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Stereoselective Synthesis of 4-Dehydroxydiversonol Employing Enantioselective Palladium-Catalysed Domino Reactions

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Dedicated to Professor Wolfgang Steglich on the occasion of his 75th birthday

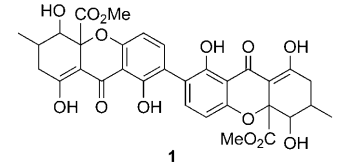
Abstract: The stereoselective synthesis of 4-dehydroxydiversonol (**4**) employing enantioselective palladium-catalysed domino processes such as the domino Wacker–Heck and the domino Wacker-carbonylation reaction for the formation of the central chroman moiety is described. Thus, reaction of **8** with palladium(II) trifluoroacetate [$Pd(OTFA)_2$] in the presence of carbon monoxide, methanol and the 2,2′-bis(oxazolin-2-yl)-1,1'-binaphthyl (BOXAX) ligand **17** led to **19** in 80% yield and 96% *ee*. Similarly, the chroman **7** was prepared using **8** and methyl acrylate (**9**) as starting material. Hydrogenation of the double bond, oxidation of the benzylic methylene group and intramolecular acylation of chromanone **6** provided the tetrahydroxanthenone core **5**, from which the synthesis of **4** was completed. The relative configuration of **4** could be established by crystal structure analysis.

Keywords: asymmetric catalysis · domino reactions · palladium · tetrahydroxanthenones · Wacker oxidation

Introduction

The secalonic acids (**1**), complex polyketides originally isolated from the fungus *Claviceps purpurea*,[1] contain the tetrahydroxanthenone moiety as the basic structural motif.[2] These compounds exhibit a widespread biological activity that includes antibacterial, cytostatic and anti-HIV properties.[3–5] So far, seven homo- and heterodimeric members of this substance class are known, each possessing a 2,2′-biaryl linkage, although with different configurations at the stereogenic centres.[6,7] Structurally related monomeric species are the fungal metabolites β-diversonolic ester (**2**) and diversonol (**3**) from *Penicillium diversum*.[8,9]

Despite their interesting profile, only recently synthetic efforts towards functionalised tetrahydroxanthenones and their derivatives have been made.[10,11]



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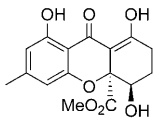

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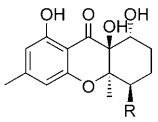

3: R = OH
4: R = H

Herein, we report the stereoselective synthesis of 4-dehydroxydiversonol (**4**) by applying a novel strategy towards enantiopure tetrahydroxanthenones that includes a domino Wacker–Heck or a domino Wacker-carbonylation reaction as the key step.[12] These enantioselective palladium-catalysed transformations were developed recently in our laboratory for the synthesis of chromans, dioxins and oxazines and have proven their efficiency in the total synthesis of

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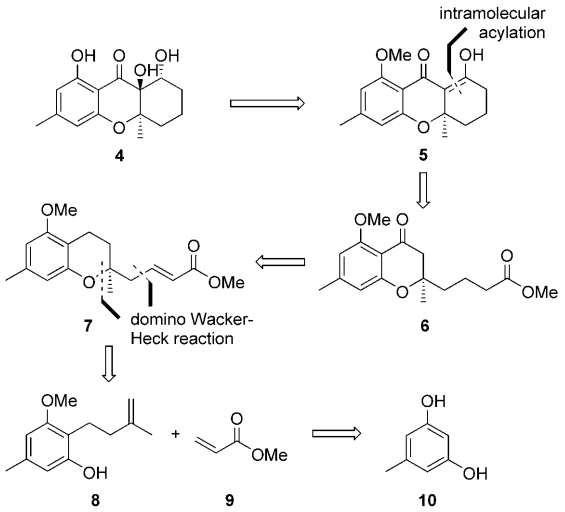
enantiopure α-tocopherol.[13,14] Our approach allows the synthesis of both enantiomers of **4** by using either the BOXAX ligand **17** or *ent*-**17**. Notably, the determination of the absolute configuration of diversonol (**3**) is questionable, though generally it is depicted as *ent*-**3**. Our attempts to reisolate diversonol for structure determination have so far failed.

Results and Discussion

The retrosynthetic analysis of **4** (Scheme 1) leads to the tetrahydroxanthenone core **5**. This is further disconnected con-

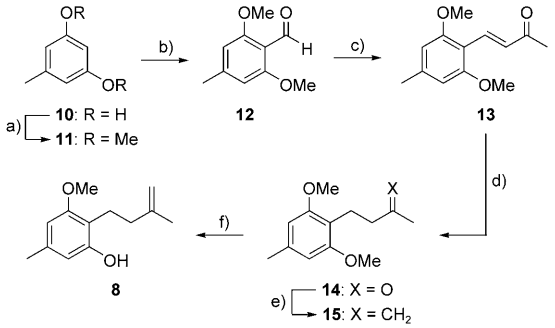


Scheme 1. Retrosynthetic analysis of 4-dehydroxydiversonol (**4**).

sidering an intramolecular acylation at the α position of the keto functionality of chromanone **6**, which in turn can be traced back to chroman **7**. For the direct synthesis of **7** with selective formation of the stereogenic tertiary ether moiety we envisaged an enantioselective domino Wacker–Heck reaction of alkenyl phenol **8** and methyl acrylate (**9**). As a second approach, an enantioselective domino Wacker-carbonylation reaction of **8** to give the chroman **19** was taken into account. Compound **8** should be easily accessible from orcinol (**10**).

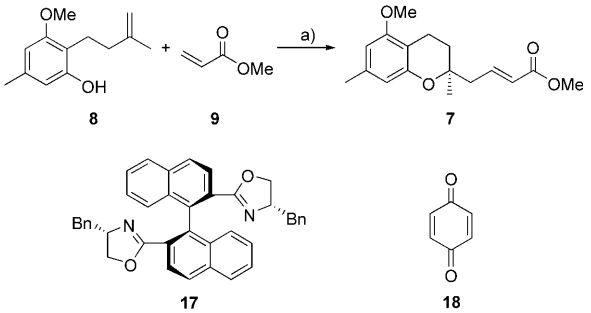
Alkenyl phenol **8** was synthesised from orcinol (**10**) through a six-step sequence (Scheme 2). First, **10** was methylated to give the corresponding dimethyl ether **11**,[15] which was subjected to *ortho*-lithiation and subsequent formylation with DMF to yield aldehyde **12**.[16] For the synthesis of the α,β-unsaturated ketone **13** initially a Wittig olefination of **12** with phosphorane **16** was employed. Despite the high yield of this transformation, aldol condensation of **12** with acetone is more appropriate for the formation of **13** due to a better atom economy. After hydrogenation, the obtained saturated ketone **14** was converted into alkene **15** by employing a Lombardo methylenation.[17] Finally, selective cleavage of one methyl ether group using sodium ethane thiolate in DMF gave access to the desired alkenyl phenol **8** with an overall yield of 48% based on **10**.

The domino Wacker–Heck reaction of **8** and methyl acrylate (**9**) in the presence of catalytic amounts of palladium(II)



Scheme 2. Synthesis of alkenyl phenol **8**: a) Me_2SO_4, K_2CO_3, acetone, reflux, 24 h, 94%; b) *n*BuLi, TMEDA, Et_2O, 0°C→reflux, 3 h, then DMF, 0°C→RT, 2 h, 87%; c) $Ph_3PCHC(O)CH_3$ (**16**), toluene, reflux, 22 h, 98%; or acetone, $NaOH_{(aq)}$, 0°C→RT, 3 h, 84%; d) H_2, Pd/C, EtOAc, RT, 3 h, 92%; e) Zn, CH_2Br_2, $TiCl_4$, THF, 0°C→RT, 1 h, 82%; f) NaSEt, DMF, 120°C, 20 h, 92%.

trifluoroacetate [$Pd(OTFA)_2$], the chiral ligand (*S*,*S*)-Bn-BOXAX (**17**)[18] and *p*-benzoquinone (**18**) as oxidant for the reoxidation of the intermediately formed Pd^0 provided the substituted chroman **7** with 88% *ee* in 55% yield, after a rather long reaction time of seven days (Scheme 3).



