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PALLADIUM-CATALYZED DOMINO-WACKER-CARBONYLATION REACTION FOR THE ENANTIOSELECTIVE SYNTHESIS OF CHROMANS AND BENZODIOXINS

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Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday.

Abstract – A palladium-catalyzed domino reaction for the formation of chromans **9** as well as **10** and benzodioxins **13** is described starting from the alkenes **6** as well as **8** and the allyl phenyl ethers **12.** The domino reaction comprises an enantioselective intramolecular Wacker oxidation, a subsequent CO-insertion and a nucleophilic substitution of the intermediately formed palladium-species.

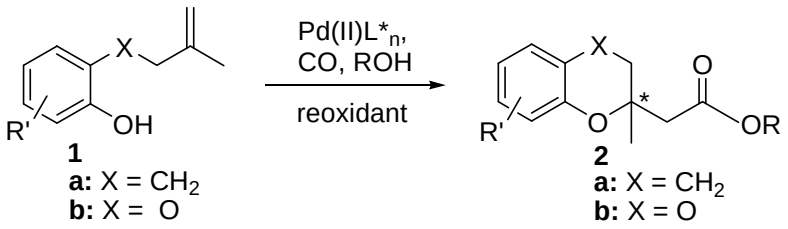
INTRODUCTION

One of the main issues in modern synthetic organic chemistry is the improvement of efficiency with ecological and economical benefits as the reduction of waste, the preservation of our resources and the increase of productivity. An excellent approach to fulfill these requirements is the development and use of domino reactions, which allow the synthesis of complex organic molecules starting from simple substrates in a very favorable way. Domino reactions are defined as processes of two or more bond forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond forming reactions.[1]

Recently we have reported on an enantioselective palladium-catalyzed domino-Wacker-Heck reaction for the total synthesis of vitamin E,[2] which not only allows the highly selective formation of the chiral chroman framework with 97% ee, but also the simultaneous introduction of a part of the side chain. Here we describe a domino process which comprises an enantioselective intramolecular Wacker oxidation, a subsequent CO-insertion and a nucleophilic substitution of the intermediately formed palladium-species. This procedure is used for the enantioselective synthesis of chromans and benzodioxins.

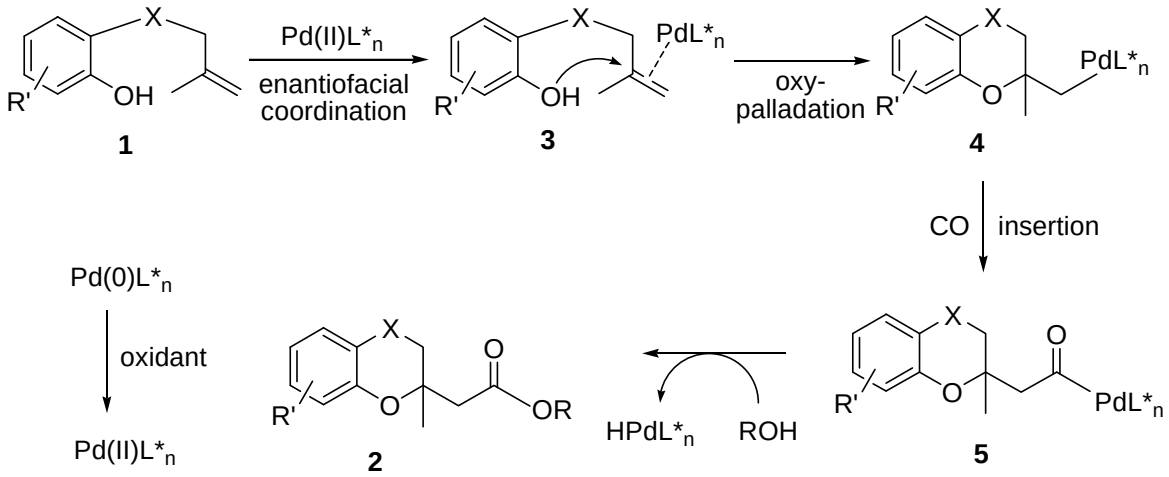
RESULTS AND DISCUSSION

The insertion of CO into metal organic species is a well known and widely used process for the synthesis of carboxylic acid derivatives.[3] Pioneering work in the enantioselective Wacker cyclization of 2-allylphenols has been reported by Hosokawa and Murahashi.[4] Hayashi and Uozumi have shown that palladium(II) BOXAX complexes give high enantioselectivities in this transformation.[5] However, CO insertion in combination with an enantioselective Wacker oxidation represents a new procedure. As shown in scheme 1, using this approach phenols of type **1** can be transformed into chromans **2a** (X = CH_2) and benzodioxins **2b** (X = O), whereas the ester moiety can be varied by using different alcohols.



Scheme 1. Domino reaction for the enantioselective synthesis of chromans and benzodioxins.

We assume that in the first step of the domino process the chiral Pd(II) complex undergoes an enantiofacial coordination to the double bond in **1** with umpolung of the latter to give **3** allowing an intramolecular nucleophilic attack of the phenolic hydroxy group with formation of the Pd-species **4**.

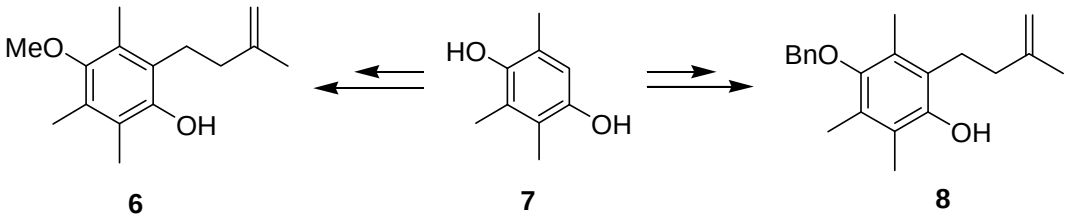


Scheme 2. Proposed mechanism for the domino-Wacker-carbonylation reaction.

However, according to investigations reported by Hayashi and Uozumi *syn*-oxypalladation involving a phenoxy(π-olefin)palladium(II) species has to be taken into account as well.[6] Compound **4** is relatively

stable due to the lack of a β-hydrogen necessary for a β-hydride-Pd elimination; thus, it can undergo an intermolecular CO insertion applying a CO-atmosphere to afford **5**, which then reacts with another nucleophile e.g. an alcohol used as solvent in an intermolecular reaction to give **2**. For the completion of the catalytic cycle, it is necessary to oxidize the formed Pd(0) to a Pd(II) species, which is achieved by using *p*-benzoquinone.

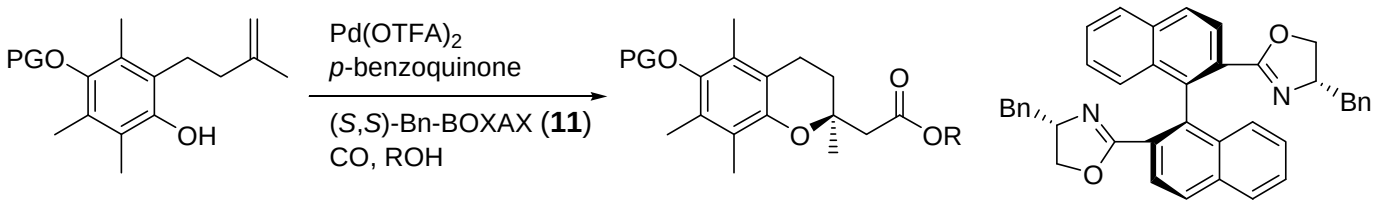
For the synthesis of the chromans **9** and **10**, which have also been employed in the synthesis of vitamin E, we prepared the alkenes **6** and **8** according to an already published procedure starting from the phenol **7** using methyl vinyl ketone in the presence of methyl orthoformate and a Brönsted acid. This was followed by the protection of the remaining phenolic hydroxy group, hydrolysis of the acetal formed in the first step and Lombardo reaction with an overall yield of 56%.[2b]



6 **7** **8**

Scheme 3. Synthesis of alkenes **6** and **8** from **7**.

