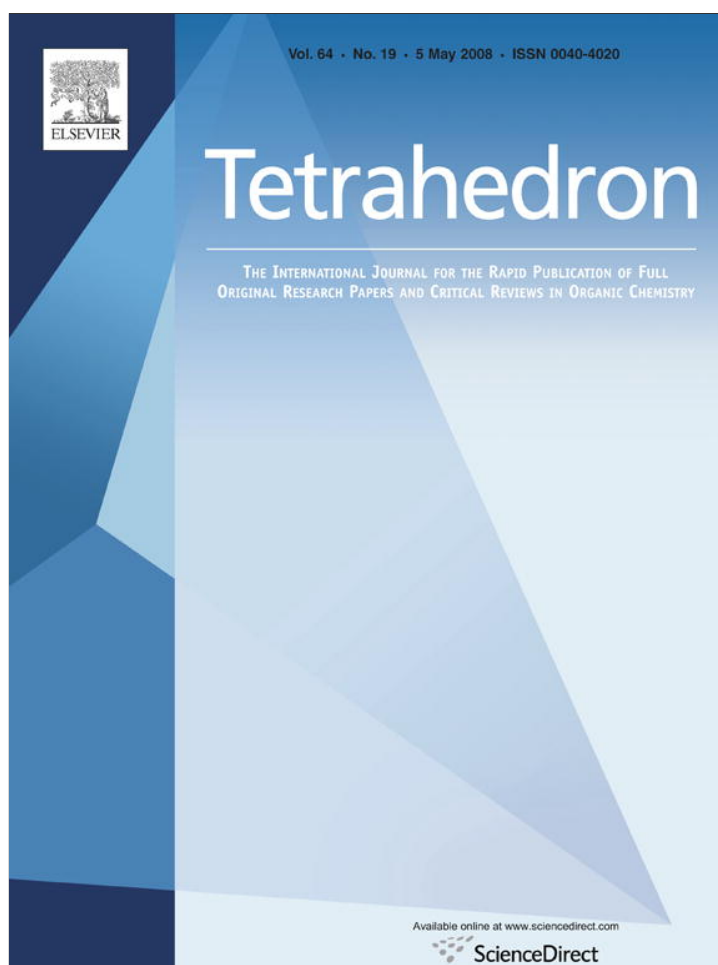


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Total synthesis of naturally occurring 5,6,7- and 5,7,8-trioxygenated coumarins

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Abstract

The synthesis of five naturally occurring polyoxygenated coumarins is described. It concerns two 5,6,7-trioxygenated coumarins, i.e., 6-hydroxy-5,7-dimethoxycoumarin (fraxinol) **1** and 5,6,7-trimethoxycoumarin **2**, and three 5,7,8-trioxygenated coumarins, i.e., 8-hydroxy-5,7-dimethoxycoumarin (leptodactylone) **3**, 5,7,8-trimethoxycoumarin **4** and 8-(3-methyl-2-butenyloxy)-5,7-dimethoxycoumarin (artanin) **5**. Key feature of the synthetic pathway is the synthesis of suitable tetraoxygenated benzaldehydes, which are then converted to the corresponding coumarins via a Wittig reaction.

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Keywords: Coumarins; Natural products; Wittig reaction; Total synthesis

1. Introduction

Coumarins form a vast class of natural products. They occur widely as secondary plant metabolites and are known to exhibit numerous interesting biological activities. More than 1800 different natural coumarins have been discovered and described to date. By far most of these coumarins are mono- or dioxygenated on the aromatic ring.¹ Recently, more attention has been drawn towards the less common tri- and tetraoxygenated coumarins, which have been shown to exert very interesting pharmacological activities. Examples include anti-bacterial,² anti-platelet aggregation³ and anti-leukemia activity.⁴ Several natural 5,6,7-trioxygenated coumarins have the capacity to induce cell differentiation in human leukemia U-937 cells, which make them potential lead compounds in the search for differentiation therapeutics.⁴ These promising findings prompted us to investigate the anti-leukemia activity

of a broader range of natural coumarins. The goal was to investigate naturally occurring coumarins with 5,7,8-trioxygenated or 5,6,7-trioxygenated substitution pattern because of the great potential of oxygenated coumarins in the anti-leukemia research.⁴ Though all of these coumarins occur in plants, a lot of them are not available in sufficient quantity and purity for in vitro evaluation of the anti-leukemia activity. Mostly, these compounds are not available at all, except from the plant sources, requiring long purification procedures. Therefore, a total synthesis for the following coumarins was developed: 6-hydroxy-5,7-dimethoxycoumarin (fraxinol) **1**,^{5–9} 5,6,7-trimethoxycoumarin **2**,^{10,11} 8-hydroxy-5,7-dimethoxycoumarin (leptodactylone) **3**,^{12,13} 5,7,8-trimethoxycoumarin **4**^{13,14} and 8-(3-methyl-2-butenyloxy)-5,7-dimethoxycoumarin (artanin) **5** (Fig. 1).¹⁵ Fraxinol **1** occurs naturally in *Fraxinus ornus*,⁵ *Corchorus olerarius*,⁶ *Seriphidium santolium*,⁷ *Toddalia asiatica*⁸ and *Pelargonium reniforme*,⁹ a plant indigenous to southern Africa. *Pelargonium reniforme* also contains 5,6,7-trimethoxycoumarin **2**.^{10,11} Leptodactylone **3** was found in *Leptodactylon* sp.¹² and *Ruta* sp. *Tene* 29662.¹³ The latter