Scheme 3. Synthesis of chroman **7**: 10 mol% [$Pd(OTFA)_2$], 40 mol% (*S*,*S*)-Bn-BOXAX (**17**), *p*-benzoquinone (**18**), 1,2-dichloroethane (DCE), RT, 7 d, 55%, 88% *ee*.

Notably, a solvent screening revealed that only CH_2Cl_2 and 1,2-dichloroethane (DCE) were suitable for this transformation providing reasonable good yield and enantioselectivity. Thus, in benzene only 73% *ee* was obtained, whereas in polar solvents (DMF, DMSO, dioxane, and methanol) no formation of **7** was observed. Moreover, attempts to increase the reaction rate by performing the domino process at elevated temperature resulted in a significant reduction of enantioselectivity, though slightly higher yields could be obtained. We therefore developed an alternative approach to key intermediate **7** involving an enantioselective domino

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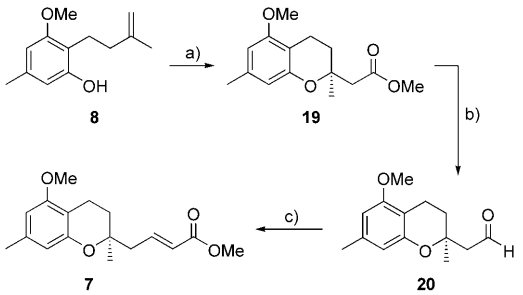
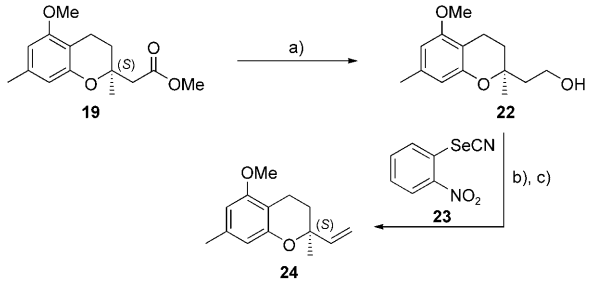
Wacker-carbonylation reaction (Scheme 4). For this purpose, **8** was reacted under an atmosphere of carbon monoxide in the presence of methanol to furnish ester **19** with 96% *ee*



Scheme 4. Alternative synthesis of **7**: a) 3 mol% $[Pd(OTFA)_2]$, 12 mol% (*S*,*S*)-Bn-BOXAX (**17**), *p*-benzoquinone (**18**), CO (1 atm), MeOH, RT, 15 h, 80%, 96% *ee*; b) DIBAL-H, toluene, −78°C, 20 min, 86%; c) $(MeO)_2P(O)CH_2CO_2Me$ (**21**), NaH, THF, 0°C→RT, 20 min, 97%, *E*/*Z* 6:1.

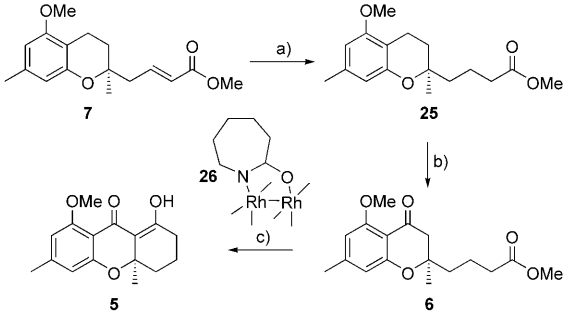
and 80% yield in only 15 h at room temperature. Moreover, the required catalyst loading could be significantly reduced obtaining satisfactory results with 3 mol% $[Pd(OTFA)_2]$ and 12 mol% of the BOXAX ligand **17**. Chain elongation of **19** giving access to the desired **7** was accomplished in two steps by diisobutylaluminium hydride (DIBAL-H) reduction and Wittig–Horner reaction of the obtained aldehyde **20** with trimethyl phosphonoacetate (**21**).

For the determination of the absolute configuration of **19** the compound was converted into the known vinyl chroman **24** to allow a comparison of the optical rotation (Scheme 5). Reduction of ester **19** yielded the corresponding alcohol **22**, which was transformed into **24** through selenoether formation using **23**, oxidation and elimination. The spectroscopic properties of **24** were in full agreement with the reference values published for the *R* enantiomer, except for the opposite sign of the optical rotation (**24**: $[\alpha]_D^{20} = -52.7$ ($c = 1.5$ in $CHCl_3$), *R* enantiomer: $[\alpha]_D^{20} = +54.0$ ($c = 2.18$ in $CHCl_3$)).[16] Hence, the *S* configuration can unambiguously be assigned to the stereogenic centre C-2 of the chroman moiety in **7** and **19**.



Scheme 5. Determination of the absolute configuration: a) $LiAlH_4$, Et_2O, 0°C→RT, 2 h, 98%; b) **23**, P*n*Bu_3, THF, RT, 1 h; c) *m*CPBA, CH_2Cl_2, −40°C, 1 h, then *i*Pr_2NH, −40°C→RT, 88% over two steps.

Prior to the formation of the tetrahydroxanthenone core **5** by intramolecular acylation, reduction of the double bond in **7** and oxidation of the chroman moiety to the corresponding chromanone **6** were required (Scheme 6). For this purpose, we tried to develop an efficient protocol for the direct conversion of the benzylic methylene unit into a carbonyl group. Several procedures failed in the benzylic oxidation, however, by treatment of **25** with excess *tert*-butylhydroperoxide in the presence of catalytic amounts of dirhodium-tetrakiscaprolactamate (**26**) and $NaHCO_3$, the desired chromanone **6** could finally be obtained in 63% yield.[19] Furthermore, an alternative procedure employing $[Mn(OAc)_3]$ as catalyst led to **6** in even 71% yield.[20] Intramolecular acylation at the α position of the keto functionality by the ester moiety in **6** in the presence of $TiCl_4$ and NEt_3 gave the tetrahydroxanthenone **5** in 63% yield. In contrast, cyclisation under basic conditions using potassium hexamethyldisilazide (KHMDS), lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) resulted in lower yields due to partial cleavage of the chroman ring.



Scheme 6. Synthesis of tetrahydroxanthenone **5**: a) H_2, Pd/C, EtOAc, RT, 6 h, 98%; b) 1 mol% **26**, *t*BuOOH, $NaHCO_3$, DCE, 40°C, 14 h, 63%; or 20 mol% $[Mn(OAc)_3]$, *t*BuOOH, molecular sieves 3 Å, EtOAc, RT, 3 d, 71%; c) $TiCl_4$, NEt_3, CH_2Cl_2, 0°C, 15 min, 63%.

With the tricyclic framework **5** in hand, completion of the synthesis of **4** required the diastereoselective introduction of the 9a-hydroxy group, reduction of the unconjugated carbonyl moiety and cleavage of the methyl ether (Scheme 7). For this purpose, enol **5** was oxidised using dimethyl dioxirane (DMDO) in acetone to afford *trans*-α-hydroxy diketone **27** in 74% yield as a single diastereomer; DMDO was superior to described procedures using *meta*-chloroperbenzoic acid (*m*CPBA) or magnesium monoperoxyphthalate.[10b] Reduction of **27** with $NaBH_4$ at −78°C gave, exclusively, *trans*-diol **28**. Finally, deprotection employing BBr_3 proceeded smoothly and furnished 4-dehydroxydiversonol (**4**) in 85% yield without epimerisation at the sensitive C-4a position.

The relative configuration of **4** was determined by crystal-structure analysis and revealed the axial orientation of the C-ring substituents (Figure 1).[21] Thus, we assume that the high *trans*-selectivity for the oxidation of **5** can be explained by shielding of the α face by the angular methyl group, whereas pre-complexation of $NaBH_4$ by the tertiary hydroxy

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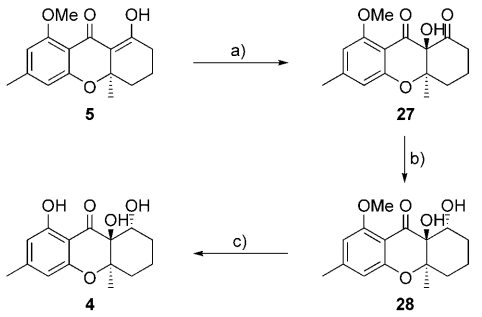

Scheme 7. Synthesis of 4-dehydroxydiversonol (**4**): a) DMDO, acetone, 0 °C, 1.5 h, 74 %; b) $NaBH_4$, $MeOH/CH_2Cl_2$, −78 °C, 20 min, 71 %; c) BBr_3, CH_2Cl_2, −78→0 °C, 30 min, 85 %.