In the optimization of the enantioselective domino-Wacker-carbonylation reaction, different alcohols, palladium catalysts as palladium(II)chloride and palladium(II)trifluoroacetate as well as different reoxidants as copper(II)chloride, copper(II)acetate and *p*-benzoquinone were used. In addition, the CO-source was varied. Thus, on the one hand CO-gas was employed under atmospheric pressure and on the other hand $Mo(CO)_6$ was used. The results of the different reactions are summarized in Table 1.



6: PG = Me
8: PG = Bn

9: PG = Me
10: PG = Bn

11

Scheme 4. Enantioselective domino-Wacker-carbonylation reactions of alkenes **6** and **8** with aliphatic alcohols.

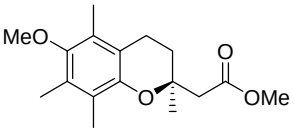
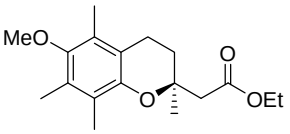
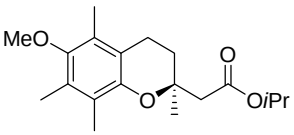
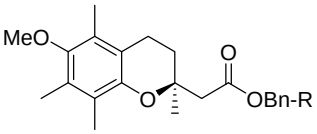
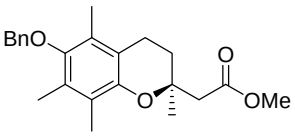
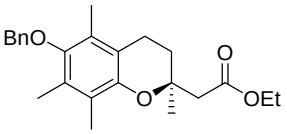
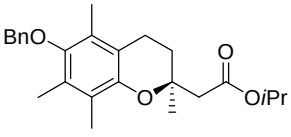
substrate	conditions	product		yield [%]	ee [%]
6	CO-atmosphere MeOH, 60 °C, 2 h		**9a**	89	95
6	CO-atmosphere EtOH CH_2Cl_2, rt, 20 h		**9b**	60	96
6	$Mo(CO)_6$ *i*PrOH, 60 °C, 24 h		**9c**	74	96
6	CO-atmosphere R-BnOH CH_2Cl_2, 50 °C, 20 h		**9da** R=H **9db** R=*m*-OMe **9dc** R=*o*-OMe	52 65 76	95 96 96
8	CO-atmosphere MeOH, rt, 2 h		**10a**	78	94
8	CO-atmosphere EtOH, 60 °C, 48 h		**10b**	56	90
8	CO-atmosphere *i*PrOH, 60 °C, 72 h		**10c**	45	93

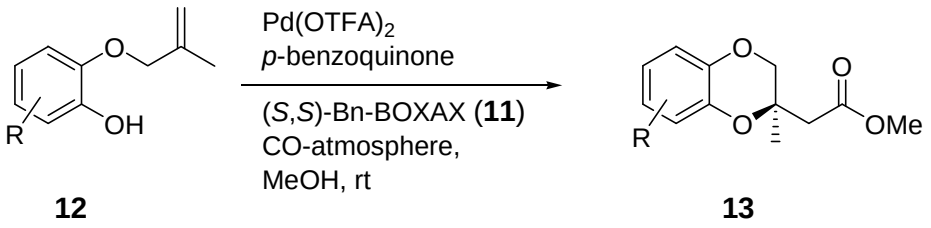
Table 1. Domino-Wacker-carbonylation reaction of alkenes **6** and **8** according to scheme 4.

The reaction conditions were optimized for the transformation of **6** with methanol to give **9a** using palladium(II)trifluoracetate as palladium source, *p*-benzoquinone as reoxidant and the chiral BOXAX-ligand **11**[7] under a CO-atmosphere at ambient pressure. These conditions were then also used for the preparation of esters **9b-da** and **10a-c**. In addition also substituted benzylic alcohols were employed as nucleophiles under the standard conditions providing the benzylic esters **9db** and **9dc** in 65% and 76% yield, respectively, and 96% ee.

In some cases better results were obtained if the reaction was performed in dichloromethane with only one equivalent of the corresponding alcohol. This procedure has the advantage that also precious alcohols can be used. Thus, ethyl ester **9b** was obtained in 60% yield and 96% ee and benzylic ester **9da** in 52% yield and 95% ee, respectively. Interestingly, the CO-source can also be of importance; while the use of a CO-atmosphere at ambient pressure in the domino-reaction of **6** in the presence of isopropanol provided **9c** in 41% yield with 93% ee, employing molybdenum hexacarbonyl as CO-source the *iso*-propyl ester **9c** could be obtained in 74% with 96% ee. The domino reactions of benzyl protected phenol **8** with aliphatic alcohols in the presence of palladium(II)trifluoroacetate, *p*-benzoquinone and the chiral BOXAX-ligand **11** under a CO-atmosphere gave similar results as the reaction of **6** providing the esters **10a-c** with 45–78% yield and ee-values of >90%.

In order to extend the scope of this type of reaction, different monoallyl ethers such as **12**, which are available from the corresponding catechol derivatives,[8] were employed in the enantioselective domino-Wacker-carbonylation reaction (Scheme 5) to give the dioxins **13** in good yields and excellent enantioselectivities. The substituents at the aromatic moiety have some influence on the reactivity, yields and selectivity, however, the effects are not very pronounced (Table 2). In the case of the non-substituted allyl phenyl ether **12a** the methyl ester **13a** was provided in 67% yield and 95% ee after a reaction time of 6 h at 25 °C. Reaction of the methoxy-substituted compounds **12b** and **12c** under the same conditions yielded the corresponding methyl esters **13b** and **13c** in 86% yield and 98% ee as well as 98% yield and 99% ee, respectively.

The methyl- and *tert*-butyl-substituted derivatives **12da**/**12db** and **12ea**/**12eb** were employed as 1.4:1 and 1:1 regioisomeric mixture since chromatographic separation was not possible and provided **13da**/**13db** and **13ea**/**13eb** in both excellent yields and enantioselectivities after an extended reaction time of 15 h at room temperature. The allyl phenyl ether **12f** containing a *tert*-butyl group in the ortho position to the reacting phenolic hydroxyl group does not react under the given conditions. This is probably due to a strong steric hindrance caused by the adjacent *tert*-butyl group.



Scheme 5. Enantioselective domino reactions of alkenes **12** with methanol.

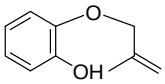
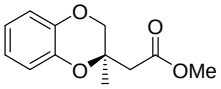
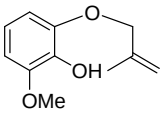
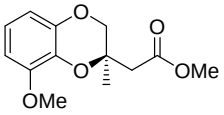
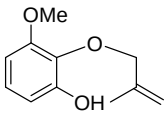
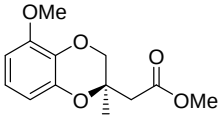
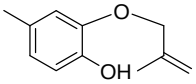
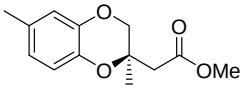
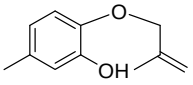
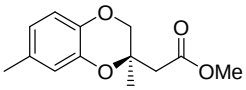
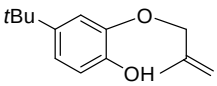
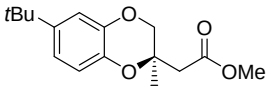
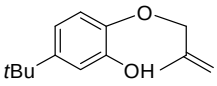
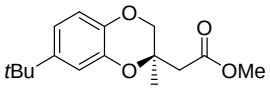
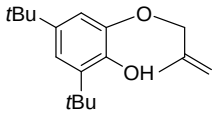
substrate		product		yield [%]	ee [%]
	**12a**		**13a**	67	95
	**12b**		**13b**	86	98
	**12c**		**13c**	98	99
	**12da**		**13da**	99[a]	98
	**12db**		**13db**		
	**12ea**		**13ea**	97[a]	99
	**12eb**		**13eb**		
	**12f**	no reaction	–	–	–

Table 2. Domino-Wacker-carbonylation reaction of allyl phenyl ethers **12**.