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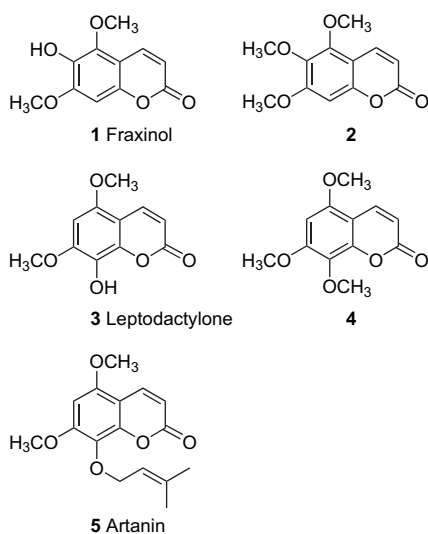
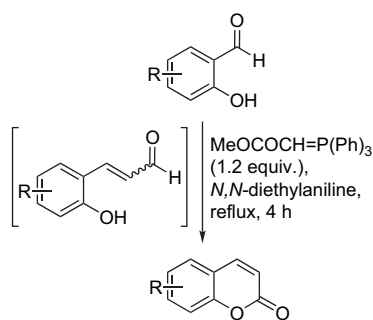


Figure 1.

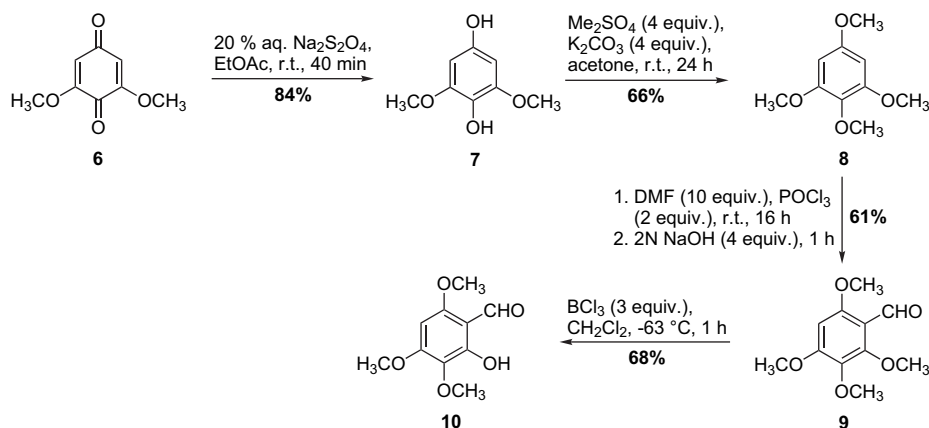
Ruta sp. *Tene* 29662 also contains 5,7,8-trimethoxycoumarin **4**, a coumarin which also has been isolated from *Toddalia aculeata*.¹⁴ Artanin **5**, a coumarin hemiterpene ether, is a natural constituent of *Artemisia* sp.¹⁵ To the best of our knowledge this is the first report on the synthesis of artanin **5**.

2. Results and discussion

In the past, coumarins have mainly been synthesized by Pechmann, Knoevenagel or Perkin reactions. These reactions



Scheme 1.



Scheme 2.

often require strongly acidic or strongly basic reaction conditions and high temperature for longer times, which makes them less suitable for the synthesis of coumarins with complex substitution patterns. Moreover, they mostly lead to coumarins with substituents in the 3- or 4-position.¹⁶ A good alternative for the synthesis of 3,4-unsubstituted coumarins is the Wittig reaction.^{17,18} In general, the synthetic strategy consists of synthesizing the suitable *o*-hydroxybenzaldehydes, which then can be converted to the corresponding coumarins via a Wittig reaction protocol (Scheme 1).

