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Wacker oxidation methodology for the synthesis of the benzo-fused acetal core of marticin

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ABSTRACT

Methodology for the synthesis of the benzo-fused acetal core of marticin is described in this paper. Condensation of readily available 1-(2-allyl-3,6-dimethoxyphenyl)ethanone with diethyl oxalate under Claisen condensation conditions furnished (*Z*)-ethyl 4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobut-2-enoate. Treatment of this with $LiAlH_4$ resulted in the formation of the diol, 1-(2-allyl-3,6-dimethoxyphenyl)-3,4-dihydroxybutan-1-one. Conversion of primary alcohol of the diol into the TBDMS ether followed by further reaction with $LiAlH_4$ and exposure to Wacker oxidation conditions resulted in the formation of (3,6-dimethoxy-9-methyl-10,13-dioxatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-11-yl)methanol, the core of marticin.

1. Introduction

An interesting class of quinone containing compounds possessing a fused cyclic acetal is shown in Fig. 1. Thus far, four examples of these quinones have been isolated from nature, including marticin **1** and isomarticin **2**, napthazirin phytotoxins that are produced by *Fusarium solani* and *Fusarium martii*.[1] Averufin **3** is a decaketide quinone intermediate in the biosynthesis of the mycotoxin aflatoxins B_1 and G_1,[2] while isagarin **4** is a tetracyclic naphthoquinone isolated from the roots of *Pentas longiflora* Oliv. (Rubiaceae).[3] All of these compounds contain either a 6,6-bicyclic fused naphthopyran ring system or a 6,5-bicyclic fused ring system.

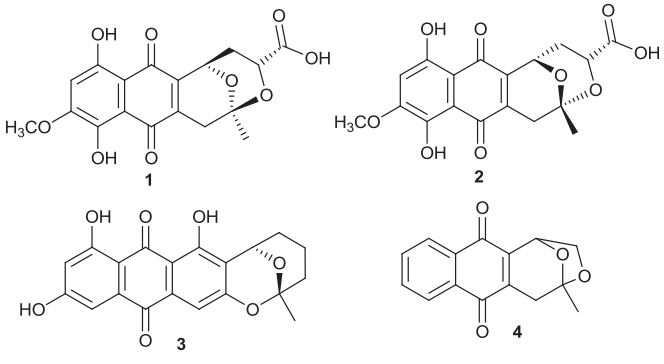

Fig. 1. Acetal-containing quinones.

Marticin and isomarticin are reported to be toxic at low pH to tomatoes and peas[4] causing extensive damage to plant tissue.[2] The marticins also possess some antimicrobial activity and were found to be active against *Staphylococcus aureus* (128 μg/mL) and *Staphylococcus pyogenes* (128 μg/mL). The toxic mechanism of action of the marticins in higher plants still remains to be elucidated, but it is possible that inhibition of malate or citrate dehydration in the citric acid cycle occurs.

Isagarin was first synthesized by De Kimpe et al.[5] in 1999 and more recently by Ploysuk.[6] In the last two years stereoselective syntheses of isagarin have been disclosed by De Kimpe[7] and Fernandes,[8] while the more complex quinone averufin was first synthesized in 1981.[9] However, there are no reported syntheses of the cyclic acetals, marticin or isomarticin.

With our experience in using the Wacker oxidation methodology for the synthesis of isochromanes such as cardinalin 3,[10] we believed that it may be possible to develop this methodology for the synthesis of the marticin and isomarticin skeletons. As such, we planned to synthesize the triol **5** and subject this to Wacker oxidation conditions for our synthesis of acetal **6** (Fig. 2). This would represent the first synthesis of the benzo-fused acetal skeleton of the marticins. Examination of the literature revealed that a similar approach had been adopted for the synthesis of the cyclic acetal **8** from the non-aromatic triol **7**.[11]

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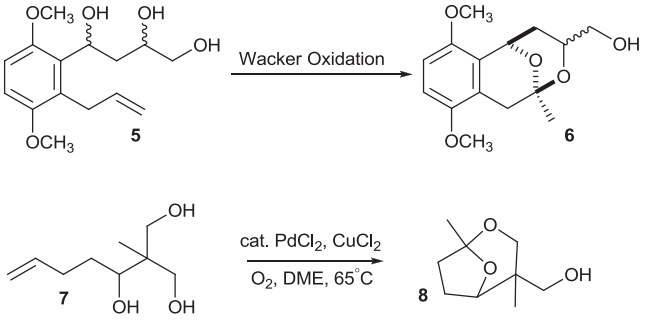
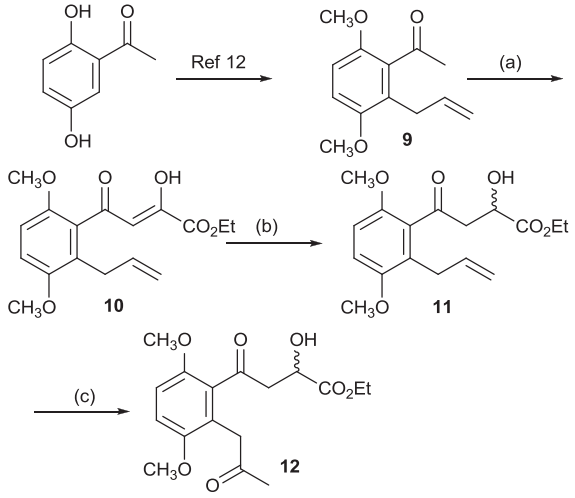


Fig. 2. Wacker oxidations for the formation of acetals.