[a] combined yield of both regioisomers.

CONCLUSION

We have developed a highly efficient and enantioselective access to chromans and substituted 2,3-dihydrobenzo[1,4]dioxins using a novel enantioselective domino-Wacker-carbonylation reaction. The starting materials are easily accessible and the enantioselectivities of the products range from 90 to 99% ee using a CO-atmosphere in the presence of $Pd(OTFA)_2$, *p*-benzoquinone as reoxidant and a chiral BOXAX ligand **11**.

EXPERIMENTAL

General: All reactions were performed under argon in flame-dried flasks or in high pressure flasks. All solvents were dried and distilled prior to use by usual 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 GmbH & Co. KG) and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Vanillin in methanolic sulphuric acid was used as staining reagent for TLC. UV spectra were taken in CH_3CN with a Perkin-Elmer Lambda 2 spectrometer. IR spectra were recorded as films with a Bruker IFS 25 spectrometer. ^1H and ^{13}C NMR spectra were recorded with Mercury-200, Unity 300, Inova 500 or Unity Inova-600 (Varian) spectrometers. Chemical shifts are reported in δ (ppm) with tetramethylsilane (TMS) as internal standard. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured with a Varian MAT 311A (low resolution) and with a MAT 731 (high resolution) instrument. Elemental analysis: Mikroanalytisches Labor, Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen.

General Procedure for the domino-Wacker-carbonylation reaction under a CO-atmosphere: A mixture of palladium trifluoroacetate (0.0214 mmol), (*S*,*S*)-Bn-BOXAX (**11**) (0.0856 mmol), *p*-benzoquinone (0.855 mmol), the phenol (0.214 mmol) and the alcohol (1.5 mL or 30 eq. in CH_2Cl_2 (1.5 mL)) was stirred under a CO-atmosphere, which was induced by a balloon filled with CO-gas. At the end of the reaction (TLC-control) the mixture was treated with 1N HCl (5 mL) and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with 1N NaOH solution (3 × 5 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/Et_2O).

2-Methoxy-2,5,7,8-tetramethylchroman-6-ol (14): Concentrated sulphuric acid (0.5 mL) and methyl vinyl ketone (29.5 g, 400 mmol) were added dropwise to a degassed and ice cooled solution of trimethyl *p*-hydroquinone (**7**) (30.4 g, 200 mmol) and trimethyl orthoformate (27.0 g, 254 mmol) in MeOH (120

mL) and stirred for 48 h at rt. The suspension was then diluted with Et_2O (500 mL), washed with brine (500 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from MeOH to yield **14** (44.2 g, 187 mmol, 94%) as a white solid. Mp: 156 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, 2-CH_3); 1.72–1.84 (m, 2 H, 3-H_2), 2.12 (s, 3 H, 8-CH_3), 2.16 (s, 6 H, 5-CH_3, 7-CH_3), 2.48–2.67 (m, 2 H, 4-H_2), 3.18 (s, 3 H, OCH_3), 4.33 (s, 1 H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.18, 11.58, 12.15 (5-CH_3, 7-CH_3, 8-CH_3), 19.94 (C-4), 23.08 (2-CH_3), 31.86 (C-3), 48.77 (OCH_3), 97.17 (C-2), 118.4, 118.7, 121.1, 122.1 (C-4a, C-5, C-7, C-8), 143.7, 145.4 (C-6, C-1a); IR (KBr): $\tilde{\nu}$ = 3452 cm^{-1}, 2986, 2946, 2882, 2836, 1638, 1546; UV (CH_3CN): λ_{max} (lg ε) = 291 nm (3.484), 199 (4.658); MS (70 eV, EI): *m/z* (%) = 236 (46) $[M]^+$, 221 (3) $[M - CH_3]^+$, 205 (38) $[M - OCH_3]^+$, 189 (13) $[M - C_2H_7O]^+$, 164 (100) $[M - C_4H_8O]^+$; HRMS: calcd for $C_{14}H_{20}O_3$: 236.1412; confirmed.

2,6-Dimethoxy-2,5,7,8-tetramethylchroman (15): To a suspension of alcohol **14** (28.8 g, 122 mmol) and K_2CO_3 (33.7 g, 244 mmol) in degassed acetone (500 mL) dimethyl sulfate (19.9 g, 134 mmol) was added and the mixture stirred for 66 h under reflux. After cooling to rt, water (1000 mL) was added and extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with brine (1000 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the methyl ester **15** (29.3 g, 117 mmol, 96%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, 2-CH_3), 1.66–1.83 (m, 2 H, 3-H_2), 2.08, 2.10, 2.13 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.42–2.67 (m, 2 H, 4-H_2), 3.16 (s, 3 H, 2-OCH_3), 3.57 (s, 3 H, 6-OCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.60, 11.62, 12.51 (5-CH_3, 7-CH_3, 8-CH_3), 19.85 (C-4), 23.12 (2-CH_3), 31.80 (C-3), 48.81 (2-OCH_3), 60.28 (6-OCH_3), 97.29 (C-2), 118.8, 122.5, 125.7, 127.6 (C-4a, C-5, C-7, C-8), 146.0 (C-1a), 150.2 (C-6); IR (film): $\tilde{\nu}$ = 2987 cm^{-1}, 2937, 2828, 1459, 1264, 1057, 1015; UV (CH_3CN): λ_{max} (lg ε) = 284 nm (3.289), 201 (4.645); MS (DCI-NH_3): *m/z* (%) = 518 (1) $[2M + NH_4]^+$, 268 (100) $[M - NH_4]^+$; HRMS: calcd for $C_{15}H_{22}O_3$: 250.1568; confirmed.

6-Methoxy-2,5,7,8-tetramethylchroman-2-ol (16): Acetal **15** (31.1 g, 125 mmol) was dissolved in acetone (120 mL) and 0.1 N HCl aq. (30 mL) was added. During 3 h the solvent was destilled by up to 80 °C. Afterwards the acetone was replaced and destilled again. Afterwards the residue was dissolved in Et_2O (200 mL), washed with water (150 mL) and 2 N HCl aq. (100 mL) and the combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. After recrystallization from Et_2O, alcohol **16** (26.0 g, 110 mmol, 88%) was obtained as colourless crystals. Mp: 109 °C; ^{1}H NMR (200 MHz, $CDCl_3$): (Oxoform) δ = 3.63 (s, 3 H, OCH_3), 2.78–2.64 (m, 2 H, 4-H_2), 2.50 (s, 1 H, OH), 2.20, 2.15, 2.10 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 1.92–1.79 (m, 2 H, 3-H_2), 1.65 (s, 3 H, 1-H_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): (Oxoform) δ = 212.3 (C=O), 150.2 (C-5), 148.6 (C-2), 128.6, 126.2, 124.1, 123.5 (C-1, C-3, C-4, C-6), 60.15 (OCH_3), 43.87 (C-3), 29.54 (C-1), 19.93 (2-CH_3), 12.67, 12.04, 12.01 (5-CH_3, 7-CH_3,

8-CH_3); IR (KBr): $\tilde{\nu}$ = 3440 cm^{-1}, 2988, 2936, 2836, 1458, 1406, 1372, 1252, 1084; UV (CH_3CN): λ_{max} (lg ε) = 285 nm (3.339), 202 (4.661); MS (DCI-NH_3): *m/z* (%) = 490 (10) $[2M + NH_4]^+$, 254 (100) $[M + NH_4]^+$; HRMS: calcd for $C_{14}H_{20}O_3$: 236.1412; confirmed.