The Wittig reaction of various *o*-hydroxybenzaldehydes with methyl (triphenylphosphoranylidene)acetate was performed at 210–215 °C in *N,N*-diethylaniline, which makes it possible to obtain isomerization of the *E*-cinnamic esters towards the *Z*-isomers, which cyclize towards the corresponding coumarins.^{17,18} This reaction is especially suitable for the synthesis of 3,4-unsubstituted coumarins, which are more difficult to access via traditional reactions like the Pechmann or Knoevenagel reactions, and has been successfully applied for the synthesis of polyoxygenated coumarins.^{19,20}

Syntheses of 5,7,8-trioxygenated coumarins **3–5** were started from commercially available 2,6-dimethoxybenzoquinone **6**. 2,6-Dimethoxybenzoquinone **6** was reduced with sodium dithionite to give the corresponding hydroquinone **7** in 84% yield. Hydroquinone **7** was then converted to 2-hydroxy-3,4,6-trimethoxybenzaldehyde **10** by a literature procedure.²¹ After methylation of hydroquinone **7** with dimethyl sulfate and formylation of the resulting 1,2,3,5-tetramethoxybenzene **8** with dimethylformamide and phosphorus(V) oxychloride, 61% of 2,3,4,6-tetramethoxybenzaldehyde **9** was obtained. Demethylation of 2,3,4,6-tetramethoxybenzaldehyde **9** with 3 equiv of boron(III) chloride in dichloromethane at low temperature cleanly gave 2-hydroxy-3,4,6-trimethoxybenzaldehyde **10** in 68% yield (Scheme 2).

Interestingly, harshening of the reaction conditions by adding 4 equiv of boron(III) chloride and leaving the reaction at room temperature for 20 h gave a single product, which clearly differed from aldehyde **10**. From the ^1H NMR spectrum (CDCl_3) it was clear that it was a dihydroxydimethoxybenzaldehyde. One of the hydroxyl protons resonated at 12.17 ppm, typical for hydroxyl protons, which are hydrogen bonded to

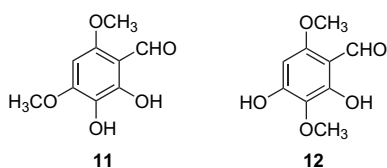


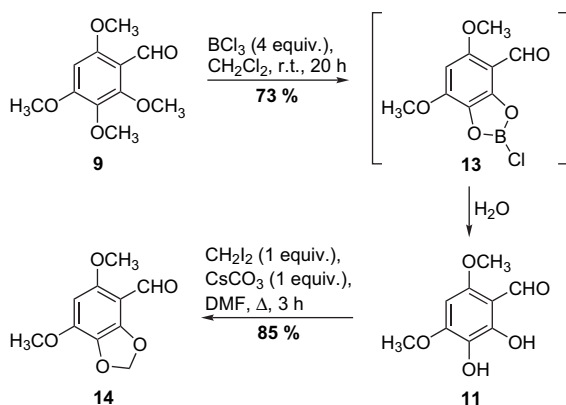
Figure 2.

the adjacent aldehyde. The other hydroxyl proton showed a broad peak at 5.08 ppm, indicating that this hydroxyl group was not in *ortho* position of the aldehyde. Hence this aldehyde had to be 2,3-dihydroxy-4,6-dimethoxybenzaldehyde **11** or 2,4-dihydroxy-3,6-dimethoxybenzaldehyde **12** (Fig. 2).

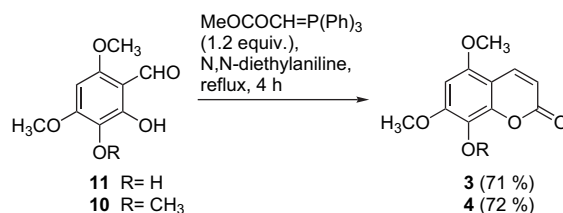
It was presumed that the correct structure had to be 2,3-dihydroxy-4,6-dimethoxybenzaldehyde **11**,²² since the formation of this product can be explained by an intermediate boron complex **13** where the boron is bound to both the oxygen atoms in the 2- and 3-position. In order to confirm this hypothesis, the compound was heated under reflux (3 h) with diiodomethane and caesium(II) carbonate in dimethylformamide. After workup, this reaction gave 85% 2,3-methylene-dioxy-4,6-dimethoxybenzaldehyde **14** and proved that the double demethylated aldehyde had the structure **11** (Scheme 3). Later, it was found that similar findings had been reported for the reaction of 2,3,4,6-tetramethoxybenzaldehyde **9** with aluminium(III) chloride.²² When 2,3,4,6-tetramethoxybenzaldehyde **9** was treated with 1.1 equiv of aluminium(III) chloride in refluxing benzene for 8 h, it was reported that, apart from 2-hydroxy-3,4,6-trimethoxybenzaldehyde **10**, small quantities of a dihydroxylated side product were formed, which proved to be 2,3-dihydroxy-4,6-dimethoxybenzaldehyde **11**.²²

Both 2-hydroxybenzaldehydes **10** and **11** could be converted to the corresponding coumarins using the Wittig reaction as described above. In this way, the naturally occurring trioxygenated coumarins 8-hydroxy-5,7-dimethoxycoumarin (leptodactylone) **3** and 5,7,8-trimethoxycoumarin **4** were obtained in 71 and 72% yield, respectively (Scheme 4).