2. Results and discussion

As a first attempt, ketone **9**, readily synthesized from 2,5-dihydroxyacetophenone in three steps,[12] was condensed with diethyl oxalate under Claisen condensation conditions to afford **10**. Reduction of **10** with $NaBH_4$ resulted in reduction of only one of the ketone functional groups to yield **11**. While this was not our desired triol, we attempted Wacker oxidation of **11** in order to assess the potential of this system to produce a cyclic hemiacetal. However, under these conditions, we were only able to isolate ketone **12** (Scheme 1).

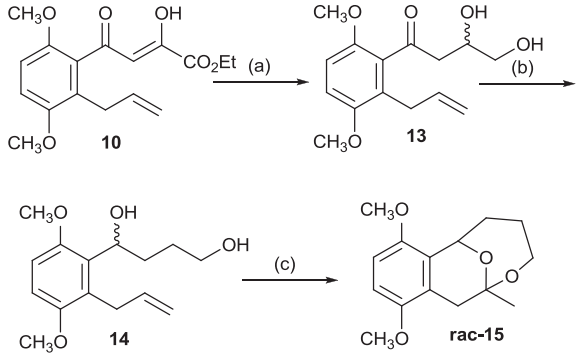


Scheme 1. (a) (i) $(COOEt)_2$, NaOEt, THF, 0 °C→rt, (ii) aq HCl, 90%; (b) $NaBH_4$, THF, 0 °C→rt, 40%; (c) 10% $PdCl_2$, $CuCl_2{\cdot}2H_2O$, DMF, O_2, 67%.

Therefore, compound **10** was treated with $LiAlH_4$ and stirred at rt for 2 h. This resulted in the formation of the diol **13** as shown in Scheme 2. In an attempt to facilitate conversion to the desired triol **5**, the diol **13** was treated with $LiAlH_4$ in THF at reflux for 3 h. Frustratingly, this resulted in the formation of the 1,4-diol **14**.

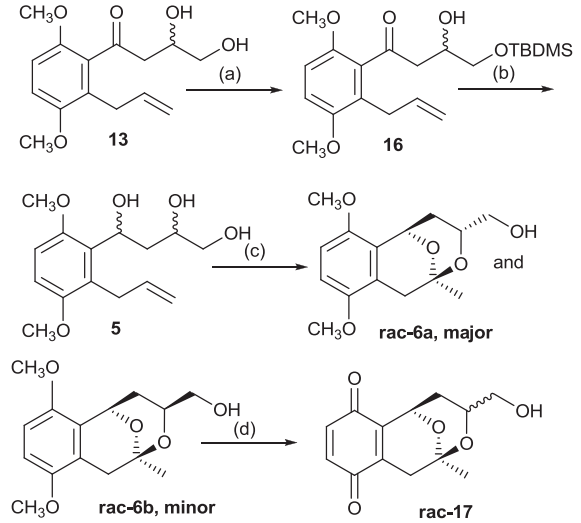
With diol **14** in hand, we once again assessed the potential to construct a cyclic acetal under Wacker oxidation conditions, although for our purposes, the product would contain the wrong size acetal rings. Nevertheless, exposure of **14** to catalytic $PdCl_2$, $CuCl_2$ and oxygen resulted in the formation of the tricyclic compound **15** containing a cyclic acetal. As this was successful, we believed that if the required triol **5** could be formed, even as an intermediate, we would be able to assemble the skeleton of marticin.

We believed that diol **14** was being formed by elimination of water from **13** to form an enol, which would tautomerise to an aldehyde, followed by reduction of both the benzylic ketone and the resulting aldehyde. As such, we decided that protection of the primary alcohol of **13** as the TBS ether may prevent the elimination of water taking place. Fortunately, the primary alcohol of **13** was



Scheme 2. (a) $LiAlH_4$, THF, 10 °C→rt, 34%; (b) $LiAlH_4$, THF, reflux, 62%; (c) 10% $PdCl_2$, $CuCl_2{\cdot}2H_2O$, DMF and H_2O, O_2, 72%.

selectively protected as the TBS ether to afford **16** in reasonable yield (Scheme 3). The resulting product **16** was then treated with $LiAlH_4$ under reflux for 2 h. The presumed intermediate triol **5** (1:1.8 ratio of diastereoisomers by ^1H NMR spectroscopy) was subjected to our normal Wacker oxidation conditions without purification to afford the required tricyclic acetal **6** as a mixture of diastereoisomers (1:2.3 ratio) in 67% yield over the two steps. Clear evidence for the mixture can be found by examining the ^1H NMR spectra. An X-ray crystal structure proved the identity of the desired product (Fig. 3). Oxidation of **6** with CAN yielded the quinone **17** in good yield.



Scheme 3. (a) TBDMSCl, imidazole, MeCN, 64%; (b) $LiAlH_4$, THF, −10 °C→reflux; (c) 10% $PdCl_2$, $CuCl_2{\cdot}2H_2O$, DMF and H_2O, O_2, 67%; (d) CAN, $MeCN/H_2O$, 89%.