Acetic acid 4-methoxy-2,3,5-trimethyl-6-(3-oxobutyl)phenyl ester (17): Chromanol **16** (11.0 g, 46.6 mmol) in pyridine (80 mL) was treated with acetic anhydride (17.5 g, 172 mmol), stirred for 20 h at rt and then for 4 h at 70 °C. Afterwards the solvent was removed and the resulting resin crystallized from MeOH at –17 °C to yield the ester **17** (12.3 g, 44.2 mmol, 95%) as a white solid. Mp: 73 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (s, 3 H, 4'-H_3), 2.15, 2.20, 2.22 (3 × s, 9 H, 2-CH_3, 3-CH_3, 5-CH_3), 2.32 (s, 3 H, 2''-H_3), 2.51–2.83 (m, 4 H, 1'-H_2, 2'-H_2), 3.65 (s, 3 H, OCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 12.08, 12.75, 13.11 (2-CH_3, 3-CH_3, 5-CH_3), 20.55 (C-2''), 21.53 (C-1'), 29.86 (C-4'), 42.87 (C-2'), 60.02 (OCH_3), 127.3, 127.4, 128.7, 129.8 (C-2, C-3, C-5, C-6), 143.8 (C-1), 154.6 (C-4), 169.7 (C-1''), 207.7 (C-3'); IR (KBr): $\tilde{\nu}$ = 2982 cm^{-1}, 2950, 2832, 1750, 1216; UV (CH_3CN): λ_{max} (lg ε) = 315 nm (3.364), 264 (4.047), 200 (4.463); MS (70 eV, EI): *m/z* (%) = 278 (15) $[M]^+$, 236 (100) $[M - C_2H_2O]^+$, 221 (15) $[M - C_2H_2O - CH_3]^+$; elemental analysis calcd (%) for $C_{16}H_{22}O_4$ (278.3): C 69.03, H 7.97; found: C 69.15, H 7.90.

Acetic acid 4-methoxy-2,3,5-trimethyl-6-(3-methylbut-3-enyl)phenyl ester (18): Ketone **17** (3.41 g, 12.3 mmol) was added dopwise to an ice cooled solution of Lombardo reagent (153.2 mL, 61.28 mmol) in CH_2Cl_2 (35 mL). The resulting suspension was then stirred for 30 min at 0 °C and 1 h at rt, before adding sat. $NaHCO_3$ aq. (400 mL). The precipitate was filtered over celite and washed with CH_2Cl_2 (3 × 300 mL). Water (700 mL) was added, the combined organic layers dried over Na_2SO_4 and the solvent was concentrated under reduced pressure. Column chromatography on silica (pentane/EtOAc 9:1) afforded alkene **18** (3.12 g, 11.3 mmol, 92%) as a white solid. Mp: 49 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.79 (s, 3 H, 3'-CH_3), 2.01, 2.20, 2.24 (3 x s, 9 H, 2-CH_3, 3-CH_3, 5-CH_3), 1.90–2.20 (m, 2 H, 2'-H_2), 2.33 (s, 3 H, 2''-H_3), 2.40–2.80 (m, 2 H, 1'-H_2), 3.66 (s, 3 H, OCH_3), 4.74 (s, 2 H, 4'-H_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.96, 12.73, 13.10 (2-CH_3, 3-CH_3, 5-CH_3), 20.58 (C-2''), 22.39 (3'-CH_3), 26.79 (C-1'), 37.35 (C-2'), 60.03 (OCH_3), 109.9 (C-4'), 127.3 (C-5), 127.4 (C-3), 128.3 (C-2), 130.8 (C-6), 143.8 (C-1), 145.7 (C-3'), 154.5 (C-4), 169.3 (C-1''); IR (KBr): $\tilde{\nu}$ = 3079 cm^{-1}, 2968, 2942, 1756, 1646, 1459, 1201; UV (CH_3CN): λ_{max} (lg ε) = 269 nm (0.025), 200 (5.085); MS (70 eV, EI): *m/z* (%) = 276 (70) $[M]^+$, 234 (100) $[M - Ac]^+$, 219 (20) $[M - Ac - CH_3]^+$; HRMS: calcd for $C_{17}H_{24}O_3$: 276.1725; confirmed, elemental analysis calcd (%): C 73.88, H 8.75; found: C 73.62, H 8.49.

4-Methoxy-2,3,5-trimethyl-6-(3-methyl-but-3-enyl)phenol (19): The acetate **18** (3.04 g, 11.0 mmol)

was dissolved in MeOH (150 mL), 5.4 M NaOMe solution (0.20 mL, 1.10 mmol) was added and the resulting mixture stirred for 2 h at rt. Afterwards the pH value was adjusted to 6–7 by adding Amberlite® IR-120. Removal of the solvent in vacuum and column chromatography on silica (pentane/Et_2O 9:1) yielded phenol **19** (2.19 g, 9.36 mmol, 85%) as a white solid. Mp: 91 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.81 (s, 3 H, 3'-CH_3), 2.23, 2.20, 2.14 (3 × s, 9 H, 2-CH_3, 3-CH_3, 5-CH_3), 2.20–2.10 (m, 2 H, 2'-H_2), 2.80–2.70 (m, 2 H, 1'-H_2), 3.63 (s, 3 H, OCH_3), 4.50 (s, 1 H, OH), 4.79 (s, 2 H, 4'-H_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 12.71, 12.14, 11.92 (2-CH_3, 3-CH_3, 5-CH_3), 22.68 (3'-CH_3), 25.96 (C-1'), 37.07 (C-2'), 60.29 (OCH_3), 110.0 (C-4'), 120.3 (C-5), 124.9 (C-3), 126.8 (C-2), 127.6 (C-6), 146.3 (C-3'), 147.8 (C-1), 150.5 (C-4); IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1}, 3070, 2985, 2941, 2827, 1647, 1005; UV (CH_3CN): λ_{max} (lg ε) = 285 nm (0.218), 201 (4.803); MS (DCI-NH_3): *m/z* (%) = 253 (95) $[M - NH_4]^+$, 235 (100) $[M + H]^+$; HRMS: calcd for $C_{15}H_{22}O_2$: 234.1620; confirmed, elemental analysis calcd (%): C 76.99, H 9.46; found: C 77.38, H 9.57.

(2*S*)-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid methyl ester (9a): According to the general procedure phenol **6** (50 mg, 0.21 mmol) was reacted in MeOH (1.5 mL) for 2 h at 60 °C. After work-up and column chromatography on silica methyl ester **9a** (56 mg, 0.19 mmol, 89%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99.5:0.5, Flow: 0.8 mL / min, t_R = 11.83 min ((+)-**9a**), t_R = 15.48 min ((–)-**9a**), ee = 95%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, 2-CH_3), 1.87 (dt, *J* = 13.7, 6.7 Hz, 1 H, 3-H_a), 2.01 (dt, *J* = 13.7, 6.7 Hz, 1 H, 3-H_b), 2.05, 2.13, 2.17 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.58 (t, *J* = 6.7 Hz, 2 H, 4-H_2), 2.61 (s, 2 H, 1'-H_2), 3.61 (s, 3 H, 6-OCH_3), 3.68 (s, 3 H, 1-OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.65, 12.51 (5-CH_3, 7-CH_3, 8-CH_3), 20.46 (C-4), 24.71 (2-CH_3), 31.10 (C-3), 43.76 (C-1'), 51.53 ($CO_2\underline{C}H_3$), 60.35 (6-OCH_3), 73.39 (C-2), 117.1 (C-4a), 123.1 (C-8), 125.8 (C-5), 128.0 (C-7), 146.9 (C-8a), 149.8 (C-6), 171.1 (C=O); IR (Film): $\tilde{\nu}$ = 2935 cm^{-1}, 1739, 1457, 1254, 1091, 1042; UV (CH_3CN): λ_{max} (lg ε) = 202.0 nm (4.694), 286.5 (3.351); MS (ESI): *m/z* (%) = 607 (17) $[2M + Na]^+$, 315 (51) $[M + Na]^+$; HRMS: calcd for $[C_{17}H_{24}O_4 + H]^+$: 293.1747; confirmed.