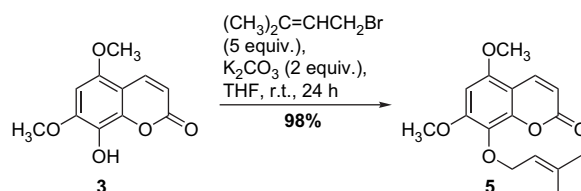
Prenylation of the 8-hydroxy group of leptodactylone **3** with excess prenyl bromide in the presence of potassium carbonate in THF at room temperature gave 8-(3-methyl-2-



Scheme 3.



Scheme 4.



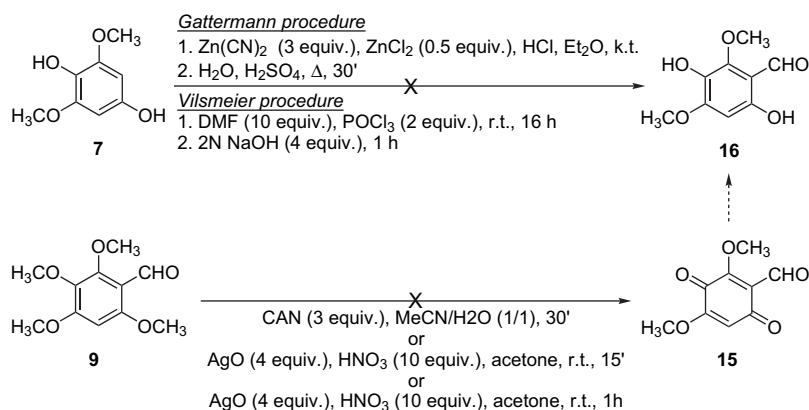
Scheme 5.

butenyloxy)-5,7-dimethoxycoumarin (artanin) **5** in 98% yield (Scheme 5).

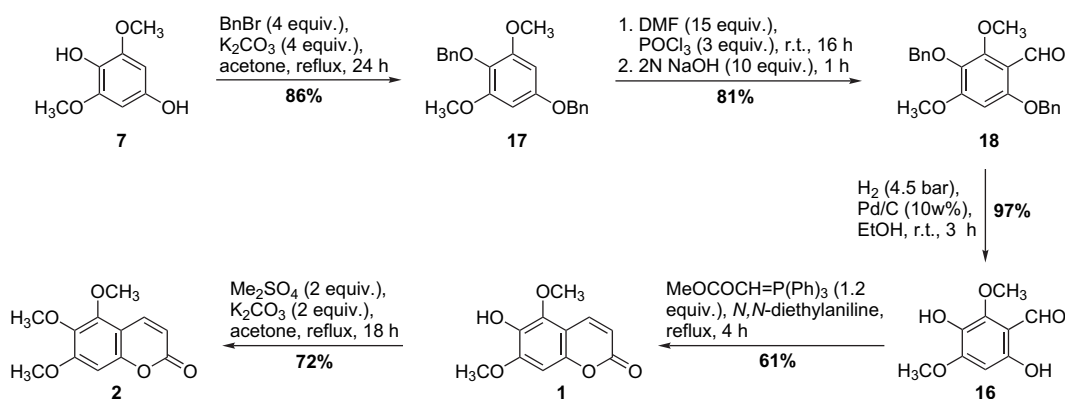
Retrosynthetic analysis indicates that a good precursor for the 5,6,7-trioxygenated coumarins 6-hydroxy-5,7-dimethoxycoumarin (fraxinol) **1** and 5,6,7-trimethoxycoumarin **2** would be 3,6-dihydroxy-2,4-dimethoxybenzaldehyde **16**. However, attempts to directly formylate 2,6-dimethoxybenzene-1,4-diol **7**, either by the Gattermann procedure²⁰ or the Vilsmeier procedure²⁰ failed. In both cases only complex reaction mixtures were obtained, probably due to oxidation of the hydroquinone **7** during the reaction (Scheme 6).

Also oxidative demethylation of 2,3,4,6-tetramethoxybenzaldehyde **9** did not lead to the desired 2,4-dimethoxy-3,6-dioxocyclohexa-1,4-dienecarbaldehyde **15** (Scheme 6). This benzoquinone **15** would lead to 3,6-dihydroxy-2,4-dimethoxybenzaldehyde **16** after reduction.