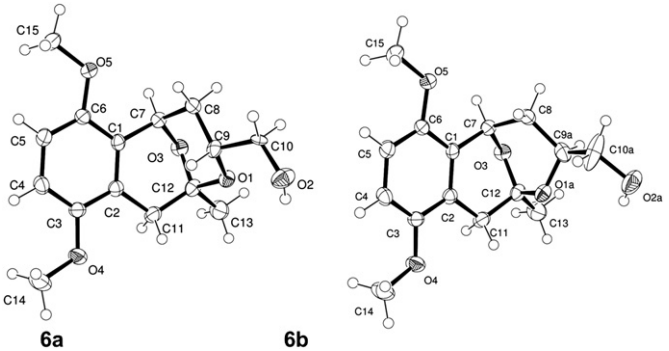


Fig. 3. Separated ORTEP diagrams of the diastereoisomeric mixture of **6a** (major) and **6b** (minor) (50% probability level). Note position of hydrogen on atom labelled C9 of both diastereoisomers.[13]

In summary, for the first time we have been able to develop methodology for the synthesis of the tricyclic core of marticin. Starting from 2,4-dihydroxyacetophenone the tricyclic quinone containing acetal portion of marticin **17** was synthesized in nine steps with an overall yield of 6%. Disappointingly, the apparently trivial reduction of **10** to **13** only proceeded in 34% yield. However, the key Wacker step proceeded to afford compound **6** in a reasonable yield of 67%. The synthesis of marticin using this methodology is currently underway.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AVANCE 300 spectrometer or a Bruker AVANCE III 500 spectrometer. All spectra were recorded in $CDCl_3$, or acetone-d_6. All chemical shift values are reported in parts per million referenced against TMS, which is given an assignment of zero parts per million. Coupling constants (*J*-values) are given in Hertz (Hz). Assignments were made using a range of 2D NMR experiments. However, assignments with the same superscript (*) may be interchanged. All mass spectroscopy data were collected on a Waters Micromass LCT TOF Mass Spectrometer. The sample was dissolved in MeOH to a concentration of 2 ng/μL and introduced by direct infusion. The ionization mode was electrospray positive with a capillary voltage of 2500 V and a desolvation temperature of 250 °C using N_2 gas at 250 L/h. Infrared spectra were recorded on a Bruker Tensor 27 standard system spectrometer. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel column chromatography with various EtOAc and hexane mixtures as the mobile phase. TLC was performed on aluminium-backed Macherey-Nagel Alugram Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60. In vacuo refers to the solvent evaporated under reduced pressure utilizing a rotary evaporator.

3.2. 1-(5-Allyloxy-2-hydroxyphenyl)ethanone

2,5-Dihydroxyacetophenone (8.00 g, 52.6 mmol) was dissolved in Me_2CO (300 mL) in a round-bottom flask (500 mL) equipped with a reflux condenser and a magnetic stirrer bar. Allyl bromide (8.28 g, 68.4 mmol) and anhydrous K_2CO_3 (9.45 g, 68.4 mmol) were added to the solution, which was then heated at reflux for 18 h under a N_2(g) atmosphere. The mixture was then allowed to cool to rt, filtered through a bed of Celite, and the solvent was removed in vacuo. The residue was purified by column chromatography (20% EtOAc/hexane) to afford 1-(5-allyloxy-2-hydroxyphenyl)ethanone (8.69 g, 86%) as a yellow crystalline solid; R_f=0.79 (20% EtOAc/hexane); mp=60–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H=11.84 (1H, s, OH), 7.16 (1H, d, *J* 3.0, H-6′), 7.08 (1H, dd, *J* 9.0, 3.0, H-4′), 6.86 (1H, d, *J* 9.0, H-3′), 6.02 (1H, ddt, *J* 17.2, 10.5, 5.3, OCH_2CH=CH_2), 5.38 (1H, dt, *J* 17.2, 3.6, one of OCH_2CH=CH_2), 5.28 (1H, dd, *J* 10.5, 1.3, one of OCH_2CH=CH_2), 4.47 (2H, dt, *J* 5.3, 1.3, OCH_2CH=CH_2), 2.56 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=204.0 (C=O), 156.8, 150.6, 133.1 (OCH_2CH=CH_2), 124.9 (C-3′), 119.2, 119.1 (C-6′), 117.8 (OCH_2CH=CH_2), 114.9 (C-4′), 69.8 (OCH_2CH=CH_2), 26.6 ($COCH_3$).[12] The spectroscopic data agreed with that reported in the literature.

3.3. 1-(2-Allyl-3,6-dimethoxyphenyl)ethanone 9

1-[5-(Allyloxy)-2-hydroxyphenyl]ethanone (5.82 g, 30.3 mmol) was loaded neat into in a round-bottom flask (50 mL) equipped with a reflux condenser and a magnetic stirrer bar. The reaction vessel was then heated to 140 °C for 18 h under a N_2(g) atmosphere. The dark viscous residue was allowed to cool to rt and was then purified via column chromatography (15% EtOAc/hexane) to yield 1-(2-allyl-3,6-dihydroxyphenyl)ethanone as a yellow oil (4.26 g, 73%); ^{1}H NMR (300 MHz, acetone) δ_H=8.39 (1H, br s, OH), 7.93 (1H, br s, OH), 6.79 (1H, d, *J* 8.7, H-4′*), 6.66 (1H, d, *J* 8.7, H-5′*), 5.92 (1H, ddt, *J* 16.5, 10.2, 6.3, $ArCH_2CH$=CH_2), 5.00–4.88 (2H, m, $ArCH_2CH$=CH_2), 3.36 (2H, d, *J* 6.3, $ArCH_2CH$=CH_2), 2.48 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, acetone) δ_C=205.4 (C=O), 149.0, 148.2, 137.8 ($ArCH_2CH$=CH_2), 131.3, 124.3, 117.8 (C-5′), 115.3 (C-4′), 115.3 ($ArCH_2CH$=CH_2), 32.6 ($COCH_3$), 31.4 ($ArCH_2CH$=CH_2). The intermediate, 1-(2-allyl-3,6-dihydroxyphenyl)ethanone (3.68 g, 19.1 mmol), anhydrous K_2CO_3 (7.94 g, 57.4 mmol) and Me_2SO_4 (9.66 g, 75.6 mmol) were dissolved in Me_2CO (200 mL). The solution was then heated at reflux for 24 h under a N_2(g) atmosphere. The mixture was then allowed to cool to rt, filtered through a bed of Celite, and the solvent was removed in vacuo. The residue was then dissolved in EtOAc (100 mL) and was successively washed with aqueous NH_3 (25%, 3×50 mL), HCl (0.5 M, 2×50 mL) and H_2O (100 mL). The EtOAc layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (10% EtOAc/hexane) of the residue afforded 1-(2-allyl-3,6-dimethoxyphenyl)ethanone **9** as a yellow oil (3.20 g, 76%); R_f=0.24 (30% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H=6.77 (1H, d, *J* 9.0, H-4′*), 6.69 (1H, d, *J* 9.0, H-5′*), 5.86 (1H, ddt, *J* 18.0, 9.3, 6.2, $ArCH_2CH$=CH_2), 4.96–4.86 (2H, m, $ArCH_2CH$=CH_2), 3.72 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.28 (2H, br d, *J* 6.3, $ArCH_2CH$=CH_2), 2.42 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=205.1 (C=O), 151.8, 149.8, 136.5 ($ArCH_2CH$=CH_2), 132.8, 125.5, 115.1 ($ArCH_2CH$=CH_2), 111.6 (C-4′), 109.4 (C-5′), 55.9 (2×OCH_3), 32.3 ($COCH_3$), 30.7 ($ArCH_2CH$=CH_2).[14] The spectroscopic data agreed with that reported in the literature.

