) ethyl acetate as the eluent. After lyophilisation a white foam is obtained in 58% yield. The foam liquified quickly to a colourless oil under normal pressure.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.95 (dd, J = 8.08, 1.98 Hz, 1 H, H-6) 6.92 (d, J = 1.98 Hz, 1 H, H-2) 6.85 (d, J = 8.08 Hz, 1 H, H-5) 6.68 (s, 1 H, H-2') 6.62 (s, 1 H, H-6') 5.55 (d, J = 7.47 Hz, 1 H, H-7) 3.90 (m, 2H, H-9a, H-9b) 3.87 (s, 3 H, 3-OCH<sub>3</sub>)\* 3.85 (s, 3 H, 4-OCH<sub>3</sub>)\* 3.67 (t, J = 6.41 Hz, 1 H, H-9') 3.60 (m, 1 H, H-8) 2.62 (t, J = 7.63 Hz, 1 H, H-7') 1.85 (m, J = 7.63, 6.41 Hz, 1 H, H-8'); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 149.47 (C-3) 149.36 (C-4) 145.06 (C-3') 139.99 (C-4') 135.92 (C-1') 133.54 (C-5') 127.48 (C-1) 118.72 (C-6) 115.92 (C-6') 115.71 (C-2') 111.41 (C-5) 109.46 (C-2) 88.18 (C-7) 63.80 (C-9) 62.31 (C-9') 56.05 (3-OCH<sub>3</sub>, 4-OCH<sub>3</sub>) 54.11 (C-8) 34.48 (C-7') 31.73 (C-8') [12]; DCI-MS (NH<sub>3</sub>): m/z = 343 (MH<sup>+</sup>-H<sub>2</sub>O); Anal. Calcd for C<sub>20</sub>H<sub>24</sub>O<sub>6</sub>: C, 66.65; H, 6.71. Found: C, 66.68; H, 6.67

## References and Notes

1. Pieters, L.; De Bruyne, T.; Van Poel, B.; Vingerhoets, B.; Totté, J.; Vanden Berghe, D.; Vlietinck, A. *Phytomed.* **1995**, *2*, 17-22.
2. Pieters, L.; Van Dyck, S.; Gao, M.; Bai, R.; Hamel, E.; Vlietinck, A.; Lemièrre G., accepted for publication in *J. Med. Chem.*
3. Pieters, L.; De Bruyne, T.; Claeys, M.; Vlietinck, A. *J. Nat. Prod.* **1993**, *56*, 6, 899-906.
4. The relative configurations in schemes 1 and 2 are depicted according to a proposal of Maerhr, H. *J. Chem. Ed.* **1985**, *62*, 114-120.
5. Antus, S.; Bauer, R.; Gottsegen, A.; Seligmann, O.; Wagner, H. *Liebigs Ann. Chem.* **1987**, 357-360.
6. Bolzacchini, E.; Brunow, G.; Meinardi, S.; Orlandi, M.; Rindone, B.; Rumakko, P.; Setela, H. *Tetrahedron Lett.* **1998**, *39*, 3291-3294.
7. For a broad review on these and other protective groups see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*; John Wiley: New York, 1974.
8. Raaijmakers, H.; Zwanenburg B.; Chittenden G. J. F. *J. Carbohydrate Chemistry* **1993**, *12*, 8, 1117-1125.
9. Einhorn, A.; Cobliner, J.; Pfeifer, H. *Ber.* **1904**, *37*, 100-128.

10. The rate of hydrolysis is very dependent to the type of solvent. In acetone or dioxane the hydrolysis is significantly slower needing reaction times of about 18h.
11. Lemière, G.; Gao, M.; De Groot, A.; Dommissse, R.; Lepoivre, J.; Pieters, L.; Buss, V. *J. Chem. Soc. Perkin I* **1995**, 1775-1779.
12. The numbering used for the assignment of  $^1\text{H}$  and  $^{13}\text{C}$ -NMR signals is as shown in the following structure. This numbering is used for easy comparison of the signals of the compounds (1)-(10) with earlier work [11] and is in accordance with a recent IUPAC recommendation [13]



13. Provisional recommendation, IUBMB-IUPAC, Joint Commission on Biochemical Nomenclature (JCBN), Nomenclature of lignans and neolignans, 30 June 1999.

*Samples Availability:* Available from the authors.