Since benzoquinone **15** could not be obtained and since direct formylation of the hydroquinone **7** towards 3,6-dihydroxy-2,4-dimethoxybenzaldehyde **16** did not work, the hydroxyl groups had to be protected prior to formylation. Therefore, 2,6-dimethoxybenzene-1,4-diol **7** was first benzylated with benzyl bromide and potassium carbonate in acetone under reflux to give 2,5-dibenzoyloxy-1,3-dimethoxybenzene **17** in 86% yield. Vilsmeier formylation of 2,5-dibenzoyloxy-1,3-dimethoxybenzene **17** has been described in 61% yield by using 1.2 equiv of POCl₃ and 6.5 equiv of DMF.²¹ When this reaction was repeated under these conditions, only low yields of 3,6-dibenzoyloxy-2,4-dimethoxybenzaldehyde **18** were obtained (42%). However, when 3 equiv of POCl₃ and 15 equiv of DMF were used, 3,6-dibenzoyloxy-2,4-dimethoxybenzaldehyde **18** could be obtained in 81% yield. This aldehyde was de-benzylated by hydrogenolysis using hydrogen (4.5 bar) on Pd/C (10 wt %) and afforded 3,6-dihydroxy-2,4-dimethoxybenzaldehyde **15** in 97% yield. After Wittig reaction of 3,6-dihydroxy-2,4-dimethoxybenzaldehyde **15** with methyl (triphenylphosphoranylidene)acetate in *N,N*-diethylaniline under reflux, 6-hydroxy-5,7-dimethoxycoumarin (fraxinol) **1** was obtained in 61% yield. Methylation of 6-hydroxy-5,7-dimethoxycoumarin



Scheme 6.



Scheme 7.

1 with dimethyl sulfate in acetone under reflux in the presence of potassium carbonate gave 5,6,7-trimethoxycoumarin **2** in 72% yield (Scheme 7).

To our knowledge, this is the first total synthesis of artanin **5**. A synthesis of leptodactylone **3** and 5,7,8-trimethoxycoumarin **4** was described in six steps from pyrogallol in overall yields of less than 1%.¹² Coumarin **4** was also synthesized in two steps from 2,4-dihydroxy-3,6-dimethoxybenzaldehyde in 4% yield. The syntheses of leptodactylone **3**, fraxinol **1** and 5,6,7-trimethoxycoumarin **2** have also been reported before in low yields (51–55%) by an unusual reaction, which comprises the transfer of the C3 unit of cinnamic acid onto the corresponding phenols.²³ 5,6,7-Trimethoxycoumarin **2** was also synthesized in 46% yield by a Pd catalyzed coupling reaction between 3,4,5-trimethoxyphenol and ethyl propynoate.²⁴ Our synthesis affords a higher yielding alternative for the synthesis of all of these coumarins from the same commercially available starting compound.

3. Conclusion

A total synthesis of five trioxxygenated coumarins: 6-hydroxy-5,7-dimethoxycoumarin (fraxinol) **1**, 5,6,7-trimethoxycoumarin **2**, 8-hydroxy-5,7-dimethoxycoumarin (leptodactylone) **3**, 5,7,8-trimethoxycoumarin **4** and 8-(3-methyl-2-butenyloxy)-5,7-dimethoxycoumarin (artanin) **5**, starting from commercially available 2,6-dimethoxybenzoquinone **6**, was developed. All these

coumarins occur in nature as secondary plant metabolites and will now be evaluated for their anti-leukemia activity.

4. Experimental section

4.1. General

¹H NMR spectra (300 MHz) and ¹³C NMR spectra (75 MHz) were recorded on a Jeol Eclipse FT 300 NMR spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrophotometer. Mass spectra were recorded on an Agilent 1100 Series VS (ES, 4000 V) mass spectrometer. HRMS analyses were performed using a Finnigan MAT 95 XP-API-GC Trap tandem mass spectrometer system. Elemental analyses were measured with a Perkin–Elmer 2400 Elemental Analyzer. Melting points were measured with a Büchi B-450 apparatus. Flash chromatography was performed with ACROS silica gel (particle size 0.035–0.070 mm, pore diameter ca. 6 nm) using a glass column.

4.2. Synthetic procedures

4.2.1. General procedure for the synthesis of coumarins **1**–**4**

The appropriate *o*-hydroxybenzaldehyde (1 mmol) and methyl (triphenylphosphoranylidene)acetate (401 mg, 1.2 mmol) were

dissolved in of *N,N*-diethylaniline (15 ml) and the resulting mixture was stirred at reflux temperature for 4 h. The solvent was distilled under reduced pressure (1 mmHg, 52 °C) and the resulting brown oil was purified by column chromatography (50% Et₂O/50% hexane).

4.2.1.1. 6-Hydroxy-5,7-dimethoxycoumarin (fraxinol) 1. Mp (°C): 170.5 (lit. 172–174⁷). IR (KBr, cm⁻¹): 3275 (br, OH); 1705 (C=O); 1621. ¹H NMR (300 MHz, CDCl₃): δ 3.97 (s, 3H, OCH₃); 4.02 (s, 3H, OCH₃); 5.53 (s, 1H, OH); 6.27 (d, 1H, 3-CH, *J*=9.7 Hz); 6.63 (s, 1H, CH_{Ar}); 7.95 (d, 1H, 4-CH, *J*=9.7 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 56.6 (OCH₃); 61.5 (OCH₃); 94.8 (CH_{Ar}); 107.5 (C_q); 113.0 (3-CH); 134.7 (C_q); 138.8 (4-CH); 141.9 (C_q); 148.7 (C_q); 151.1 (C_q); 161.4 (C=O). MS (70 eV, ES⁻, *m/z* (%)): 221 (M-H⁺). HRMS calcd for C₁₁H₁₁O₅ (M+H⁺): 223.06010, found: 223.06002.