(2*S*)-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid ethyl ester (9b): According to the general procedure phenol **6** (50 mg, 0.21 mmol) was reacted with EtOH (290 mg, 6.3 mmol) in CH_2Cl_2 (1.5 mL) for 20 h at rt. After work-up and column chromatography on silica ethyl ester **9b** (39 mg, 0.13 mmol, 60%) was provided as a yellow oil. HPLC (Chiralcel IB): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99.5:0.5, Flow: 0.8 mL / min, t_R = 8.15 min ((+)-**9b**), t_R = 8.71 min ((–)-**9b**), ee = 96%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.40 (s, 3 H, 2-CH_3), 1.88 (m_c, 1 H, 3-H_a), 2.03 (m_c, 1 H, 3-H_b), 2.06, 2.12, 2.16 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.54–2.63 (m,

4 H, 1'-H_2, 4-H_2), 3.61 (s, 3 H, OCH_3), 4.13 (q, J = 7.2 Hz, 2 H, $OC\underline{H}_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.66, 11.69, 12.52 (5-CH_3, 7-CH_3, 8-CH_3), 14.21 ($OCH_2\underline{C}H_3$), 20.48 (C-4), 24.69 (2-CH_3), 31.13 (C-3), 44.09 (C-1'), 60.37 ($O\underline{C}H_2CH_3$), 60.38 (OCH_3), 73.46 (C-2), 117.2 (C-4a), 123.1 (C-8), 125.8 (C-5), 128.0 (C-7), 147.0 (C-8a), 149.8 (C-6), 170.7 (C=O); IR (Film): $\tilde{\nu}$ = 2934 cm^{-1}, 1734, 1457, 1254, 1091; UV (CH_3CN): λ_{max} (lg ε) = 202.0 nm (4.651), 286.5 (3.347); MS (ESI): *m/z* (%) = 635 (34) $[2M + Na]^+$, 329 (100) $[M + Na]^+$; HRMS: calcd for $[C_{18}H_{26}O_4 + H]^+$: 307.1094; confirmed.

(2*S*)-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid *iso*-propyl ester (9c): A mixture of palladium trifluoroacetate (7.1 mg, 0.021 mmol) and (*S*,*S*)-Bn-BOXAX **11** (49 mg, 0.086 mmol) in *iso*-propanol (1.5 mL) was stirred for 30 min at 60 °C, then treated with *p*-benzoquinone (96 mg, 0.86 mmol) and stirred for a further 10 min. $Mo(CO)_6$ (29 mg, 0.11 mmol) and alkene **6** (50 mg, 0.21 mmol) were added and the resulting mixture stirred at 60 °C for 24 h. At the end of the reaction the mixture was treated with 1N HCl (5 mL) and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with 1N NaOH solution (3 × 5 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/diethyl ether) to povide the *iso*-propyl ester **9c** (50.4 mg, 74%) as a yellow oil. HPLC (Chiralcel IB): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99.7:0.3, Flow: 0.8 mL / min, t_R = 14.91 min ((+)-**9c**), t_R = 15.72 min ((–)-**9c**), ee = 96%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22, 1.23 (2 × d, J = 6.2 Hz, 6 H, $CH(C\underline{H}_3)_2$), 1.40 (s, 3 H, 2-CH_3), 1.82 (dt, J = 13.4, 6.8 Hz, 1 H, 3-H_a), 2.01 (dt, J = 13.4, 6.8 Hz, 1 H, 3-H_b), 2.06, 2.12, 2.16 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.51–2.62 (m, 4 H, 1'-H_2, 4-H_2), 3.61 (s, 3 H, OCH_3), 5.01 (sept, J = 6.2 Hz, 2 H, $C\underline{H}(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.66, 11.74, 12.52 (5-CH_3, 7-CH_3, 8-CH_3), 20.50 (C-4), 21.83 ($CH(\underline{C}H_3)_2$), 24.67 (2-CH_3), 31.15 (C-3), 44.44 (C-1'), 60.37 (OCH_3), 67.70 ($\underline{C}H(CH_3)_2$), 73.53 (C-2), 117.2 (C-4a), 123.1 (C-8), 125.8 (C-5), 128.0 (C-7), 147.0 (C-8a), 149.8 (C-6), 170.2 (C=O); IR (Film): $\tilde{\nu}$ = 2935 cm^{-1}, 1730, 1457, 1254, 1091; UV (CH_3CN): λ_{max} (lg ε) = 202.5 nm (4.656), 287.0 (3.335); MS (ESI): *m/z* (%) = 663 (57) $[2M + Na]^+$, 343 (100) $[M + Na]^+$; HRMS: calcd for $[C_{19}H_{28}O_4 + H]^+$: 321.2064; confirmed.

(2*S*)-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid benzylic ester (9da): According to the general procedure phenol **6** (50 mg, 0.21 mmol) was reacted with benzylic alcohol (680 mg, 6.3 mmol) in CH_2Cl_2 (1.5 mL) for 20 h at 50 °C. After work-up and column chromatography on silica benzylic ester **9da** (40 mg, 0.11 mmol, 52%) was provided as a yellow oil. HPLC (Chiralcel IB): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99:1, Flow: 0.8 mL / min t_R = 7.81 min ((+)-**9da**), t_R = 8.72 min ((–)-**9da**), ee = 95%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, 2-CH_3), 1.87 (dt, J = 13.7, 6.9 Hz, 1 H, 3-H_a), 1.97 (dt, J = 13.7, 6.9 Hz, 1 H, 3-H_b), 2.02, 2.13, 2.16 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.60

(t, J = 6.9 Hz, 2 H, 4-H_2), 2.66 (s, 2 H, 1'-H_2), 3.62 (s, 3 H, OCH_3), 5.12 (s, 2 H, CH_2Ph), 7.30–7.38 (m_c, 5 H, 5 × Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.62, 11.65, 12.48 (5-CH_3, 7-CH_3, 8-CH_3), 20.43 (C-4), 24.76 (2-CH_3), 31.10 (C-3), 43.90 (C-1'), 60.32 (OCH_3), 66.25 (CH_2Ph), 73.45 (C-2), 117.1 (C-4a), 123.1 (C-8), 125.8 (C-5), 128.0 (C-7), 128.2, 128.5 (C-5, 5 × Ph-CH), 135.8 (Ph-C), 146.9 (C-8a), 149.8 (C-6), 170.5 (C=O); IR (Film): $\tilde{\nu}$ = 2934 cm^{-1}, 1735, 1456, 1090, 698; UV (CH_3CN): λ_{max} (lg ε) = 202.5 nm (4.716), 287.0 (3.342); MS (ESI): *m/z* (%) = 635 (34) $[2M + Na]^+$, 329 (100) $[M + Na]^+$; HRMS: calcd for $[C_{18}H_{26}O_4 + H]^+$: 307.1094; confirmed.