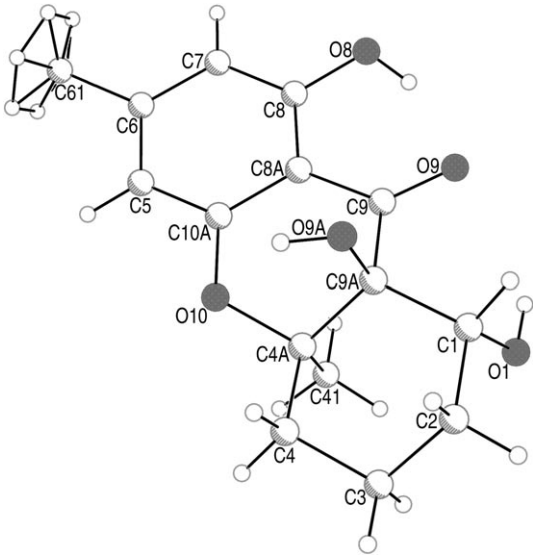

Figure 1. X-ray structure plot of 4-dehydroxydiversonol (**4**). The methyl group at C6 is disordered.

group favours hydride attack from the β face in the reduction of **27**.

To date, we have not been able to introduce the 4-hydroxy group of diversonol (**3**) by oxidation of an enolate derived from ester **19** or allylic oxidation of **7**. Therefore, current research in our laboratory is focusing on the extension of the scope of the domino reactions to appropriate precursors allowing for an early-stage introduction of this functionality.

Conclusion

We have developed a novel strategy for the enantioselective synthesis of the tetrahydroxanthenone core as found in secalonic acids, diversonolic esters and diversonol. We have described the synthesis of 4-dehydroxydiversonol (**4**). Key steps involve enantioselective palladium-catalysed domino reactions for the formation of chromans, benzylic oxidation of the chroman moiety and intramolecular acylation of the obtained chromanone. Diastereoselective functionalisation of the tricyclic framework completes the synthesis of **4**.

Experimental Section

General: Air- and moisture-sensitive reactions were carried out under argon in flame-dried glassware. Solvents were dried and distilled prior to use by means of standard laboratory methods. All reagents obtained from commercial sources were used without further purification. Thin layer chromatography (TLC) was performed on precoated silica-gel SIL G/UV_{254} plates (Macherey–Nagel), and silica gel 60A (0.037–0.070 mm, Acros) was used for column chromatography. Phosphomolybdic acid dissolved in MeOH (PMA) or vanillin dissolved in methanolic sulfuric acid (VSS) were used as staining agents for TLC analysis. UV/Vis spectra were recorded on a Perkin–Elmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films between NaCl plates on a Bruker Vector 22 instrument. ^1H and ^{13}C NMR spectra were recorded in deuterated solvents with Mercury-200, VXR-200, Unity-300, Inova-500, Unity-600 (Varian) or AMX-300 (Bruker) spectrometers using TMS or the indicated solvent as internal standard. Multiplicities of ^{13}C NMR peaks were determined with the attached proton test (APT) pulse sequence. Mass spectra were recorded on a Finnigan MAT 95, TSQ 7000 or LCQ instrument. High resolution mass spectrometry was performed using a Bruker APEX IV spectrometer equipped with a Bruker Apollo source and a Cole–Parmer syringe pump (74900 series).

1,3-Dimethoxy-5-methyl-benzene (11): Dimethyl sulfate (54.0 mL, 72.4 g, 575 mmol) was added dropwise to a mixture of orcinol monohydrate (**10**) (35.5 g, 250 mmol) and anhydrous K_2CO_3 (70.0 g, 507 mmol) in acetone (500 mL) at RT. The resulting mixture was heated at reflux for 24 h before being treated with concd aq NH_3 solution (25 mL) and heated for further 15 min. After cooling to RT the mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in water (400 mL) and Et_2O (100 mL), the layers were separated and the aqueous layer was extracted with Et_2O (2×100 mL). The combined organic layers were washed with water (100 mL), 3 M aq NaOH solution (2×100 mL) and sat. aq NaCl solution (100 mL), and dried ($MgSO_4$). After evaporation of the solvent in vacuo and distillation in vacuo orcinol dimethyl ether (**11**) was obtained as a colourless liquid (35.8 g, 235 mmol, 94 %). R_f=0.56 (*n*-pentane/EtOAc 9:1); b.p. 110–112 °C (20 mbar); ^1H NMR (300 MHz, $CDCl_3$): δ=2.32 (s, 3H; Ar-CH_3), 3.78 (s, 6H; 2OCH_3), 6.30 (m, 1H; 2-H), 6.35 ppm (m, 2H; 4-H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.8 (Ar-CH_3), 55.2 (OCH_3), 97.5 (C-2), 107.1 (C-4, C-6), 140.2 (C-5), 160.7 ppm (C-1, C-3); IR (film): $\tilde{\nu}$=3059, 2955, 2838, 1597, 1461, 1321, 1295, 1205, 1151, 1070, 921, 828, 686 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=204.0 (4.645), 273.0 (3.181), 279.5 nm (3.182); MS (70 eV, EI): *m*/*z* (%): 152.2 (100) [M^+], 123.1 (37) [M^+-2CH_3+H]; HRMS (EI): *m*/*z*: calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0841.

2,6-Dimethoxy-4-methyl-benzaldehyde (12): *n*-Butyllithium (32.4 mL of a 2.5 M solution in hexanes, 81.0 mmol) was added dropwise to a solution of orcinol dimethyl ether (**11**) (10.3 g, 67.4 mmol) and *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethane (TMEDA) (20.4 mL, 15.7 g, 135 mmol) in Et_2O (100 mL) at 0 °C. The resulting mixture was heated at reflux for 3 h before being cooled to 0 °C and treated dropwise with DMF (19.0 mL, 203 mmol). Stirring was continued at RT for further 2 h and the reaction was quenched with water (300 mL). After separation of the organic layer the aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Column chromatography on silica gel (*n*-pentane/EtOAc 7:3) provided aldehyde **12** as a pale-yellow solid (10.6 g, 58.8 mmol, 87 %). R_f=0.28 (*n*-pentane/EtOAc 7:3); ^1H NMR (300 MHz, $CDCl_3$): δ=2.32 (s, 3H; Ar-CH_3), 3.82 (s, 6H; 2OCH_3), 6.34 (s, 2H; 2Ar-H), 10.39 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.6 (Ar-CH_3), 55.7 (OCH_3), 104.6 (C-1), 111.9 (C-3, C-5), 147.7 (C-4), 162.2 (C-2, C-6), 189.0 ppm (CHO); IR (KBr): $\tilde{\nu}$= 3026, 2974, 2787, 1668, 1611, 1241, 1124, 814, 575 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=192.0 (4.375), 219.0 (4.274), 273.5 (4.125), 319.0 nm (3.587); MS (70 eV, EI): *m*/*z* (%): 180.2 (100) [M^+], 165.2 (11) [M^+-CH_3]; HRMS (EI): *m*/*z*: calcd for $C_{10}H_{12}O_3$: 180.0786; found: 180.0779.