4.2.1.2. 5,6,7-Trimethoxycoumarin 2. Mp (°C): 72–73 (lit. 74–75¹⁰). IR (KBr, cm⁻¹): 1744 (C=O); 1614. ¹H NMR (300 MHz, CDCl₃): δ 3.86 (s, 3H, OCH₃); 3.93 (s, 3H, OCH₃); 4.02 (s, 3H, OCH₃); 6.24 (d, *J*=9.6 Hz, 1H, 3-CH); 6.62 (s, 1H, CH_{Ar}); 7.94 (d, *J*=9.6 Hz, 1H, 4-CH). ¹³C NMR (75 MHz, CDCl₃): δ 56.3 (OCH₃); 61.2 (OCH₃); 61.8 (OCH₃); 95.5 (CH_{Ar}); 107.2 (C_q); 112.4 (3-CH); 138.1 (C_q); 138.9 (4-CH); 149.3 (C_q); 151.5 (C_q); 157.2 (C_q); 161.2 (C=O). MS (70 eV, ES⁺, *m/z* (%)): 237 (M+H⁺). Anal. Calcd for C₁₂H₁₂O₅: C, 61.01%; H, 5.12%. Found: C, 61.40%; H, 5.22%.

4.2.1.3. 8-Hydroxy-5,7-dimethoxycoumarin (leptodactylone) 3. Mp (°C): 163 (lit. 152–155;¹² 166–167⁸). IR (KBr, cm⁻¹): 3400; 1718 (C=O); 1615. ¹H NMR (300 MHz, CDCl₃): δ 3.90 (s, 3H, OCH₃); 4.00 (s, 3H, OCH₃); 5.40 (br s, 1H, OH); 6.17 (d, *J*=9.6 Hz, 1H, 3-CH); 6.37 (s, 1H, 6-CH_{Ar}); 8.00 (d, *J*=9.6 Hz, 1H, 4-CH). ¹³C NMR (75 MHz, CDCl₃): δ 56.2 (OCH₃); 56.6 (OCH₃); 91.3 (CH_{Ar}); 103.7 (C_q); 111.1 (3-CH); 126.8 (C_q); 139.1 (4-CH); 142.7 (C_q); 149.6 (C_q); 150.0 (C_q); 160.5 (C=O). MS (70 eV, ES⁺, *m/z* (%)): 223 (M+H⁺). HRMS calcd for C₁₁H₁₁O₅ (M+H⁺): 223.06010, found: 223.06001.

4.2.1.4. 5,7,8-Trimethoxycoumarin 4. Mp (°C): 178 (lit. 179–180¹³). IR (KBr, cm⁻¹): 2947; 1718 (C=O); 1610. ¹H NMR (300 MHz, CDCl₃): δ 3.91 (s, 3H, OCH₃); 3.92 (s, 3H, OCH₃); 3.97 (s, 3H, OCH₃); 6.16 (d, *J*=9.6 Hz, 1H, 3-CH); 6.34 (s, 1H, 6-CH_{Ar}); 7.98 (d, *J*=9.6 Hz, 1H, 4-CH). ¹³C NMR (75 MHz, CDCl₃): δ 56.0 (OCH₃); 56.5 (OCH₃); 61.6 (OCH₃); 91.4 (CH_{Ar}); 104.0 (C_q); 111.2 (3-CH); 130.2 (C_q); 138.8 (4-CH); 148.8 (C_q); 152.4 (C_q); 156.2 (C_q); 160.9 (C_q). MS (70 eV, ES⁺, *m/z* (%)): 237 (M+H⁺). Anal. Calcd for C₁₂H₁₂O₅: C, 61.01%; H, 5.12%. Found: C, 61.38%; H, 5.07%.

4.2.2. 8-(3-Methyl-2-butenyloxy)-5,7-dimethoxycoumarin (artanin) 5

8-Hydroxy-5,7-dimethoxy-coumarin **3** (111 mg, 0.5 mmol) was dissolved in THF (2.5 ml). Potassium carbonate (138 mg,

1 mmol) and prenyl bromide (372 mg, 2.5 mmol) were added and the reaction was left at room temperature for 24 h. Diethyl ether was added (5 ml), the reaction mixture was filtered and the organic phase was washed with water (5 ml). After drying over magnesium sulfate, filtration and evaporation of the solvent, 142 mg of 8-(3-methyl-2-butenyloxy)-5,7-dimethoxycoumarin (artanin) **5** was obtained, which appeared as white crystals after crystallization from diethyl ether/hexane.