(2*S*)-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid methyl ester (10a): According to the general procedure phenol **8** (66 mg, 0.21 mmol) was reacted in MeOH (1.5 mL) for 5 h at rt. After work-up and column chromatography on silica methyl ester **10a** (61 mg, 0.17 mmol, 78%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99:1, Flow: 0.8 mL / min, t_R = 16.21 min ((+)-**10a**), t_R = 22.32 min ((–)-**10a**), ee = 94%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 3 H, 2-CH_3), 1.90 (dt, J = 13.7, 6.8 Hz, 1 H, 3-H_a), 2.04 (dt, J = 13.7, 6.8 Hz, 1 H, 3-H_b), 2.08, 2.17, 2.22 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.60 (t, J = 6.7 Hz, 2 H, 4-H_2), 2.63 (s, 2 H, 1'-H_2), 3.69 (s, 3 H, OCH_3), 4.69 (s, 2 H, CH_2Ph), 7.31–7.52 (m, 5 H, 5 × Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.72, 11.96, 12.83 (5-CH_3, 7-CH_3, 8-CH_3), 20.51 (C-4), 24.71 (2-CH_3), 31.11 (C-3), 43.78 (C-1'), 51.55 (OCH_3), 73.42 (CH_2Ph), 74.67 (C-2), 117.2 (C-4a), 123.1 (C-8), 126.1 (C-5), 127.7, 127.8 (3 × Ph-CH), 128.2 (C-7), 128.4 (2 × Ph-CH), 137.9 (Ph-C), 147.1 (C-6), 148.5 (C-8a), 171.2 (C=O); IR (Film): $\tilde{\nu}$ = 2933 cm^{-1}, 1738, 1455, 1254, 1090; UV (CH_3CN): λ_{max} (lg ε) = 202.5 nm (4.733), 281.0 (3.268), 286.5 (3.319); MS (ESI): *m/z* (%) = 759 (53) $[2M + Na]^+$, 391 (100) $[M + Na]^+$; HRMS: calcd for $[C_{23}H_{28}O_4 + H]^+$: 369.2060; confirmed.

(2*S*)-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid ethyl ester (10b): According to the general procedure phenol **8** (66 mg, 0.21 mmol) was reacted in EtOH (1.5 mL) for 48 h at 60 °C. After work-up and column chromatography on silica ethyl ester **10b** (46 mg, 0.12 mmol, 56%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99:1, Flow: 0.8 mL / min, t_R = 14.68 min ((+)-**10b**), t_R = 17.19 min ((–)-**10b**), ee = 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.43 (s, 3 H, 2-CH_3), 1.90 (dt, J = 13.7, 6.8 Hz, 1 H, 3-H_a), 2.04 (dt, J = 13.7, 6.8 Hz, 1 H, 3-H_b), 2.08, 2.19, 2.21 (3 x s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.60 (s, 2 H, 1'-H_2), 2.61 (t, J = 6.8 Hz, 2 H, 4-H_2), 4.13 (q, J = 7.1 Hz, 2 H, C$H_2$$CH_3$), 4.68 (s, 2 H, C$H_2$Ph), 7.27–7.55 (m, 5 H, Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.72, 11.97, 12.84 (5-CH_3, 7-CH_3, 8-CH_3), 14.21 ($CH_2$$CH_3$), 20.53 (C-4), 24.71 (2-CH_3), 31.16 (C-3), 44.10 (C-1'), 60.37 (C$H_2$$CH_3$), 73.49 (C$H_2$Ph), 74.69 (C-2), 117.2 (C-4a), 123.1 (C-8), 126.1 (C-5), 127.7, 127.8 (3 × Ph-CH), 128.2 (C-7), 128.5 (2 × Ph-CH), 137.9

(Ph-C), 147.1 (C-6), 148.5 (C-8a), 170.7 (C=O); IR (Film): $\tilde{\nu}$ = 2931 cm^{-1}, 1732, 1455, 1254, 1088; UV (CH_3CN): λ_{max} (lg ε) = 202.5 nm (4.814), 280.5 (3.312), 286.5 (3.357); MS (70 eV, EI): *m/z* (%) = 382 (17) $[M]^+$, 191 (100) $[M - CH_2Ph]^+$, 245 $[M - 2CH_3 - CH_2Ph]^+$; HRMS: calcd for $[C_{24}H_{30}O_4 + H]^+$: 383.2217; confirmed.

(2*S*)-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid *iso*-propyl ester (10c): According to the general procedure phenol **8** (66 mg, 0.21 mmol) was reacted in *iso*-propanol (1.5 mL) for 72 h at 60 °C. After work-up and column chromatography on silica *iso*-propyl ester **10c** (46 mg, 0.12 mmol, 56%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99.2:0.8, Flow: 0.8 mL / min, t_R = 12.30 min ((+)-**10c**), t_R = 13.28 min ((–)-**10c**), ee = 93%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.2 Hz, 6 H, $CH(C\underline{H}_3)_2$), 1.43 (s, 3 H, 2-CH_3), 1.98 (dt, *J* = 13.8, 6.7 Hz, 1 H, 3-H_a), 2.04 (dt, *J* = 13.8, 6.7 Hz, 1 H, 3-H_b), 2.09, 2.17, 2.21 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.58–2.65 (m, 4 H, 1'-H_2, 4-H_2), 4.69 (s, 2 H, $C\underline{H}_2$Ph), 5.03 (sept, *J* = 6.2 Hz, 1 H, $C\underline{H}(CH_3)_2$), 7.27–7.51 (m, 5 H, 5 × Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.80, 11.97, 12.83 (5-CH_3, 7-CH_3, 8-CH_3), 20.53 (C-4), 21.83 ($CH(\underline{C}H_3)_2$) 24.68 (2-CH_3), 31.17 (C-3), 44.43 (C-1'), 67.71 ($\underline{C}H(CH_3)_2$), 73.56 ($\underline{C}H_2$Ph), 74.68 (C-2), 117.3 (C-4a), 123.1 (C-8), 126.0 (C-5), 127.7, 127.8 (3 × Ph-$\underline{C}$H), 128.2 (C-7), 128.5 (2 × Ph-$\underline{C}$H), 137.9 (Ph-$\underline{C}$), 147.2 (C-6), 148.5 (C-8a), 170.7 (C=O); IR (Film): $\tilde{\nu}$ = 2931 cm^{-1}, 1729, 1455, 1373, 1254, 1089; UV (CH_3CN): λ_{max} (lg ε) = 202.5 nm (4.752), 286.0 (3.335); MS (70 eV, EI): *m/z* (%) = 396 (18) $[M]^+$, 305 (92) $[M - CH_2Ph]^+$, 245 $[M - 4CH_3 - CH_2Ph]^+$; HRMS: calcd for $[C_{25}H_{32}O_4 + H]^+$: 397.2373; confirmed.

(2*S*)-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid-3-methoxybenzylic ester (9db): According to the general procedure phenol **6** (50 mg, 0.21 mmol) was reacted with 3-methoxybenzylic alcohol (887 mg, 6.4 mmol) in CH_2Cl_2 (1.5 mL) for 24 h at 50 °C. After work-up and column chromatography on silica the 3-methoxy benzylic ester **9db** (55 mg, 0.14 mmol, 65%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: 290 nm, Eluent: *n*-hexane / *iso*-propanol 99:1, Flow: 0.8 mL / min, t_R = 18.75 min ((+)-**9db**), t_R = 26.03 min ((–)-**9db**), ee = 96%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, 2-CH_3), 1.87 (dt, *J* = 13.7, 7.0 Hz, 1 H, 3-H_a), 2.04 (dt, *J* = 13.7, 7.0 Hz, 1 H, 3-H_b), 2.01, 2.12, 2.15 (3 × s, 9 H, 5-CH_3 7-CH_3 8-CH_3), 2.59 (t, *J* = 7.0 Hz, 2 H, 4-H_2), 2.66 (s, 2 H, 1'-H_2), 3.61 (s, 3 H, 6-OCH_3), 3.78 (s, 3 H, 3"-OCH_3), 5.09 (s, 2 H, OCH_2), 6.83–6.92 (m, 3 H, 2"-H, 4"-H, 6"-H), 7.22–7.28 (m, 1 H, 5"-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.64, 11.67, 12.50 (5-CH_3, 7-CH_3, 8-CH_3), 20.48 (C-4), 24.82 (2-CH_3), 31.16 (C-3), 43.98 (C-1'), 55.19 (3"-OCH_3), 60.33 (6-OCH_3), 66.15 (OCH_2), 73.49 (C-2), 113.6, 113.7 (C-2", C-4"), 117.1 (C-4a), 120.34 (C-6"), 123.1 (C-8), 125.8 (C-5), 128.0 (C-7), 129.6 (C-5"), 137.4 (C-1"), 146.9 (C-8a), 149.9 (C-6), 159.7 (C-3"), 170.4 (C=O); IR (Film):