4-(2,6-Dimethoxy-4-methyl-phenyl)-but-3-en-2-one (13): A solution of aldehyde **12** (10.0 g, 55.5 mmol) in acetone (80 mL) was treated dropwise with 1 M aq NaOH solution (35 mL) at 0 °C. The resulting mixture was

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stirred at RT for 3 h before being cooled to 0 °C and treated dropwise with 1 M aq HCl solution (40 mL). Water (300 mL) was added and the mixture was extracted with EtOAc (3×100 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. After column chromatography on silica gel (*n*-pentane/EtOAc 7:3) unsaturated ketone **13** was obtained as a colourless solid (10.3 g, 46.8 mmol, 84 %). R_f=0.34 (*n*-pentane/EtOAc 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.36 (s, 6H; 1′-H_3, Ar-CH_3), 3.86 (s, 6H; 2OCH_3), 6.38 (s, 2H; 2Ar-H), 7.12 (d, J=16.7 Hz, 1H; 3′-H), 7.96 ppm (d, J=16.7 Hz, 1H; 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.5 (Ar-CH_3), 26.9 (C-1′), 55.7 (OCH_3), 104.6 (C-1), 109.4 (C-3, C-5), 129.2 (C-3′), 135.0 (C-4′), 143.6 (C-4), 159.9 (C-2, C-6), 200.6 ppm (C-2′); IR (KBr): $\tilde{\nu}$=3052, 3006, 2975, 2945, 2845, 1677, 1567, 1250, 1116, 994, 823, 549 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=201.0 (4.384), 233.5 (3.940), 314.5 nm (4.367); MS (70 eV, EI): *m*/*z* (%): 220.1 (15) [M^+], 205.1 (21) [M^+-CH_3], 189.1 (100) [M^+-2CH_3-H]; HRMS (EI): *m*/*z*: calcd for [$C_{13}H_{16}O_3+H^+$]: 221.1172; found: 221.1173.

4-(2,6-Dimethoxy-4-methyl-phenyl)-butan-2-one (14): A solution of the unsaturated ketone **13** (9.75 g, 44.5 mmol) in EtOAc (250 mL) was treated with Pd/C (1.45 g, 10 % Pd, 1.34 mmol) at RT. Hydrogen was passed through the resulting mixture for 30 min before being stirred under a hydrogen atmosphere for further 2.5 h (TLC monitoring). The catalyst was removed by filtration over Celite (washing with CH_2Cl_2) and the solvent was evaporated in vacuo. Column chromatography (*n*-pentane/EtOAc 3:1) on silica gel yielded saturated ketone **14** as a colourless solid (9.10 g 41.0 mmol, 92 %). R_f=0.35 (*n*-pentane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.15 (s, 3H; 1′-H_3), 2.34 (s, 3H; Ar-CH_3), 2.57–2.63 (m, 2H; 3′-H_2), 2.83–2.93 (m, 2H; 4′-H_2), 3.78 (s, 6H; 2OCH_3), 6.36 ppm (s, 2H; 2Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.5 (C-4′), 21.9 (Ar-CH_3), 29.5 (C-1′), 43.3 (C-3′), 55.4 (OCH_3), 104.4 (C-3, C-5), 113.9 (C-1), 137.1 (C-4), 157.8 (C-2, C-6), 209.6 ppm (C-2′); IR (KBr): $\tilde{\nu}$=3064, 2994, 2938, 2838, 1704, 1589, 1466, 1246, 1127, 968, 814, 579 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=206.5 (4.650), 271.0 (2.924), 278.5 nm (2.880); MS (ESI): *m*/*z* (%): 245.1 (100) [M+Na^+], 223.1 (27) [M+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{13}H_{18}O_3$+Na^+]: 245.1148; found: 245.1148.

1,3-Dimethoxy-5-methyl-2-(3-methyl-but-3-enyl)-benzene (15): A slurry of zinc powder (13.2 g, 202 mmol) and CH_2Br_2 (5.36 mL, 11.7 g, 67.5 mmol) in THF (220 mL) was treated dropwise with $TiCl_4$ (5.46 mL, 9.35 g, 49.5 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 15 min. Subsequently, a solution of ketone **14** (10.0 g, 45.0 mmol) in THF (50 mL) was added dropwise at 0 °C and stirring was continued at RT for further 45 min. The solids were removed by filtration over Celite (washing with Et_2O) and the filtrate was washed with 1 M aq HCl solution (500 mL) and sat. aq NaCl solution (500 mL). After drying (Na_2SO_4), concentration in vacuo and column chromatography on silica gel (*n*-pentane/Et_2O 97:3) alkene **15** was obtained as a colourless oil (8.13 g, 36.9 mmol, 82 %). R_f=0.47 (*n*-pentane/Et_2O 97:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.79 (s, 3H; 3′-CH_3), 2.09–2.19 (m, 2H; 2′-H_2), 2.33 (s, 3H; Ar-CH_3), 2.70–2.79 (m, 2H; 1′-H_2), 3.79 (s, 6H; 2OCH_3), 4.70 (d, J= 1.0 Hz, 2H; 24′-H), 6.36 ppm (s, 2H; 2Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.2 (C-1′), 21.8 (Ar-CH_3), 22.4 (3′-CH_3), 37.2 (C-2′), 55.5 (OCH_3), 104.6 (C-3, C-5), 109.1 (C-4′), 115.9 (C-1), 136.7 (C-4), 147.0 (C-3′), 158.2 ppm (C-2, C-6); IR (film): $\tilde{\nu}$=3072, 2937, 2835, 1588, 1464, 1314, 1241, 1123, 970, 884, 813 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)= 207.0 (4.682), 271.0 nm (2.924); MS (70 eV, EI): *m*/*z* (%): 220.3 (13) [M^+], 165.2 (100) [$M^+-C_4H_7$]; EI-HRMS: *m*/*z*: calcd for $C_{14}H_{20}O_2$: 220.1463; found: 220.1469.

3-Methoxy-5-methyl-2-(3-methyl-but-3-enyl)-phenol (8): A solution of **15** (5.00 g, 22.7 mmol) in DMF (35 mL) was treated with NaSEt (4.23 g, technical grade (90 % (w/w)), 45.4 mmol) and stirred at 120 °C for 20 h. After cooling to RT the mixture was poured into water (200 mL) and extracted with Et_2O (3×100 mL). The combined organic layers were washed with water (2×100 mL) and sat. aq NaCl solution (100 mL) and dried (Na_2SO_4). After evaporation of the solvent in vacuo and column chromatography on silica gel (*n*-pentane/Et_2O 97:3→93:7) phenol **8** was obtained as a pale-yellow oil that solidified upon storage at −30 °C (4.31 g, 20.9 mmol, 92 %). R_f=0.34 (*n*-pentane/Et_2O 95:5); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.82 (s, 3H; 3′-CH_3), 2.17–2.27 (m, 2H; 2′-H_2), 2.29 (s, 3H; Ar-CH_3), 2.73–2.82 (m, 2H; 1′-H_2), 3.82 (s, 3H; OCH_3), 4.78 (m, 2H; 4′-H_2), 4.93 (s, 1H; OH), 6.29 (s, 1H; Ar-H), 6.34 ppm (s, 1H; Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5 (Ar-CH_3), 21.7 (C-1′), 22.7 (3′-CH_3), 37.0 (C-2′), 55.6 (OCH_3), 104.3, 109.0 (C-4, C-6), 109.6 (C-4′), 113.6 (C-2), 136.9 (C-5), 146.8 (C-3′), 154.0, 158.4 ppm (C-1, C-3); IR (film): $\tilde{\nu}$=3442, 3072, 2937, 1619, 1593, 1464, 1163, 1097, 886, 816 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=206.5 (4.639), 271.0 (2.898), 206.5 (4.639), 279.0 nm (2.847); MS (70 eV, EI): *m*/*z* (%): 206.1 (28) [M^+], 151.1 (100) [$M^+-C_4H_7$]; HRMS (EI): *m*/*z*: calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1302.