Mp (°C): 104–107 (lit. 108–111¹⁵). IR (KBr, cm⁻¹): 2925; 1724 (C=O); 1604. ¹H NMR (300 MHz, CDCl₃): δ 1.69 (s, 3H, CH₃); 1.75 (s, 3H, CH₃); 3.91 (s, 3H, OCH₃); 3.95 (s, 3H, OCH₃); 4.56 (d, *J*=7.4 Hz, 2H, =CHCH₂O); 5.59 (t, *J*=7.4 Hz, 1H, =CHCH₂O); 6.15 (d, *J*=9.6 Hz, 1H, 3-CH); 6.33 (s, 1H, 6-CH_{Ar}); 7.96 (d, *J*=9.6 Hz, 1H, 4-CH). ¹³C NMR (75 MHz, CDCl₃): δ 17.99 (CH₃); 25.82 (CH₃); 56.0 (OCH₃); 56.4 (OCH₃); 70.0 (=CHCH₂O); 91.3 (CH_{Ar}); 103.9 (C_q); 111.2 (3-CH); 120.1 (CH=C(CH₃)₂); 128.9 (C_q); 138.7 (4-CH); 139.1 (C_q); 149.1 (C_q); 152.3 (C_q); 156.5 (C_q); 160.9 (C=O). MS (70 eV, ES⁺, *m/z* (%)): 291 (M+H⁺). Anal. Calcd for C₁₆H₁₈O₅: C, 66.19%; H, 6.25%. Found: C, 66.29%; H, 6.39%.

4.2.3. 2,3-Dihydroxy-4,6-dimethoxybenzaldehyde 11

2,3,4,6-Tetramethoxybenzaldehyde **9**²¹ (452 mg, 2 mmol) was dissolved in 2.5 ml of dry dichloromethane and cooled to 0 °C. A 1 N boron(III) chloride solution in dichloromethane (8 ml) was added and the reaction mixture was allowed to warm up to room temperature and was left at room temperature for 20 h. Subsequently, the reaction mixture was poured into 30 ml of water and 20 ml of dichloromethane were added. The resulting mixture was filtered over Celite[®], the organic phase was collected and the aqueous phase was extracted twice with 20 ml of dichloromethane. The combined organic layers were washed with 30 ml of water and dried over magnesium sulfate. After filtration and evaporation of the solvent in vacuo, the residue was crystallized from ethanol and gave 290 mg (73%) of pure 2,3-dihydroxy-4,6-dimethoxybenzaldehyde **11** as yellowish brown crystals.

Mp (°C): 144 (lit. 147.8–148.3²²). IR (KBr, cm⁻¹): 3500 (br); 1655 (C=O); 1619. ¹H NMR (300 MHz, CDCl₃): δ 3.87 (s, 3H, OCH₃); 3.98 (s, 3H, OCH₃); 5.08 (br s, 1H, 3-OH); 6.00 (s, 1H, CH_{Ar}); 10.15 (s, 1H, CHO); 12.17 (s, 1H, 2-OH). ¹³C NMR (75 MHz, CDCl₃): δ 55.9 (OCH₃); 56.3 (OCH₃); 86.6 (CH_{Ar}); 105.9 (C_q); 126.9 (C_q); 150.4 (C_q); 154.1 (C_q); 157.2 (C_q); 192.7 (CHO). MS (70 eV, ES⁺, *m/z* (%)): 199 (M+H⁺). Anal. Calcd for C₉H₁₀O₅: C, 54.55%; H, 5.09%. Found: C, 54.78%; H, 5.01%.

4.2.4. 2,3-Methylenedioxy-4,6-dimethoxybenzaldehyde 14

2,3-Dihydroxy-4,6-dimethoxybenzaldehyde **11** (40 mg, 0.2 mmol) and diiodomethane (54 mg, 0.2 mmol) were dissolved in *N,N*-dimethylformamide (5 ml). Caesium carbonate was added (39 mg, 0.2 mmol) and the reaction was stirred under reflux for 3 h. Subsequently, the solvent was evaporated in vacuo and the resulting crude product was dissolved in dichloromethane (10 ml). The organic phase was extracted with 10 ml 2.5 N aqueous sodium hydroxide and washed twice

with 10 ml of water. After drying over magnesium sulfate, filtration and evaporation of the solvent in vacuo, 36 mg (86%) of pure 2,3-methylenedioxy-4,6-dimethoxybenzaldehyde **14** was obtained as a white powder.