3.4. Ethyl-(*Z*)-4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobut-2-enoate 10

To a stirred solution of 1-(2-allyl-3,6-dihydroxyphenyl)ethanone **9** (3.00 g, 13.6 mmol) and diethyl oxalate (3.98 g, 27.2 mmol) in dry THF (50 mL) at 0 °C, NaOEt (1.85 g, 27.2 mmol) was slowly added. The reaction mixture was then stirred vigorously for 3 h at rt before being acidified with aqueous HCl (100 mL, 2.0 M). EtOAc (100 mL) was then added to the mixture. The organic layer was then separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (10% EtOAc/hexane) of the residue afforded ethyl-(*Z*)-4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobut-2-enoate **10** as a yellow solid (3.92 g, 90%); R_f=0.55 (20% EtOAc/hexane); mp=65–66 °C; IR ν_{max} (cm^{-1})=3007 (OH), 1738 (C=O), 1730 (C=O), 1625 (C=C), 1597 (C=C), 1228, 1216; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H=14.30 (1H, br s, OH), 6.89 (1H, d, *J* 9.0, H-4′*), 6.77 (1H, d, *J* 9.0, H-5′*), 6.57 (1H, s, $COCH$=C(OH)CO_2Et), 5.87 (1H, ddt, *J* 16.6, 10.3, 6.2, $ArCH_2CH$=CH_2), 4.97–4.84 (2H, m, $ArCH_2CH$=CH_2), 4.34 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.78 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.35 (2H, d, *J* 6.2, $ArCH_2CH$=CH_2), 1.35 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=197.6 (C=O), 164.5 (COCH=*C*(OH)CO_2Et), 162.3 (*CO*CH=C(OH)CO_2Et), 151.8, 150.5, 136.1 ($ArCH_2CH$=CH_2), 128.8, 127.5, 115.3 ($ArCH_2CH$=CH_2), 113.15 (C-4′), 109.7 (C-5′), 105.9 (*CO*CH=C(OH)CO_2Et), 62.8 ($CO_2CH_2CH_3$), 56.2 (2×OCH_3), 30.9 ($ArCH_2CH$=CH_2), 13.9 ($CO_2CH_2CH_3$); HR-TOF-MS: *m*/*z* found 321.1338 $[M+H]^+$ (calculated for $C_{17}H_{21}O_6$, 321.1342).

3.5. Ethyl 4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobutanoate 11

Ethyl-(*Z*)-4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobut-2-enoate **10** (3.00 g, 9.37 mmol) was dissolved in dry THF (50 mL) and cooled to 0 °C in an ice bath. Sodium borohydride (0.711 g, 18.7 mmol) was added to the stirred reaction solution over 15 min. The reaction mixture was then stirred vigorously for 2 h at rt, before

being acidified with a dilute aqueous solution of HCl (100 mL, 0.5 M). Once the fizzing stopped, the mixture was extracted with EtOAc (100 mL). The organic layer was then separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (20% EtOAc/hexane) of the residue afforded ethyl 4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobutanoate **11** as a yellow oil (1.20 g, 40%); R_f=0.15 (30% EtOAc/hexane); IR ν_{max} (cm^{-1})=3015 (OH), 1738 (C=O), 1588 (C=C), 1228, 1216; ^1H NMR (300 MHz, $CDCl_3$) δ_H=6.82 (1H, d, *J* 9.0, H-4′)*, 6.72 (1H, d, *J* 9.0, H-5′)*, 5.97–5.81 (1H, m, $ArCH_2CH{=}CH_2$), 5.01–4.90 (2H, m, $ArCH_2CH{=}CH_2$), 4.56 (1H, br s, $COCH_2CH(OH)CO_2Et$), 4.25 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.76 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.34 (1H, dd, *J* 18.3, 3.7, one of $COCH_2CH(OH)CO_2Et$), 3.32 (1H, br s, OH), 3.26 (2H, d, *J* 6.3, $ArCH_2CH{=}CH_2$), 3.23 (1H, dd, *J* 18.3, 6.3, one of $COCH_2CH(OH)CO_2Et$), 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=204.4 (C=O), 173.8 (CO_2Et), 151.9, 149.9, 136.4 ($ArCH_2CH{=}CH_2$), 131.1, 126.4, 115.3 ($ArCH_2CH{=}CH_2$), 112.2 (C-4′)*, 109.4 (C-5′)*, 66.9 ($COCH_2CH(OH)CO_2Et$), 61.6 ($CO_2CH_2CH_3$), 56.1 (2×OCH_3), 48.3 ($COCH_2CH(OH)CO_2Et$), 30.9 ($ArCH_2CH{=}CH_2$), 14.1 ($CO_2CH_2CH_3$); HR-TOF-MS: *m*/*z* found 323.1495, $[M+H]^+$ (calculated for $C_{17}H_{23}O_6$, 323.1484).