(2*S*)-(5-Methoxy-2,7-dimethyl-chroman-2-yl)-acetic acid methyl ester (19): A solution of [Pd(OTFA)$_2$] (49.0 mg, 148 μmol, 3 mol %) and (*S*,*S*)-Bn-BOXAX (**17**) (338 mg, 590 μmol, 12 mol %) in MeOH (5.0 mL) was stirred at RT for 15 min. After addition of a solution of phenol **8** (1.00 g, 4.92 mmol) in MeOH (10 mL) and *p*-benzoquinone (**18**) (2.12 g, 19.7 mmol) carbon monoxide was passed through the resulting mixture for 5 min before being stirred under a CO atmosphere (balloon) at RT for further 15 h. The slurry was poured into 1 N HCl (100 mL) and extracted with Et_2O (3×50 mL). The combined extracts were washed with 1 N NaOH (3×50 mL) and dried (Na_2SO_4). After evaporation of the solvent in vacuo and column chromatography on silica gel (*n*-pentane/Et_2O 9:1) chroman **19** was obtained as a yellowish oil (1.04 g, 3.94 mmol, 80 %, 96 % *ee*). HPLC (column: Daicel Chiralcel OD): wavelength: 272 nm, flow: 0.8 mL min^{-1}, eluent: *n*-hexane/isopropanol 98:2, t_R=19.7 min ((−)-**19**), 28.9 min ((+)-**19**); R_f=0.28 (*n*-pentane/Et_2O 9:1); $[\alpha]_D^{20}$=−7.0 (c= 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.42 (s, 3H; 2-CH_3), 1.85 (dt, J=13.8, 6.8 Hz, 1H; 3-H_a), 1.99 (dt, J=13.8, 6.8 Hz, 1H; 3-H_b), 2.26 (s, 3H; Ar-CH_3), 2.55–2.66 (m, 4H; 2′-H_2, 4-H_2), 3.68 (s, 3H; CO_2CH_3) 3.79 (s, 3H; Ar-OCH_3), 6.24 (s, 1H; Ar-H), 6.29 ppm (s, 1H; Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.4 (C-4), 21.5 (Ar-CH_3), 24.6 (2-CH_3), 30.3 (C-3), 43.5 (C-2′), 51.5 (CO_2CH_3), 55.3 (Ar-OCH_3), 74.2 (C-2), 102.9, 110.4 (C-6, C-8), 106.8 (C-4a), 137.1 (C-7), 153.5, 157.5 (C-5, C-8a), 170.9 ppm (C-1′); IR (film): $\tilde{\nu}$=2949, 2856, 1738, 1619, 1586, 1354, 1227, 1108, 1023, 814 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=207.5 (4.658), 271.5 (2.975), 280.0 nm (2.955); MS (70 eV, EI): *m*/*z* (%): 264.3 (58) [M^+], 191.2 (49) [$M^+-CH_2CO_2CH_3$], 151.2 (100); HRMS (EI): *m*/*z*: calcd for [$C_{15}H_{20}O_4$+H^+]: 265.1434; found: 265.1435.

(2*S*)-(5-Methoxy-2,7-dimethyl-chroman-2-yl)-acetaldehyde (20): DIBAL-H (9.45 mL of a 1.0 M solution in toluene, 9.45 mmol) was added dropwise over a period of 15 min to a solution of ester **19** (1.00 g, 3.78 mmol) in toluene (30 mL) at −78 °C. After complete addition the mixture was stirred at −78 °C for further 20 min before being quenched with MeOH/H_2O (5 mL, 1:1). Water (100 mL) was added and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. After column chromatography on silica gel (*n*-pentane/Et_2O 9:1) aldehyde **20** was obtained as a colourless oil (762 mg, 3.25 mmol, 86 %). R_f=0.24 (*n*-pentane/Et_2O 9:1); $[\alpha]_D^{20}$= +19.0 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40 (s, 3H; 2-CH_3), 1.83 (dt, J=13.6, 6.8 Hz, 1H; 3-H_a), 1.89 (dt, J=13.6, 6.8 Hz, 1H; 3-H_b), 2.28 (s, 3H; Ar-CH_3), 2.57 (dd, J=15.2, 3.2 Hz, 1H; 2′-H_a), 2.62 (t, J=6.8 Hz, 2H; 4-H_2), 2.71 (dd, J=15.2, 2.4 Hz, 1H; 2′-H_b), 3.80 (s, 3H; OCH_3), 6.26 (s, 1H; Ar-H), 6.31 (s, 1H; Ar-H), 9.89 ppm (t, J=2.8 Hz, 1H; CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.4 (C-4), 21.6 (Ar-CH_3), 24.7 (2-CH_3), 32.3 (C-3), 52.2 (C-2′), 55.3 (OCH_3), 74.2 (C-2), 103.1, 110.3 (C-6, C-8), 106.6 (C-4a), 137.4 (C-7), 153.4, 157.6 (C-5, C-8a), 201.6 ppm (C-1′); IR (film): $\tilde{\nu}$=2938, 2853, 1723, 1619, 1586, 1463, 1353, 1231, 1108, 816 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=207.0 (4.634), 271.5 (2.951), 280.0 nm (2.937); MS (ESI): *m*/*z* (%): 257.1 (31) [M+Na^+], 235.1 (100) [M+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{14}H_{18}O_3$+H^+]: 235.1329; found: 235.1330.

(2*S*)-(*E*)-4-(5-Methoxy-2,7-dimethyl-chroman-2-yl)-but-2-enoic acid methyl ester (7)

*Method A (Wittig–Horner reaction of **20**)*: A solution of trimethyl phosphonoacetate (**21**) (390 μL, 492 mg, 2.70 mmol) in THF (10 mL) was treated with sodium hydride (86.4 mg, 60 % (w/w) in mineral oil, 2.16 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before a solution of aldehyde **20** (421 mg, 1.80 mmol) in THF (4.0 mL) was added dropwise at 0 °C. After complete addition the slurry was stirred at RT for further 20 min before being quenched with sat. aq

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NH_4Cl solution (5 mL). The mixture was poured into sat. aq NH_4Cl solution (100 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatographic separation on silica gel (*n*-pentane/Et_2O 95:5→8:2) provided the title compound **7** (435 mg, 1.50 mmol, 83%) and the corresponding *Z* isomer (73.1 mg, 252 μmol, 14%) as pale-yellow oils.

*Method B (domino Wacker–Heck reaction of **8**)*: A solution of $[Pd(OTFA)_2]$ (8.3 mg, 24.7 μmol, 10 mol%) and (*S*,*S*)-Bn-BOXAX (**17**) (56.5 mg, 98.7 μmol, 40 mol%) in dichloroethane (0.15 mL) was stirred at RT for 30 min before being treated with *p*-benzoquinone (107 mg, 987 μmol) and stirred for further 10 min. A solution of phenol **8** (51.0 mg, 247 μmol) and methyl acrylate (**9**) (111 μL, 106 mg, 1.23 mmol) in dichloroethane (0.15 mL) was added and the resulting mixture was stirred at RT for 7 d. The slurry was poured into 1 N HCl (10 mL) and the aqueous phase was extracted with Et_2O (3×10 mL). The combined extracts were washed with 1 N NaOH (3×10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography on silica gel afforded the *E*-isomer **7** exclusively as a pale-yellow oil (39.4 mg, 136 μmol, 55%, 88% *ee*). Analytical data for the *E*-isomer **7**: HPLC (column: Daicel Chiralcel OD): wavelength: 272 nm, flow: 0.8 mL min^{-1}, eluent: *n*-hexane/isopropanol 98:2, t_R=13.7 min ((+)-**7**), 14.6 min ((−)-**7**); R_f=0.28 (*n*-pentane/Et_2O 9:1); $[\alpha]_D^{20}$=+24.0 (*c*=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (s, 3H; 2-CH_3), 1.74 (dt, *J*=13.8, 6.9 Hz, 1H; 3-H_a), 1.80 (dt, *J*=13.8, 6.9 Hz, 1H; 3-H_b), 2.28 (s, 3H; Ar-CH_3), 2.47 (ddd, *J*=14.1, 7.8, 1.1 Hz, 1H; 4′-H_a), 2.53 (ddd, *J*=14.1, 7.8, 1.1 Hz, 1H; 4′-H_b), 2.60 (t, *J*=6.9 Hz, 2H; 4-H_2), 3.74 (s, 3H; CO_2CH_3), 3.80 (s, 3H; Ar-OCH_3), 5.90 (dt, *J*=15.6, 1.1 Hz, 1H; 2′-H), 6.25 (s, 1H; Ar-H), 6.31 (s, 1H; Ar-H), 7.03 ppm (dt, *J*=15.6, 7.8 Hz, 1H; 3′-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.4 (C-4), 21.6 (Ar-CH_3), 24.3 (2-CH_3), 30.5 (C-3), 42.2 (C-4′), 51.4 (CO_2CH_3), 55.3 (Ar-OCH_3), 75.0 (C-2), 102.7, 110.4 (C-6, C-8), 106.7 (C-4a), 123.9 (C-2′), 137.2 (C-7), 144.3 (C-3′), 153.7, 157.6 (C-5, C-8a), 166.6 ppm (C-1′); IR (film): $\tilde{\nu}$=2946, 2853, 1725, 1657, 1619, 1586, 1463, 1353, 1109, 815 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=207.5 (4.749), 271.0 (3.038), 280.0 nm (2.980); MS (ESI): *m*/*z* (%): 603.3 (37) [2*M*+Na^+], 313.1 (100) [*M*+Na^+], 291.2 (73) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{17}H_{22}O_4$+H^+]: 291.1591; found: 291.1592. Analytical data for the *Z* isomer: R_f=0.34 (*n*-pentane/Et_2O 9:1); $[\alpha]_D^{20}$=+6.6 (*c*=0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.27 (s, 3H; 2-CH_3), 1.71–1.89 (m, 2H; 3-H_2), 2.28 (s, 3H; Ar-CH_3), 2.58 (dt, *J*=17.8, 6.7 Hz, 1H; 4-H_a), 2.66 (dt, *J*=17.8, 6.7 Hz, 1H; 4-H_b), 2.97 (ddd, *J*=15.8, 7.0, 1.7 Hz, 1H; 4′-H_a), 3.08 (ddd, *J*=15.8, 7.8, 1.7 Hz, 1H; 4′-H_b), 3.71 (s, 3H; CO_2CH_3), 3.80 (s, 3H; Ar-OCH_3), 5.92 (dt, *J*=11.7, 1.7 Hz, 1H; 2′-H), 6.24 (s, 1H; Ar-H), 6.31 (s, 1H; Ar-H), 6.47 ppm (dt, *J*=11.7, 7.4 Hz, 1H; 3′-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.5 (C-4), 21.6 (Ar-CH_3), 24.0 (2-CH_3), 30.8 (C-3), 38.5 (C-4′), 51.0 (CO_2CH_3), 55.3 (Ar-OCH_3), 75.1 (C-2), 102.7, 110.3 (C-6, C-8), 107.0 (C-4a), 121.1 (C-2′), 137.1 (C-7), 145.6 (C-3′), 154.0, 157.6 (C-5, C-8a), 166.8 ppm (C-1′); IR (film): $\tilde{\nu}$=2947, 2854, 1723, 1619, 1586, 1439, 1353, 1203, 1109, 814 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=207.5 (4.724), 209.0 (4.724), 271.0 (3.034), 280.0 nm (2.975); MS (ESI): *m*/*z* (%): 603.3 (16) [2*M*+Na^+] 313.1 (100) [*M*+Na^+], 291.2 (63) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{17}H_{22}O_4$+H^+]: 291.1591; found: 291.1591.