Mp (°C): 167 (lit. 166–167²²). IR (KBr, cm⁻¹): 1672 (C=O); 1639. ¹H NMR (300 MHz, CDCl₃): δ 3.87 (s, 3H, OCH₃); 4.00 (s, 3H, OCH₃); 6.04 (s, 1H, CH_{Ar}); 6.08 (s, 2H, -OCH₂O-) 10.23 (s, 1H, CHO). ¹³C NMR (75 MHz, CDCl₃): δ 56.4 (OCH₃); 57.0 (OCH₃); 90.7 (CH_{Ar}); 102.9 (-OCH₂O-); 105.7 (C_q); 129.8 (C_q); 148.1 (C_q); 149.9 (C_q); 158.1 (C_q); 186.7 (CHO). MS (70 eV, ES⁺, *m/z* (%)): 211 (M+H⁺). Anal. Calcd for C₁₀H₁₀O₅: C, 57.14%; H, 4.80%. Found: C, 56.97%; H, 4.87%.

4.2.5. 3,6-Dihydroxy-2,4-dimethoxybenzaldehyde **16**

3,6-Dibenzoyloxy-2,4-dimethoxybenzaldehyde **18** (378 mg, 1 mmol) was dissolved in 10 ml of absolute ethanol, and 38 mg (10w%) of Pd on carbon (10%) was added to the solution and the mixture was stirred at room temperature under hydrogen atmosphere (4.5 bar) for 3 h. The mixture was filtered and the solvent was evaporated in vacuo, yielding 191 mg (97%) 3,6-dihydroxy-2,4-dimethoxybenzaldehyde **16** as yellow crystals after crystallization from diethyl ether/hexane.

Mp (°C): 126–127. IR (KBr, cm⁻¹): 3422 (br, OH); 1630 (CHO). ¹H NMR (300 MHz, CDCl₃): δ 3.94 (s, 3H, OCH₃); 4.04 (s, 3H, OCH₃); 5.10 (s, 1H, OH); 6.22 (s, 1H, CH_{Ar}); 10.08 (s, 1H, CHO); 11.91 (s, 1H, OH). ¹³C NMR (75 MHz, CDCl₃): δ 56.5 (OCH₃); 61.9 (OCH₃); 94.6 (CH_{Ar}); 108.5 (C_q); 130.5 (C_q); 147.9 (C_q); 156.0 (C_q); 158.3 (C_q); 192.9 (CHO). MS (70 eV, ES⁺, *m/z* (%)): 199 (M+H⁺). Anal. Calcd for C₉H₁₀O₅: C, 54.55%; H, 5.09%. Found: C, 53.93%; H, 5.18%.

4.2.6. 3,6-Dibenzoyloxy-2,4-dimethoxybenzaldehyde **18**

Phosphorus(V) oxychloride (1.840 g, 12 mmol) was added to *N,N*-dimethylformamide (4.380 g, 60 mmol) and the reaction mixture was stirred for 10 min at room temperature. Subsequently, 4 mmol (1.512 g) of 2,5-dibenzoyloxy-1,3-dimethoxybenzene **17**²¹ was added to the reaction mixture and the reaction was left at room temperature for 16 h. The reaction was cooled to 0 °C, 100 ml of a 2.5 N aqueous sodium hydroxide solution was added, and the reaction was left at room temperature for 1 h. The reaction mixture was extracted three times with 100 ml of ethyl acetate and the combined organic layers were washed with 100 ml of 2 M aqueous hydrochloric acid and 2 × 100 ml of water. After drying over magnesium sulfate, filtration and evaporation of the solvent, 1.224 g (81%) of 3,6-dibenzoyloxy-2,4-dimethoxybenzaldehyde **18** was obtained as a yellow oil.

IR (KBr, cm⁻¹): 1682 (C=O); 1594; 1568. ¹H NMR (300 MHz, CDCl₃): δ 3.83 (s, 3H, OCH₃); 3.95 (s, 3H, OCH₃); 4.95 (s, 2H, OCH₂Ar); 5.08 (s, 2H, OCH₂Ar); 6.31

(s, 1H, CH_{Ar}); 7.29–7.48 (m, 10H, CH_{Ar}); 10.40 (s, 1H, CHO). ¹³C NMR (75 MHz, CDCl₃): δ 56.1 (OCH₃); 62.2 (OCH₃); 71.2 (OCH₂Ar); 75.6 (OCH₂Ar); 93.6 (CH_{Ar}); 113.2 (C_q); 127.1 (CH_{Ar}); 128.0 (CH_{Ar}); 128.1 (CH_{Ar}); 128.3 (CH_{Ar}); 128.4 (CH_{Ar}); 128.7 (CH_{Ar}); 135.2 (C_q); 136.1 (C_q); 137.3 (C_q); 156.6 (C_q); 158.3 (C_q); 159.3 (C_q); 187.9 (CHO). MS (70 eV, ES⁺, *m/z* (%)): 379 (M+H⁺). Anal. Calcd for C₂₃H₂₂O₅: C, 73.00%; H, 5.86%. Found: C, 72.82%; H, 6.09%.

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