3.6. Ethyl 4-[3,6-dimethoxy-2-(2-oxopropyl)phenyl]-2-hydroxy-4-oxobutanoate 12

Ethyl 4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobutanoate **11** (1.10 g, 3.41 mmol) was dissolved in a DMF/H_2O mixture (1:1 v/v, 20 mL). $PdCl_2$ (0.0605 g, 0.341 mmol) and $CuCl_2\cdot 2H_2O$ (0.582 g, 3.41 mmol) were added to the solution. Oxygen gas was bubbled through the solution, which was stirred vigorously for 2 h at 70 °C. The reaction mixture was filtered, and EtOAc (30 mL) was added. The organic layer was washed with H_2O (3×30 mL), separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (30% EtOAc/hexane) of the residue afforded ethyl 4-[3,6-dimethoxy-2-(2-oxopropyl)phenyl]-2-hydroxy-4-oxobutanoate **12** as a yellow liquid (0.773 g, 67%); R_f=0.15 (40% EtOAc/hexane); IR ν_{max} (cm^{-1})=3015 (OH), 1738 (C=O), 1257, 1216; ^1H NMR (300 MHz, $CDCl_3$) δ_H=6.86 (1H, d, *J* 9.0, H-4′)*, 6.79 (1H, d, *J* 9.0, H-5′)*, 4.54 (1H, ddd, *J* 6.8, 5.6, 3.6, $COCH_2CH(OH)CO_2Et$), 4.24 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.77 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.68 (2H, s, $ArCH_2COCH_3$), 3.39 (1H, dd, *J* 17.6, 3.6, one of $COCH_2CH(OH)CO_2Et$), 3.25 (1H, d, *J* 5.6, OH), 3.23 (1H, dd, *J* 17.6, 6.8, one of $COCH_2CH(OH)CO_2Et$), 2.16 (3H, s, $ArCH_2COCH_3$), 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=206.3 ($ArCH_2COCH_3$), 204.3 ($COCH_2CH(OH)CO_2Et$), 173.6 ($COCH_2CH(OH)CO_2Et$), 151.9, 150.4, 122.6, 112.5, 110.3 (C-4′)*, 77.1 (C-5′)*, 67.4 ($COCH_2CH(OH)CO_2Et$), 61.7 ($CO_2CH_2CH_3$), 56.1 (2×OCH_3), 48.0 ($COCH_2CH(OH)CO_2Et$), 41.1 ($ArCH_2COCH_3$), 29.6 ($ArCH_2COCH_3$), 14.1 ($CO_2CH_2CH_3$); HR-TOF-MS: *m*/*z* found 339.1444, $[M+H]^+$ (calculated for $C_{17}H_{23}O_7$, 339.1437).

3.7. 1-(2-Allyl-3,6-dimethoxyphenyl)-3,4-dihydroxybutan-1-one 13

Ethyl-(*Z*)-4-(2-allyl-3,6-dimethoxyphenyl)-2-hydroxy-4-oxobut-2-enoate **10** (1.00 g, 3.12 mmol) was dissolved in dry THF (20 mL). The solution was cooled to −10 °C in a Me_2CO/ice bath and lithium aluminium hydride (0.237 g, 6.24 mmol) was added slowly over 5 min. The reaction mixture was then stirred vigorously for 2 h at rt under a N_2(g) atmosphere. The solution was then cooled to 0 °C in an ice bath and cold H_2O (10 mL) was added drop-wise until the fizzing stopped. EtOAc (20 mL) was added and the solution was washed with aqueous HCl (2 M, 20 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (40% EtOAc/hexane) of the residue afforded 1-(2-allyl-3,6-dimethoxyphenyl)-3,4-dihydroxybutan-1-one **13** as a yellow liquid (0.30 g, 34%); R_f=0.26 (50% EtOAc/hexane); IR ν_{max} (cm^{-1})=3015 (OH), 1738 (C=O), 1595 (C=C), 1255, 1228; ^1H NMR (300 MHz, $CDCl_3$) δ_H=6.78 (1H, d, *J* 9.0, H-4′)*, 6.69 (1H, d, *J* 9.0, H-5′)*, 5.92–5.76 (1H, m, $ArCH_2CH{=}CH_2$), 4.95–4.85 (2H, m, $ArCH_2CH{=}CH_2$), 4.31–4.21 (1H, m, $COCH_2CH(OH)CH_2OH$), 3.72 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.63 (1H, dd, *J* 11.7, 2.8, one of $COCH_2CH(OH)CH_2OH$ and OH), 3.48 (1H, dd, *J* 11.3, 6.6, one of $COCH_2CH(OH)CH_2OH$), 3.25 (2H, d, *J* 5.0, $ArCH_2CH{=}CH_2$), 2.92 (2H, d, *J* 6.1, $COCH_2CH(OH)CH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=207.3 (C=O), 151.8, 149.7, 136.4 ($ArCH_2CH{=}CH_2$), 131.6, 126.3, 115.3 ($ArCH_2CH{=}CH_2$), 112.1 (C-4′)*, 109.5 (C-5′)*, 68.6 ($COCH_2CH(OH)CH_2OH$), 65.8 ($COCH_2CH(OH)CH_2OH$), 55.8 (2×OCH_3), 47.7 ($COCH_2CH(OH)CH_2OH$), 30.1 ($ArCH_2CH{=}CH_2$); HR-TOF-MS: *m*/*z* found 281.1389, $[M+H]^+$ (calculated for $C_{15}H_{21}O_5$, 281.1382).