(2*S*)-2-(5-Methoxy-2,7-dimethyl-chroman-2-yl)-ethanol (22): A solution of ester **19** (253 mg, 957 mmol) in Et_2O (3.0 mL) was added dropwise to a suspension of $LiAlH_4$ (40.0 mg, 1.05 mmol) in Et_2O (3.0 mL) at 0°C. The resulting mixture was stirred at RT for 1 h before being carefully quenched with water (10 mL). After separation of the organic layer the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent evaporated in vacuo. Column chromatography on silica gel (*n*-pentane/EtOAc 7:3) furnished alcohol **22** as a colourless oil (221 mg, 935 μmol, 98%). R_f=0.28 (*n*-pentane/EtOAc 7:3); $[\alpha]_D^{20}$=−4.5 (*c*=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.31 (s, 3H; 2-CH_3), 1.68–2.05 (m, 4H; 2′-H_2, 3-H_2), 2.27 (s, 3H; Ar-CH_3), 2.44 (t, *J*=4.9 Hz, 1H; OH), 2.50–2.63 (m, 1H; 4-H_a), 2.69 (dt, *J*=17.3, 6.0 Hz, 1H; 4-H_b), 3.77–3.99 (m, 2H; 1′-H_2), 3.80 (s, 3H; OCH_3), 6.25 (s, 1H; Ar-H), 6.28 ppm (s, 1H; Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.3 (C-4), 21.5 (Ar-CH_3), 23.4 (2-CH_3), 31.2 (C-3), 41.8 (C-2′), 55.3 (OCH_3), 59.0 (C-1′), 76.3 (C-2), 102.9, 110.3 (C-6, C-8), 106.9 (C-4a), 137.1 (C-7), 153.5, 157.6 ppm (C-5, C-8a); IR (film): $\tilde{\nu}$=3375, 2939, 2855, 1618, 1586, 1463, 1353, 1231, 1109, 1023, 880, 814 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=207.5 (4.635), 272.0 (2.954), 280.0 nm (2.942); MS (ESI): *m*/*z* (%): 495.2 (27) [2*M*+Na^+], 259.1 (100) [*M*+Na^+], 237.2 (8) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{14}H_{20}O_3$+Na^+]: 259.1305; found: 259.1305.

(2*S*)-5-Methoxy-2,7-dimethyl-2-vinyl-chroman (24): P*n*Bu_3 (110 μL, 87.4 mg, 394 μmol) was added dropwise to a solution of alcohol **22** (46.6 mg, 197 μmol) and 2-nitrophenyl selenocyanate (**23**) (91.4 mg, 394 μmol) in THF (4.0 mL) at 0°C. The resulting mixture was stirred at 0°C for 1 h before being poured into sat. aq $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3×10 mL). The combined organic fractions were dried (Na_2SO_4) and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (4.0 mL), the solution was cooled to −40°C, Na_2HPO_4 (175 mg, 985 μmol) and *m*CPBA (116 mg, 70% (w/w), 470 μmol) were added and the resulting suspension was stirred at −40°C for 1 h. After addition of *i*Pr_2NH (140 μL, 99.7 mg, 985 μmol) the mixture was allowed to reach RT, and stirring was continued for further 14 h before silica gel (500 mg) was added. Evaporation of the solvent under reduced pressure and column chromatography of the residue on silica gel (*n*-pentane/Et_2O 98:2) yielded vinyl chroman **24** as a pale-yellow oil (37.7 mg, 173 μmol, 88%). R_f=0.42 (*n*-pentane/EtOAc 98:2); $[\alpha]_D^{20}$=−52.7 (*c*=1.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.42 (s, 3H; 2-CH_3), 1.78 (ddd, *J*=13.6, 9.8, 5.9 Hz, 1H; 3-H_a), 1.92 (ddd, *J*=13.6, 6.0, 5.0 Hz, 1H; 3-H_b), 2.31 (s, 3H; Ar-CH_3), 2.46 (ddd, *J*=16.8, 9.8, 6.2 Hz, 1H; 4-H_a), 2.67 (dt, *J*=16.8, 5.5 Hz, 1H; 4-H_b), 3.81 (s, 3H; OCH_3), 5.07 (dd, *J*=10.8, 1.2 Hz, 1H; 2′-H), 5.20 (dd, *J*=17.4, 1.2 Hz, 1H; 2′-H), 5.88 (dd, *J*=17.4, 10.8 Hz, 1H; 1′-H), 6.25 (s, 1H; Ar-H), 6.39 ppm (s, 1H; Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.7 (C-4), 21.6 (Ar-CH_3), 26.8 (2-CH_3), 31.3 (C-3), 55.3 (OCH_3), 76.2 (C-2), 102.6, 110.0 (C-6, C-8), 107.3 (C-4a), 113.6 (C-2′), 136.9 (C-7), 141.3 (C-1′), 154.3, 157.4 ppm (C-5, C-8a); IR (film): $\tilde{\nu}$=3088, 2976, 2936, 2852, 1619, 1586, 1463, 1353, 1232, 1140, 1024, 923, 813 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=207.0 (4.665), 271.5 (2.995), 280.0 (2.976), 406.0 nm (1.956); MS (ESI): *m*/*z* (%): 219.1 (100) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{14}H_{18}O_2$+H^+]: 219.1379; found: 219.1379.