$\tilde{\nu}$ = 2936 cm^{-1}, 1735, 1588, 1457, 1090, 912, 734; UV (CH_3CN): λ_{max} (lg ε) = 197.5 nm (4.879), 199.0 (4.874), 280.0 (3.537); MS (70 eV, EI): *m/z* (%) = 398.3 (98) $[M]^+$, 179.2 (24) $[C_{10}H_{11}O_3]^+$, 121.1 (80) $[CH_2C_6H_4OCH_3]^+$; HRMS: calcd for $[C_{24}H_{30}O_5 + Na]^+$: 421.1987; confirmed.

(2*S*)-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid-2-methoxybenzylic ester (9dc): According to the general procedure phenol **7** (50 mg, 0.21 mmol) was reacted with 2-methoxybenzylic alcohol (887 mg, 6.4 mmol) in CH_2Cl_2 (1.5 mL) for 24 h at 50 °C. After work-up and column chromatography on silica the 2-methoxy benzylic ester **9dc** (65 mg, 0.16 mmol, 76%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: 290 nm, Eluent: *n*-hexane / *iso*-propanol 99.5:0.5, Flow: 0.8 mL / min, t_R = 39.43 min ((+)-**9dc**), t_R = 43.33 min ((–)-**9dc**), ee = 96%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, 2-CH_3), 1.87 (dt, *J* = 13.6, 6.8 Hz, 1 H, 3-H_a), 2.02 (dt, *J* = 13.6, 6.8 Hz, 1 H, 3-H_b), 2.01, 2.13, 2.16 (3 × s, 9 H, 5-CH_3, 7-CH_3, 8-CH_3), 2.61 (m_c, 2 H, 4-H_2), 2.65 (m_c, 1 H, 1'-H_a), 2.66 (m_c, 1 H, 1'-H_b), 3.61 (s, 3 H, 6-OCH_3), 3.81 (s, 3 H, 2"-OCH_3), 5.17 (d, *J* = 1.2 Hz, 2 H, OCH_2), 6.87–6.97 (m, 2 H, 2 ×Ph-H), 7.24–7.33 (m, 2 H, 2 × Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.62, 12.48 (5-CH_3, 7-CH_3, 8-CH_3), 20.46 (C-4), 24.79 (2-CH_3), 30.98 (C-3), 43.93 (C-1'), 55.24 (2"-OCH_3), 60.33 (6-OCH_3), 61.84 (OCH_2), 73.52 (C-2), 110.3 (C-3"), 117.2 (C-4a), 120.3 (C-5"), 123.1 (C-8), 124.0 (C-5), 125.7 (C-7), 127.9 (C-1"), 129.6 (C-6"), 129.8 (C-4"), 147.0 (C-8a), 149.7 (C-6), 157.4 (C-2"), 170.6 (C=O); IR (Film): $\tilde{\nu}$ = 2936 cm^{-1}, 1733, 1461, 1253, 1090; UV (CH_3CN): λ_{max} (lg ε) = 197.0 nm (4.873), 277.5 (3.559); MS (ESI): *m/z* (%) = 819.4 (100) $[2M+Na]^+$, 421.2 (65) $[M+Na]^+$, 399.2 (32) $[M+H]^+$; HRMS: calcd for $[C_{24}H_{30}O_5 + Na]^+$: 421.1987; confirmed.

(2*R*)-(2-Methyl-2,3-dihydrobenzo[1,4]dioxin-2-yl)acetic acid methyl ester (13a): According to the general procedure phenol **12a** (35 mg, 0.21 mmol) was reacted in MeOH (1.5 mL) for 6 h at rt. After work-up and column chromatography on silica methyl ester **13a** (32 mg, 0.15 mmol, 67%) was provided as a colourless oil. HPLC (Chiralcel OD): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99:1, Flow: 0.8 mL / min, t_R = 12.03 min ((+)-**13a**), t_R = 13.96 min ((–)-**13a**), ee = 95%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, 2-CH_3), 2.66 (d, *J* = 15.0 Hz, 1 H, 1'-H_a), 2.75 (d, *J* = 15.0 Hz, 1 H, 1'-H_b), 3.69 (s, 3 H, OCH_3), 3.94 (d, *J* = 11.3 Hz, 1 H, 3-H_a), 4.25 (d, *J* = 11.3 Hz, 1 H, 3-H_b), 6.80–6.92 (m, 4 H, 5-H, 6-H, 7-H, 8-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.38 (2-CH_3), 40.18 (C-1'), 51.77 (OCH_3), 69.48 (C-3), 76.36 (C-2), 117.0, 117.6 (C-5, C-8), 121.2, 122.0 (C-6, C-7), 141.9 (C-4a), 142.1 (C-8a), 170.2 (C=O); IR (Film): $\tilde{\nu}$ = 2926 cm^{-1}, 1742, 1494, 1262, 748; UV (CH_3CN): λ_{max} (lg ε) = 277.5 nm (3.164), 218 (3.559), 200 (2.047); MS (DCI-NH_3): *m/z* (%) = 240 (100) $[M + NH_3]^+$, 294 (22) $[M + NH_3 + NH_4]^+$, 462 $[2M + NH_4]^+$; HRMS: calcd for $[C_{25}H_{32}O_4 + H]^+$: 223.0965; confirmed.

(2*R*)-(8-Methoxy-2-methyl-2,3-dihydrobenzo[1,4]dioxin-2-yl)acetic acid methyl ester (13b):

According to the general procedure phenol **12b** (42 mg, 0.21 mmol) was reacted in MeOH (1.5 mL) for 6 h at rt. After work-up and column chromatography on silica methyl ester **13b** (46 mg, 0.18 mmol, 86%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99:1, Flow: 0.8 mL / min, t_R = 11.79 min ((–)-**13b**), t_R = 29.07 min ((+)-**13b**), ee = 98%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, 2-CH_3), 2.64 (d, *J* = 15.3 Hz, 1 H, 1'-H_a), 2.72 (d, *J* = 15.3 Hz, 1 H, 1'-H_b), 3.65 (s, 3 H, CO_2CH_3), 3.85 (s, 3 H, OCH_3), 3.95 (d, *J* = 11.3 Hz, 1 H, 3-H_a), 4.30 (d, *J* = 11.3 Hz, 1 H, 3-H_b), 6.45–6.50 (m, 2 H, 5-H, 7-H), 6.77 (t, *J* = 8.2 Hz, 1 H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.30 (2-CH_3), 39.95 (C-1'), 51.71 ($CO_2\underline{C}H_3$), 55.99 (OCH_3), 69.99 (C-3), 72.64 (C-2), 103.7 (C-7), 110.3 (C-5), 120.8 (C-6), 131.7 (C-8a), 142.5 (C-4a), 148.8 (C-8), 170.2 (C=O); IR (Film): $\tilde{\nu}$ = 2952 cm^{-1}, 1738, 1598, 1474, 1098, 767; UV (CH_3CN): λ_{max} (lg ε) = 268.5 nm (2.840), 205 (4.655); MS (DCI-NH_3): *m/z* (%) = 253 (8) $[M + H]^+$, 270 (100) $[M + NH_4]^+$, 522 (24) $[2M + NH_4]^+$; HRMS: calcd for $[C_{13}H_{16}O_5 + K]^+$: 291.0631; confirmed.