3.8. 1-(2-Allyl-3,6-dimethoxyphenyl)butane-1,4-diol 14

1-(2-Allyl-3,6-dimethoxyphenyl)-3,4-dihydroxybutan-1-one **13** (2.20 g, 7.85 mmol) was dissolved in dry THF (50 mL). The solution was cooled to −10 °C in a Me_2CO/ice bath and lithium aluminium hydride (0.447 g, 11.8 mmol) was added slowly over 5 min. The reaction mixture was then heated for 3 h at reflux under a N_2(g) atmosphere. The solution was then cooled to 0 °C in an ice bath and cold H_2O (10 mL) was added drop-wise until the fizzing stopped. EtOAc (50 mL) was added and the solution was washed with aqueous HCl (2 M, 50 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (40% EtOAc/hexane) of the residue afforded 1-(2-allyl-3,6-dimethoxyphenyl)butane-1,4-diol **14** as a colourless liquid (1.30 g, 62%); R_f=0.25 (50% EtOAc/hexane); IR ν_{max} (cm^{-1})=3373 (OH), 1596 (C=C), 1228, 1217, 1051; ^1H NMR (300 MHz, $CDCl_3$) δ_H=6.74 (1H, d, *J* 9.0, H-4′)*, 6.70 (1H, d, *J* 9.0, H-5′)*, 5.88 (1H, ddt, *J* 16.3, 10.2, 5.8, $ArCH_2CH{=}CH_2$), 5.02–4.87 (2H, m, $ArCH_2CH{=}CH_2$), 4.83 (1H, dd, *J* 9.6, 3.2, $CH(OH)CH_2CH_2CH_2OH$), 3.80 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.68–3.58 (2H, m, $CH(OH)CH_2CH_2CH_2OH$), 3.54–3.32 (2H, m, $ArCH_2CH{=}CH_2$), 2.09–1.55 (4H, m, $CH(OH)CH_2CH_2CH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.8, 151.7, 136.5 ($ArCH_2CH{=}CH_2$), 131.6, 126.4, 114.9 ($ArCH_2CH{=}CH_2$), 109.6 (C-4′)*, 109.5 (C-5′)*, 71.3 ($CH(OH)CH_2CH_2CH_2OH$), 62.7 ($CH(OH)CH_2CH_2CH_2OH$), 55.8 (2×OCH_3), 34.4 ($CH(OH)CH_2CH_2CH_2OH$), 30.2 ($CH(OH)CH_2CH_2CH_2OH$), 29.9 ($ArCH_2CH{=}CH_2$); HR-TOF-MS: *m*/*z* found 249.1488, $[M-OH]^+$ (calculated for $C_{15}H_{21}O_3$, 249.1491).

3.9. 3,6-Dimethoxy-9-methyl-10,13-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene 15

1-(2-Allyl-3,6-dimethoxyphenyl)butane-1,4-diol **14** (1.20 g, 4.51 mmol) was dissolved in a DMF/H_2O mixture (1:1 v/v, 50 mL). $PdCl_2$ (0.0800 g, 0.451 mmol) and $CuCl_2\cdot 2H_2O$ (0.768 g, 4.51 mmol) were added to the solution. Oxygen gas was bubbled through the solution, which was stirred vigorously for 2 h at 70 °C. The reaction mixture was filtered, and EtOAc (20 mL) was added. The organic layer was washed with H_2O (3×20 mL), separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (30% EtOAc/hexane) of the residue afforded **15** as a colourless liquid (0.858 g, 72%); R_f=0.54 (40% EtOAc/hexane); IR ν_{max} (cm^{-1})=1254, 1228, 1065; ^1H NMR (300 MHz, $CDCl_3$) δ_H=6.67 (1H, d, *J* 9.0, H-4)*, 6.63 (1H, d, *J* 9.0, H-5)*, 5.17 (1H, br d, *J* 4.8, H-1), 3.80 (1H, dd, *J* 11.8, 1.5, H-11a), 3.76 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.56 (1H, ddd, *J* 11.8, 3.3, 2.0, H-11b), 3.05 (1H, d, *J* 16.8, H-8a), 2.65–2.54 (1H, m, H-13a), 2.50 (1H, d, *J* 16.8, H-8b), 1.90–1.76 (1H, m, H-13b), 1.64–1.54 (1H, m, H-12a), 1.49 (3H, s, CH_3), 1.47–1.32 (1H, m, H-12b); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=151.1, 149.4, 125.1 (C-2), 123.0 (C-7), 107.8 (C-5)*, 107.4 (C-4)*, 97.4 (C-9), 72.2 (C-1), 61.8 (C-11), 55.4 (2×OCH_3), 33.6 (C-8), 32.3 (C-13), 27.6 (C-12), 25.0 (CH_3); HR-TOF-MS: *m*/*z* found 265.1440, $[M+H]^+$ (calculated for $C_{15}H_{21}O_4$, 265.1429).