(2*R*)-4-(5-Methoxy-2,7-dimethyl-chroman-2-yl)-butyric acid methyl ester (25): Pd/C (1.00 g, 10% Pd, 909 μmol) was added to a solution of unsaturated ester **7** (2.64 g of an *E*/*Z* mixture, 9.09 mmol) in EtOAc (75 mL). Hydrogen was passed through the resulting mixture for 30 min before being stirred under a H_2 atmosphere at RT for further 6 h. The catalyst was removed by filtration over silica gel (eluting with EtOAc), and after evaporation of the solvent in vacuo and column chromatography on silica gel (*n*-pentane/Et_2O 9:1) saturated ester **25** was obtained as a colourless oil (2.60 g, 8.89 mmol, 98%). R_f=0.29 (*n*-pentane/Et_2O 9:1); $[\alpha]_D^{20}$=+7.6 (*c*=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.27 (s, 3H; 2-CH_3), 1.55–1.66 (m, 2H), 1.67–1.87 (m, 6H; 3-H_2, 3′-H_2, 4′-H_2), 2.27 (s, 3H; Ar-CH_3), 2.33 (m, 2H; 2′-H_2), 2.59 (m, 2H; 4-H_2), 3.66 (s, 3H; CO_2CH_3), 3.80 (s, 3H; Ar-OCH_3), 6.23 (s, 1H; Ar-H), 6.28 ppm (s, 1H; Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.4 (C-4), 19.2 (C-3′), 21.6 (Ar-CH_3), 23.8 (2-CH_3), 30.4 (C-3), 34.2 (C-2′), 38.7 (C-4′), 51.4 (CO_2CH_3), 55.3 (Ar-OCH_3), 75.3 (C-2), 102.4, 110.3 (C-6, C-8), 106.9 (C-4a), 136.9 (C-7), 154.1, 157.5 (C-5, C-8a), 173.9 ppm (C-1′); IR (film): $\tilde{\nu}$=2948, 2731, 1739, 1618, 1586, 1462, 1353, 1110, 813 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε)=208.0 (4.636), 272.0 (2.943), 280.5 nm (2.932); MS (ESI): *m*/*z* (%): 607.3 (44) [2*M*+Na^+], 315.2 (94) [*M*+Na^+], 293.2 (100) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{17}H_{24}O_4$+Na^+]: 315.1567; found: 315.1568.

(2*R*)-4-(5-Methoxy-2,7-dimethyl-4-oxo-chroman-2-yl)-butyric acid methyl ester (6)

Method A (Rh-catalysed oxidation): A solution of chroman **25** (300 mg, 1.03 mmol) and dirhodium-tetrakiscaprolactamate ([Rh_2(cap)$_4$], **26**) (3.4 mg, 5.15 μmol, 0.5 mol%) in dichloroethane (4.0 mL) was treated with $NaHCO_3$ (43.3 mg, 515 μmol). The reaction flask was sealed with a septum and an empty balloon was attached by a needle to capture oxygen generated during the reaction. *tert*-Butyl hydroperoxide (0.94 mL of a 5.5 M solution in decane, 5.17 mmol) was added and the resulting deep-red solution was heated with stirring at 40°C in a preheated oil bath. After 3 h the mixture was treated with additional [Rh_2(cap)$_4$] (3.4 mg, 5.15 μmol) and *t*BuOOH (0.94 mL of a 5.5 M solution in decane,

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5.17 mmol). Stirring was continued at 40 °C for further 11 h before the solids were removed by filtration over silica gel (eluting with EtOAc). After evaporation of the solvent under reduced pressure and column chromatography on silica gel (*n*-pentane/EtOAc 3:2) chromanone **6** was obtained as a yellow oil (199 mg, 649 μmol, 63 %).

Method B (Mn-catalysed oxidation): A solution of chroman **25** (1.00 g, 3.42 mmol) and *tert*-butyl hydroperoxide (6.22 mL of a 5.5 M solution in decane, 34.2 mmol) in EtOAc (12 mL) was treated with powdered molecular sieves 3 Å (1.20 g) and the resulting mixture was stirred at RT for 30 min. After addition of anhydrous $[Mn(OAc)_3]$ (160 mg, 684 μmol, 20 mol %) stirring was continued for further 3 d before the mixture was filtered over silica gel (eluting with EtOAc). After concentration in vacuo and column chromatography on silica gel (*n*-pentane/EtOAc 3:2) chromanone **6** was obtained as a yellow oil (741 mg, 2.42 mmol, 71 %). $R_f = 0.34$ (*n*-pentane/EtOAc 3:2); $[\alpha]_D^{20} = +11.8$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (s, 3H; 2-CH_3), 1.58–1.80 (m, 4H; 3′-H_2, 4′-H_2), 2.21–2.34 (m, 2H; 2′-H_2), 2.25 (s, 3H; Ar-CH_3), 2.55 (d, $J = 15.8$ Hz, 1H; 3-H_a), 2.70 (d, $J = 15.8$ Hz, 1H; 3-H_b), 3.63 (s, 3H; CO_2CH_3), 3.86 (s, 3H; Ar-OCH_3), 6.26 (s, 1H; Ar-H), 6.32 ppm (s, 1H; Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.0$ (C-3′), 22.3 (Ar-CH_3), 23.5 (2-CH_3), 33.8 (C-2′), 38.5 (C-4′), 48.6 (C-3), 51.5 (CO_2CH_3), 56.0 (Ar-OCH_3), 80.0 (C-2), 104.2, 110.7 (C-6, C-8), 108.3 (C-4a), 147.5 (C-7), 160.0, 161.1 (C-5, C-8a), 173.6 (C-1′), 190.8 ppm (C-4); IR (film): $\tilde{\nu} =$ 2952, 2849, 1737, 1683, 1614, 1568, 1464, 1114, 824 cm^{-1}; UV/Vis (CH_3CN): λ_{max} ($\log \varepsilon$) = 196.0 (4.362), 221.0 (4.277), 269.0 (4.039), 324.5 nm (3.562); MS (ESI): *m*/*z* (%): 635.3 (27) [2*M*+Na^+], 329.1 (21) [*M*+Na^+], 307.2 (100) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{17}H_{22}O_5$+H^+]: 307.1540; found: 307.1541.

(4a*R*)-1-Hydroxy-8-methoxy-4a,6-dimethyl-2,3,4,4a-tetrahydroxanthen-9-one (5): $TiCl_4$ (3.82 mL of a 1.0 M solution in CH_2Cl_2, 3.82 mmol) was added slowly through a syringe to a solution of chromanone **6** (532 mg, 1.74 mmol) in CH_2Cl_2 at 0 °C. Subsequently, NEt_3 (600 μL, 440 mg, 4.35 mmol) was added slowly through a syringe, and the resulting solution was stirred at 0 °C for further 15 min (TLC monitoring) before being quenched with sat. aq NH_4Cl solution (5 mL). Water (100 mL) was added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Column chromatography on silica gel (*n*-pentane/EtOAc 3:1) yielded tetrahydroxanthenone **5** as a pale-yellow solid (302 mg, 1.10 mmol, 63 %). $R_f = 0.34$ (*n*-pentane/EtOAc 3:1); $[\alpha]_D^{20} = +49.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (s, 3H; 4a-CH_3), 1.68–1.86 (m, 1H; 3-H_a), 1.89–2.11 (m, 3H; 3-H_b, 4-H_2), 2.28–2.57 (m, 2H; 2-H_2), 2.32 (s, 3H; Ar-CH_3), 3.92 (s, 3H; OCH_3), 6.35 (s, 2H; 2 Ar-H), 16.01 ppm (s, 1H; OH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$ (C-3), 22.4 (Ar-CH_3) 25.5 (4a-CH_3), 30.2 (C-2), 35.8 (C-4), 56.1 (OCH_3), 78.1 (C-4a), 105.4, 111.2 (C-5, C-7), 108.2 (C-8a), 108.7 (C-9a), 147.1 (C-6), 160.2, 160.6 (C-8, C-10a), 180.3 (C-1), 182.0 ppm (C-9); IR (KBr): $\tilde{\nu} = 2953$, 1609, 1469, 1356, 1227, 1108, 878, 822 cm^{-1}; UV/Vis (CH_3CN): λ_{max} ($\log \varepsilon$) = 205.0 (4.396), 282.0 (3.658), 326.0 nm (4.121); MS (ESI): *m*/*z* (%): 571.2 (100) [2*M*+Na^+], 297.1 (31) [*M*+Na^+], 275.1 (77) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{16}H_{18}O_4$+H^+]: 275.1278; found: 275.1279.