(2*R*)-(5-Methoxy-2-methyl-2,3-dihydrobenzo[1,4]dioxin-2-yl)acetic acid methyl ester (13c):

According to the general procedure phenol **12c** (42 mg, 0.21 mmol) was reacted in MeOH (1.5 mL) for 6 h at rt. After work-up and column chromatography on silica methyl ester **13c** (53 mg, 0.21 mmol, 98%) was provided as a yellow oil. HPLC (Chiralcel OD): Wavelength: Max. Abs., Eluent: *n*-hexane / *iso*-propanol 99:1, Flow: 0.8 mL / min, t_R = 16.69 min ((–)-**13c**), t_R = 22.32 min ((+)-**13c**), ee = 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H, 2-CH_3), 2.68 (d, *J* = 15.1 Hz, 1 H, 1'-H_a), 2.77 (d, *J* = 15.1 Hz, 1 H, 1'-H_b), 3.67 (s, 3 H, CO_2CH_3), 3.84 (s, 3 H, OCH_3), 3.92 (d, *J* = 11.3 Hz, 1 H, 3-H_a), 4.26 (d, *J* = 11.3 Hz, 1 H, 3-H_b), 6.48, 6.55 (2 × dd, *J* = 8.5, 1.5 Hz, 2 H, 6-H, 8-H), 6.76 (t, *J* = 8.5 Hz, 1 H, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.37 (2-CH_3), 39.95 (C-1'), 51.78 ($CO_2\underline{C}H_3$), 56.19 (OCH_3), 69.60 (C-3), 72.88 (C-2), 104.8 (C-6), 109.8 (C-8), 120.1 (C-7), 131.7 (C-4a), 143.0 (C-8a), 149.3 (C-5), 170.4 (C=O); IR (Film): $\tilde{\nu}$ = 2952 cm^{-1}, 1737, 1597, 1256, 1096, 919, 768; UV (CH_3CN): λ_{max} (lg ε) = 206.0 nm (4.619), 268.5 (2.820); MS (ESI): *m/z* (%) = 526.8 (56) $[2M+Na]^+$, 275.1 (100) $[M+Na]^+$; HRMS: calcd for $[C_{13}H_{16}O_5 + H]^+$: 253.1072; confirmed.

(2*R*)-(2,6-Dimethyl-2,3-dihydrobenzo[1,4]dioxin-2-yl)acetic acid methyl ester and (2*R*)-(2,7-Dimethyl-2,3-dihydrobenzo[1,4]dioxin-2-yl)acetic acid methyl ester (13da and 13db):

According to the general procedure a 1.4:1 mixture of phenols **12da** and **12db** (38 mg, 0.21 mmol) was reacted in MeOH (1.5 mL) for 15 h at rt. After work-up and column chromatography on silica the unseparable regioisomeric methyl esters **13da** and **13db** were obtained as yellow oil (50 mg, 0.21 mmol, 99%). HPLC (Chiralcel OD): Wavelength: 272 nm, Eluent: *n*-hexane / *iso*-propanol 40:60, Flow:

0.6 mL / min, t_R = 7.62 min ((+)-**13da** or (+)-**13db**), t_R = 8.06 min ((+)-**13da** or (+)-**13db**), t_R = 8.41 min ((–)-**13da** and (–)-**13db**), ee = 98%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, 2-CH_3), 2.24, 2.25 (2 × s, 3 H, Ar-CH_3), 2.61 (d, *J* = 15.0 Hz, 1 H, 1'-H_a), 2.70, 2.71 (2 × d, *J* = 15.0 Hz, 1 H, 1'-H_b), 3.68, 3.69 (2 × s, 3 H, CO_2CH_3), 3.88, 3.89 (2 × d, *J* = 11.3 Hz, 1 H, 3-H_a), 4.20, 4.21 (2 × d, *J* = 11.3 Hz, 1 H, 3-H_b), 6.62–6.79 (m, 3 H, 3 × Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.44, 20.50 (Ar-CH_3), 21.37 (2-CH_3), 40.00, 40.07 (C-1'), 51.65 ($CO_2\underline{C}H_3$), 69.82, 69.87 (C-3), 72.45, 72.66 (C-2), 116.7 , 117.3, 117.4, 118.0 (C-5), 121.9, 122.6 (C-7), 131.0, 131.7 (C-6), 139.7, 140.0, 141.7, 141.9 (C-4a, C-8a), 170.6 (C=O); IR (Film): $\tilde{\nu}$ = 2952 cm^{-1}, 1739, 1507, 1279, 1050, 806; UV (CH_3CN): λ_{max} (lg ε) = 202.5 nm (5.613), 283.0 (3.446); MS (ESI): *m/z* (%) = 259.1 (100) $[M+Na]^+$, 237.1 (35) $[M+H]^+$; HRMS: calcd for $[C_{13}H_{16}O_4 + H]^+$: 237.1121; confirmed.

(2*R*)-(6-*tert*-Butyl-2-methyl-2,3-dihydrobenzo[1,4]dioxin-2-yl)acetic acid methyl ester and (2*R*)-(7-*tert*-Butyl-2-methyl-2,3-dihydrobenzo[1,4]dioxin-2-yl)acetic acid methyl ester (13ea and 13eb): According to the general procedure a 1:1 mixture of phenols **12ea** and **12eb** (47 mg, 0.21 mmol) was reacted in MeOH (1.5 mL) for 15 h at rt. After work-up and column chromatography on silica the unseparable regioisomeric methyl esters **13da** and **13db** were obtained as yellow oil (58 mg, 0.20 mmol, 97%). HPLC (Chiralcel OD): Wavelength: 272 nm, Eluent: *n*-hexane / *iso*-propanol 40:60, Flow: 0.6 mL / min, t_R = 6.58 min ((+)-**13ea** or (+)-**13eb**), t_R = 6.84 min ((+)-**13ea** or (+)-**13eb**), t_R = 7.63 min ((–)-**13ea** or (–)-**13eb**), t_R = 8.42 min ((–)-**13ea** or (–)-**13eb**), ee = 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 9 H, $C(CH_3)_3$)), 1.43, 1.44 (2 × s, 3 H, 2-CH_3), 2.60, 2.62 (2 × d, *J* = 15.0 Hz, 1 H, 1'-H_a), 2.72 (d, *J* = 15.0 Hz, 1 H, 1'-H_b), 3.68 (s, 3 H, CO_2CH_3), 3.89, 3.90 (2 × d, *J* = 11.2 Hz, 1 H, 3-H_a), 4.23, 4.26 (2 × d, *J* = 11.2 Hz, 1 H, 3-H_b), 6.74–6.90 (m, 3 H, 3 × Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.24 (2-CH_3), 31.29 ($C(\underline{C}H_3)_3$), 34.00, 34.06 ($\underline{C}(CH_3)_3$), 40.09, 40.13 (C-1'), 51.65 ($CO_2\underline{C}H_3$), 69.81, 69.87 (C-3), 72.59, 72.74 (C-2), 114.1, 114.6 (C-5), 116.4, 116.9 (C-8) 118.2, 118.9 (C-6, C-7), 139.6 (C-4a), 141.3, 141.5 (C-8a), 144.7, 145.5 (C-6, C-7), 170.6, 170.7 (C=O); IR (Film): $\tilde{\nu}$ = 2962 cm^{-1}, 1740, 1504, 1283, 1050, 812; UV (CH_3CN): λ_{max} (lg ε) = 202.0 nm (4.686), 281.0 (3.495); MS (ESI): *m/z* (%) = 579.3 (53) $[2M+Na]^+$, 301.1 (100) $[M+Na]^+$, 278.2 (21) $[M+H]^+$; HRMS: calcd for $[C_{13}H_{16}O_4 + H]^+$: 279.1591; confirmed.

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