3.10. 1-(2-Allyl-3,6-dimethoxyphenyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxybutan-1-one 16

1-(2-Allyl-3,6-dimethoxyphenyl)-3,4-dihydroxybutan-1-one **13** (2.44 g, 8.74 mmol) was dissolved in dry CH_3CN (35 mL) at 0 °C under a N_2(g) atmosphere. Imidazole (0.595 g, 8.74 mmol) and *tert*-butyldimethylsilyl chloride (1.32 g, 8.74 mmol) were added in three portions to the reaction mixture, every 15 min for a 45 min period. Once addition of the reactants was complete, the mixture was stirred for 1 h at rt. The solution was then filtered and the solvent was removed in vacuo. The residue was then dissolved in EtOAc (50 mL), and was sequentially washed with aqueous $NaHCO_3$ (50 mL) followed by aqueous NaCl (50 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (10% EtOAc/hexane) of the residue afforded 1-(2-allyl-3,6-dimethoxyphenyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxybutan-1-one **16** as a colourless liquid (2.20 g, 64%); R_f=0.37 (20% EtOAc/hexane); IR ν_{max} (cm^{-1})=3015 (OH), 1738 (C=O), 1255, 1228; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H=6.83 (1H, d, *J* 9.0, H-4′)*, 6.74 (1H, d, *J* 9.0, H-5′)*, 5.90 (1H, ddt, *J* 16.6, 10.4, 6.2, $ArCH_2CH$=CH_2), 5.01–4.90 (2H, m, $ArCH_2CH$=CH_2), 4.31–4.19 (1H, m, $COCH_2CH(OH)CH_2OTBS$), 3.78 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.69–3.56 (2H, m, $COCH_2CH(OH)CH_2OTBS$), 3.30 (2H, dd, *J* 6.2, 1.4, $ArCH_2CH$=CH_2), 3.04 (1H, dd, *J* 17.9, 4.4, one of $COCH_2$-$CH(OH)CH_2OTBS$), 2.98 (1H, d, *J* 3.6, OH), 2.91 (1H, dd, *J* 17.9, 7.8, one of $COCH_2CH(OH)CH_2OTBS$), 0.89 (9H, s, 3×CH_3), 0.07 (6H, s, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=207.0 (C=O), 151.9, 149.8, 136.4, 131.5, 126.1 ($ArCH_2CH$=CH_2), 115.3 ($ArCH_2CH$=CH_2), 111.9 (C-4′)*, 109.4 (C-5′)*, 68.3 ($COCH_2CH(OH)CH_2OTBS$), 66.4 ($COCH_2CH(OH)CH_2OTBS$), 56.1 (2×OCH_3), 48.1 ($COCH_2CH(OH)CH_2OTBS$), 30.9 ($ArCH_2CH$=CH_2), 25.9 ($OSi(CH_3)_2C(CH_3)_3$), 18.3 ($OSi(CH_3)_2C(CH_3)_3$), −5.4 ($OSi(CH_3)_2C(CH_3)$); HR-TOF-MS: *m*/*z* found 395.2254, $[M+H]^+$ (calculated for $C_{21}H_{35}O_5Si$, 395.2245).

3.11. (3,6-Dimethoxy-9-methyl-10,13-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-yl)methanol 6

1-(2-Allyl-3,6-dimethoxyphenyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxybutan-1-one **16** (2.10 g, 5.34 mmol) was dissolved in dry THF (80 mL). The solution was cooled to −10 °C in a Me_2CO/ice bath and lithium aluminium hydride (0.303 g, 8.00 mmol) was added slowly over 5 min. The reaction mixture was then heated for 2 h at reflux under a N_2(g) atmosphere. The solution was then cooled to 0 °C in an ice bath and cold water was added drop-wise until the fizzing stopped. EtOAc (60 mL) was added and the solution was washed with aqueous HCl (2 M, 60 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford an impure crystalline compound (0.700 g) of 4-(2-allyl-3,6-dimethoxyphenyl)butane-1,2,4-triol **5** in a ratio of 1.8:1 as determined by ^{1}H NMR spectroscopy. A ^{1}H NMR spectrum of the crude mixture confirmed that no starting material was present as signals for the silicon-protecting group were absent. The impure crystalline compound could not be isolated in sizable quantities after purification by silica gel column chromatography, and was treated as an intermediate. However, on one occasion, trace amounts (13 mg) of a single diastereoisomer of **5** were isolated from a silica gel column (70% EtOAc/hexane) after conducting the reaction on a 2 g scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H=6.78 (2H, s, 4-H and 5-H), 5.96–5.85 (1H, m, $ArCH_2CH$=CH_2), 5.16 (1H, dd, *J* 10.5, 2.8, $ArCH(OH)CH_2CH(OH)CH_2OH$), 5.01 (1H, dd, *J* 10.1, 1.6, one of $ArCH_2CH$=CH_2), 4.94 (1H, dd, *J* 17.1, 1.7, one of $ArCH_2CH$=CH_2), 4.06–3.97 (1H, m, $ArCH(OH)CH_2CH(OH)CH_2OH$), 3.87 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.63 (1H, dd, *J* 11.2, 3.5, one of $ArCH(OH)CH_2CH(OH)CH_2OH$), 3.55–3.45 (3H, m, one of $ArCH(OH)CH_2CH(OH)CH_2OH$ and $ArCH_2CH$=CH_2), 2.30–2.16 (1H, m, one of $ArCH(OH)CH_2CH(OH)CH_2OH$), 1.69 (1H, dt, *J* 14.6, 2.8, one of $ArCH(OH)CH_2CH(OH)CH_2OH$).