(4a*R*,9a*R*)-9a-Hydroxy-8-methoxy-4a,6-dimethyl-3,4,4a,9a-tetrahydro-2*H*-xanthene-1,9-dione (27): A solution of enol **5** (200 mg, 7.29 μmol) in acetone (40 mL) was treated sequentially every 15 min with dimethyl dioxirane (DMDO) (5.0 mL of a 0.07 M solution in acetone, 350 μmol, altogether 5 × 5.0 mL, 1.75 mmol) at 0 °C. After the last addition the solution was stirred for further 30 min (TLC monitoring) before being concentrated in vacuo at 0 °C. The residue was dissolved in MeOH, silica gel (1.5 g) was added and the solvent was evaporated in vacuo. Column chromatography on silica gel (*n*-pentane/EtOAc 1:1) provided α-hydroxy diketone **27** as a colourless solid (156 mg, 539 μmol, 74 %). $R_f = 0.23$ (*n*-pentane/EtOAc 1:1); $[\alpha]_D^{20} = -172.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (s, 3H; 4a-CH_3), 1.54–1.73 (m, 1H; 3-H_a), 1.74–1.86 (m, 1H; 4-H_a), 1.95–2.11 (m, 1H; 3-H_b), 2.19 (m, 1H; 2-H_a), 2.30 (s, 3H; Ar-CH_3), 2.72 (ddd, ^2J(H,H) = 13.2 Hz, ^3J(H,H) = 13.2, 5.5 Hz, 1H; 4-H_b), 3.40 (ddd, ^2J(H,H) = 13.2 Hz, ^3J(H,H) = 13.2, 7.3 Hz, 1H; 2-H_b), 3.74 (s, 3H; OCH_3), 4.60 (s_{br}, 1H; OH), 6.26 (s, 1H; 7-H), 6.36 ppm (s, 1H; 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.8$ (4a-CH_3), 20.6 (C-3), 22.4 (Ar-CH_3), 31.3 (C-4), 37.4 (C-2), 55.8 (OCH_3), 78.1 (C-4a), 83.6 (C-9a), 105.2 (C-7), 107.7 (C-8a), 110.7 (C-5), 148.0 (C-6), 159.2 (C-10a), 161.7 (C-8), 186.3 (C-9), 207.0 ppm (C-1); IR (KBr): $\tilde{\nu} = 3366$, 2970, 1728, 1616, 1462, 1232, 1121, 821 cm^{-1}; UV/Vis (CH_3CN): λ_{max} ($\log \varepsilon$) = 195.5 (4.335), 221.0 (4.209), 274.0 (4.046), 330.0 nm (3.546); MS (ESI): *m*/*z* (%): 603.2 (29) [2*M*+Na^+], 329.1 (12) [*M*+K^+], 313.1 (22) [*M*+Na^+], 291.1 (100) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{16}H_{18}O_5$+H^+]: 291.1227; found: 291.1228.

(1*R*,4a*R*,9a*S*)-1,9a-Dihydroxy-8-methoxy-4a,6-dimethyl-1,2,3,4,4a,9a-hexahydroxanthen-9-one (28): A solution of diketone **27** (138 mg, 476 μmol) in MeOH/CH_2Cl_2 (2:1, 7.5 mL) was treated slowly with powdered $NaBH_4$ (20.0 mg, 528 μmol) at −78 °C. The resulting mixture was stirred at −78 °C for further 15 min (TLC monitoring) before being quenched with water (5 mL). Water (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. After column chromatography on silica gel (*n*-pentane/EtOAc 3:2) diol **28** was obtained as a colourless solid (98.8 mg, 338 μmol, 71 %). $R_f = 0.27$ (*n*-pentane/EtOAc 3:2); $[\alpha]_D^{20} = -121.7$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.56$ (s, 3H; 4a-CH_3), 1.61–1.81 (m, 4H; 2-H_a, 3-H_2, 4-H_a), 1.92–2.01 (m, 1H; 2-H_b), 2.15 (ddd, ^2J(H,H) = 12.8 Hz, ^3J(H,H) = 12.8, 4.1 Hz, 1H; 4-H_b), 2.32 (s, 3H; Ar-CH_3), 2.95 (s, 1H; 9a-OH), 3.15 (t, $J = 2.2$ Hz, 1H; 1-OH), 3.85 (s, 3H; OCH_3), 4.39 (m, 1H; 1-H), 6.32 (s, 1H; 7-H), 6.38 ppm (s, 1H; 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.9$ (C-3), 19.6 (4a-CH_3), 22.4 (Ar-CH_3), 26.9 (C-2), 32.3 (C-4), 55.9 (OCH_3), 68.5 (C-1), 73.8 (C-4a), 83.0 (C-9a), 105.0 (C-7), 107.3 (C-8a), 110.9 (C-5), 148.2 (C-6), 159.4 (C-10a), 161.2 (C-8), 193.4 ppm (C-9); IR (KBr): $\tilde{\nu} = 3502$, 3390, 2953, 1679, 1612, 1566, 1236, 1115, 965, 830, 547, 503 cm^{-1}; UV/Vis (CH_3CN): λ_{max} ($\log \varepsilon$) = 195.5 (4.373), 221.5 (8.236), 275.5 (4.042), 330.0 nm (3.544); MS (ESI): *m*/*z* (%): 607.3 (38) [2*M*+Na^+], 315.1 (33) [*M*+Na^+], 293.1 (100) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{16}H_{20}O_5$+H^+]: 293.1384; found: 293.1384.

(1*R*,4a*R*,9a*S*)-1,8,9a-Trihydroxy-4a,6-dimethyl-1,2,3,4,4a,9a-hexahydroxanthen-9-one (4-dehydroxydiversonol) (4): BBr_3 (2.91 mL of a 1.0 M solution in CH_2Cl_2, 2.91 mmol) was added slowly to a solution of methyl ether **28** (85.1 mg, 291 μmol) in CH_2Cl_2 (15 mL) at −78 °C. The resulting dark-red solution was stirred for 15 min at −78 °C and further 30 min at 0 °C (TLC monitoring) before being quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. After column chromatography on silica gel (*n*-pentane/EtOAc 8:2) 4-dehydroxydiversonol (**4**) was obtained as a colourless solid (68.8 mg, 247 μmol, 85 %). $R_f = 0.30$ (*n*-pentane/EtOAc 4:1); $[\alpha]_D^{20} = -102.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta =$ 1.57 (s, 3H; 4a-CH_3), 1.63–1.82 (m, 4H; 2-H_a, 3-H_2, 4-H_a), 1.99 (dddd, ^2J(H,H) = 14.6 Hz, ^3J(H,H) = 14.6, 4.1, 4.1 Hz, 1H; 2-H_b), 2.14 (ddd, ^2J(H,H) = 12.6 Hz, ^3J(H,H) = 12.6, 4.2 Hz, 1H; 4-H_b), 2.29 (s, 3H; Ar-CH_3), 2.58 (s, 1H; 1-OH), 3.04 (s, 1H; 9a-OH), 4.45 (m, 1H; 1-H), 6.26 (s, 1H; 5-H), 6.37 (s, 1H; 7-H), 10.96 ppm (s, 1H; Ar-OH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.9$ (C-3), 19.8 (4a-CH_3), 22.5 (Ar-CH_3), 26.7 (C-2), 32.2 (C-4), 67.3 (C-1), 74.1 (C-4a), 83.6 (C-9a), 104.7 (C-8a), 109.2 (C-5), 110.5 (C-7), 150.8 (C-6), 157.6 (C-10a), 162.4 (C-8), 197.8 ppm (C-9); IR (KBr): $\tilde{\nu} = 3567$, 3342, 2935, 1634, 1567, 1395, 1202, 1099, 962, 840, 696, 505 cm^{-1}; UV (CH_3CN): λ_{max} ($\log \varepsilon$) = 195.5 (4.324), 210.0 (4.251), 281.5 (4.059), 349.0 nm (3.438); MS (ESI): *m*/*z* (%): 301.1 (41) [*M*+Na^+], 279.1 (100) [*M*+H^+]; HRMS (EI): *m*/*z*: calcd for [$C_{15}H_{18}O_5$+H^+]: 279.1227; found: 279.1227.

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