A portion of the impure crystalline material, **5** as a mixture of diastereoisomers (0.423 g, 2.48 mmol) was dissolved in a mixture of DMF/H_2O mixture (1:1 v/v, 40 mL). $PdCl_2$ (0.0439 g, 0.248 mmol) and $CuCl_2\cdot 2H_2O$ (0.423 g, 2.48 mmol) were added to the solution. Oxygen gas was bubbled through the solution, which was stirred vigorously for 2 h at 70 °C. The reaction mixture was filtered, and EtOAc (50 mL) was added. The organic layer was washed with H_2O (3×30 mL), separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (50% EtOAc/hexane) of the residue afforded of mixture of diastereoisomers of **6** as a white solid (0.601 g, 67% from **16**) in a ratio of 2.3:1 as determined by ^{1}H NMR spectroscopy; R_f=0.58 (50% EtOAc); mp=142–143 °C; IR ν_{max} (cm^{-1})=1229, 1215, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) major diastereomer δ_H=6.67 (1H, d, *J* 8.8, H-4)*, 6.64 (1H, d, *J* 8.8, H-5)*, 5.40 (1H, br d, *J* 3.9, H-1), 3.91–3.83 (1H, m, H-11), 3.79 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.48 (2H, br s, CH_2OH), 2.98 (1H, d, *J* 18.8, H-8a), 2.85 (1H, d, *J* 18.8, H-8b), 2.20 (1H, br t, *J* 5.8, OH), 2.09–2.02 (1H, m, H-12a), 1.53 (3H, s, CH_3), 1.40 (1H, dt, *J* 12.9, 2.0, H-12b); minor diastereomer δ_H=6.67 (1H, d, *J* 8.8, H-4)*, 6.63 (1H, d, *J* 8.8, H-5)*, 5.25 (1H, br d, *J* 9.1, H-1), 4.09–4.03 (1H, m, H-11), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.60–3.54 (1H, m, one of CH_2OH), 3.41–3.35 (1H, m, one of CH_2OH), 2.83 (1H, d, *J* 17.3, H-8a), 2.59 (1H, d, *J* 17.3, H-8b), 2.30 (1H, ddd, *J* 13.0, 10.1, 5.3, H-12a), 2.08 (1H, br s, OH), 1.57 (1H, ddd, *J* 13.0, 11.1, 1.55, H-12b), 1.52 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) major diastereomer δ_C=149.9, 148.7, 126.0 (C-7), 124.1 (C-2), 107.8 (C-5)*, 107.3 (C-4)*, 96.0 (C-9), 68.3 (C-11), 65.9 (CH_2OH), 65.7 (C-1), 55.9 (OCH_3), 55.3 (OCH_3), 32.8 (C-8), 30.4 (C-12), 29.5 (CH_3); minor diastereomer δ_C=151.2, 148.6, 128.9 (C-2), 121.5 (C-7), 107.9 (C-5), 107.0 (C-4), 97.4 (C-9), 66.7 (C-11), 65.0 (C-1), 64.9 (CH_2OH), 55.5 (OCH_3), 55.4 (OCH_3), 33.2 (C-8), 32.8 (C-12), 24.6 (CH_3); HR-TOF-MS: *m*/*z* found 281.1389, $[M+H]^+$ (calculated for $C_{15}H_{21}O_5$, 281.1382).

3.12. 11-(Hydroxymethyl)-9-methyl-10,13-dioxatricyclo[7.3.1.0^{2,7}]trideca-2(7),4-diene-3,6-dione 17

Compound **6** (0.400 g, 1.44 mmol) was dissolved in a mixture of CH_3CN and H_2O (40 mL, 50:50 v/v ratio). CAN (2.36 g, 4.31 mmol) was added to the reaction mixture, which was then stirred vigorously for 30 min at rt. EtOAc (40 mL) and aqueous NaCl (940 mL) were then added and the upper organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (30% EtOAc/hexane) of the residue afforded **17** as an amorphous red solid (0.320 g, 89%); R_f=0.36 (50% EtOAc/hexane); IR ν_{max} (cm^{-1})=3015 (OH), 1754 (C=O), 1111; ^{1}H NMR (300 MHz, $CDCl_3$) major diastereomer δ_H=6.79 (1H, d, *J* 10.2, H-4)*, 6.74 (1H, d, *J* 10.2, H-5)*, 5.15 (1H, d, *J* 5.3, H-1), 3.90–3.80 (1H, m, H-11), 3.55 (2H, br s, CH_2OH), 2.82 (1H, d, *J* 20.9, H-8a), 2.82 (1H, d, *J* 20.9, H-8b), 2.17–2.06 (1H, m, H-12a), 1.52 (3H, s, CH_3), 1.40–1.33 (1H, m, H-12b); minor diastereomer δ_H=6.77 (1H, d, *J* 10.1, H-4)*, 6.74 (1H, d, *J* 10.2, H-5)*, 5.03 (1H, br d, *J* 10.7, H-1), 4.06–3.95 (1H, m, H-11), 3.58–3.69 (1H, m, one of CH_2OH), 3.50–3.37 (1H, m, one of CH_2OH), 2.64 (1H, d, *J* 19.1, H-8a), 2.82 (1H, d, *J* 19.1, H-8b), 2.36–2.23 (1H, m, H-12a), 1.58–1.52 (1H, m, H-12b), 1.52 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) major diastereomer δ_C=185.3 (C=O), 184.7 (C=O), 141.3 (C-2), 141.1 (C-7), 136.1 (C-4)*, 136.0 (C-5)*, 96.0 (C-9), 68.2 (C-11), 65.6 (CH_2OH), 64.4 (C-1), 32.3 (C-8), 28.8 (C-12), 29.4 (CH_3); minor diastereomer δ_C=186.4 (C=O), 185.3 (C=O), 143.6 (C-2), 137.7 (C-7), 136.1 (C-4)*, 136.0 (C-5)*, 97.5 (C-9), 66.1 (C-11), 64.6 (CH_2OH), 63.7 (C-1), 33.6 (C-8), 29.7 (C-12), 24.1 (CH_3).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.052. These data include MOL files and InChiKeys of the most important compounds described in this article.

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