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Synthesis of 3-Arylated 3,4-Dihydrocoumarins: Combining Continuous Flow Hydrogenation with Laccase-Catalysed Oxidation

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Abstract: A convenient arylation of diverse 3,4-dihydrocoumarins with a number of catechols is described leading to a new class of compounds. As key step, a laccase-catalysed oxidation/Michael addition sequence is applied using commercially available laccase from *Agaricus bisporus*. 3,4-Dihydrocoumarins were obtained in a rapid and facile two-step sequence starting from salicylaldehydes: The corresponding coumarins were synthesised through a Knoevenagel condensation in up to 83% yield followed by a quantitative reduction performed in a flow system. Combining the reductive flow reaction with the laccase-catalysed arylation also led to successful consecutive one-pot approaches. Overall, the enzyme-catalysed arylations were carried out with yields ranging from 63 to 94%.

Keywords: C–C coupling; enzyme catalysis; flow chemistry; green chemistry; hydrogenation

Introduction

Coumarins (2*H*-1-benzopyran-2-ones) (**1**) are a prominent class of compounds that can be of natural or synthetic descent. Over 1300 coumarins were identified as secondary metabolites found in numerous plants, bacteria, and fungi.[1] They possess a variety of pharmacological properties such as antimicrobial,[2,3] anti-inflammatory,[4] antitumour,[5] antidepressant[6] or antiviral[7,8] activity. Interesting examples are warfarin (**2**), brodifacoum (**3**) and ensaculin (**4**). Moreover, 7-hydroxycoumarin (umbelliferone) (**5**), a fluorescent, or 3,3′-carbonylbis(7-methoxycoumarin) (CBC) (**6**) as a laser dye-sensitised photo initiator, play an important role in industry and in scientific research (Figure 1).[9] Synthetic coumarin derivatives also show potent monoamine oxidase (MAO) inhibition.[10,11] Hence, they are used as important drugs in the treatment of depression[12–14] and Alzheimer's disease.[15–18] Furthermore, various arylcoumarin derivatives, e.g., 3-arylcoumarin **7** ($IC_{50} = 2.79 \pm 0.19$ μM) and **8** ($IC_{50} = 8.98 \pm 1.42$ nM) were recently reported to be the most effective inhibitors of MAO-B, an isoenzyme of MAO (Figure 1).[19,20]

In addition, the motif of 3-arylated dihydroisocoumarins, for example, thunberginol G (**9**), a herbal medical ingredient,[21] is prevalent in nature (Figure 2). In comparison to this, the corresponding dihydrocoumarins were investigated far less: A notable exception is calomelanol G (**10**) a flavanone also containing a 4-aryldihydrocoumarin motif.[22] Nevertheless, in general dihydrocoumarins[23,24] beyond this structural restriction show a broad range of activities, for example, aldolase reductase and HIV replication inhibition, making them promising lead compounds in drug discovery.[25] A convenient access to 3-arylated dihydrocoumarins might be an attractive alternative starting point. One feasible route would be the synthesis of phenylcoumarins with subsequent reduction.[26] Condensation–cyclisation-type reactions like Knoevenagel,[27] Perkin[28] and Pechmann[29] reactions were commonly used, starting from aromatic carbonyl building blocks. Of this selection, the Perkin condensation is the most direct route to 3-arylcoumarins.[30] Alternatives include the direct 3-arylations of the coumarin scaffolds by transition metal-catalysed cross-couplings using organometallic reagents as nucleophiles and aryl halides as electrophiles: Here, the pioneering achievements of Suzuki,[31] starting with bor-

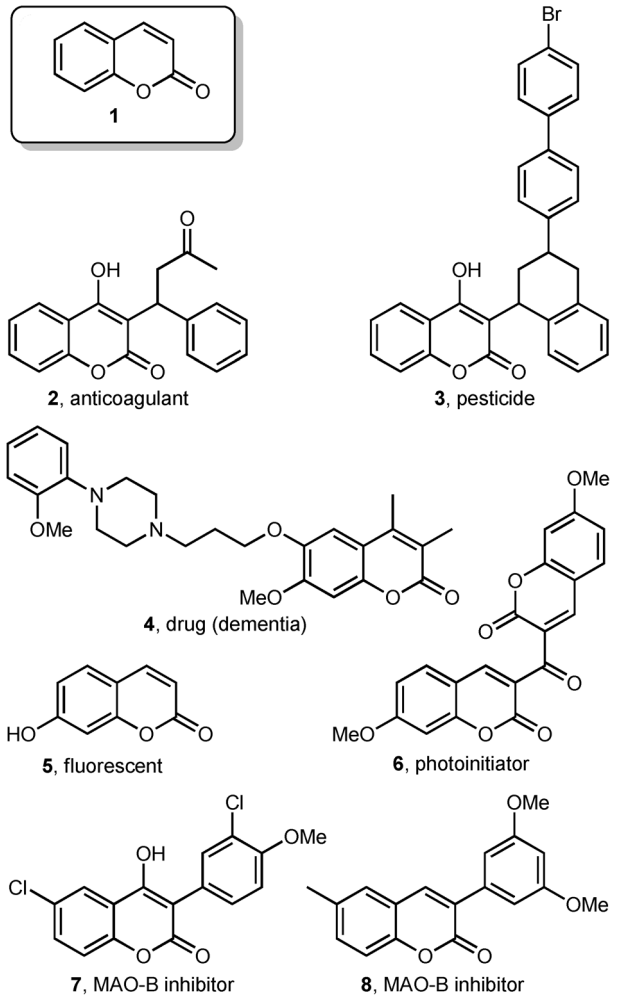


Figure 1. Common coumarin motifs.

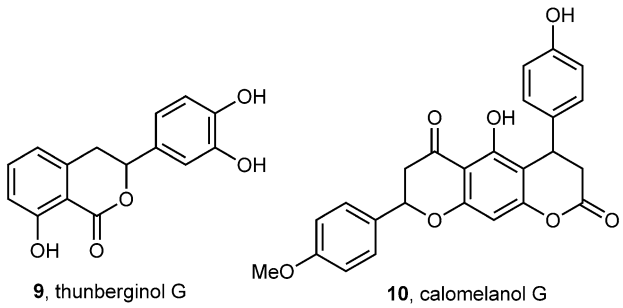
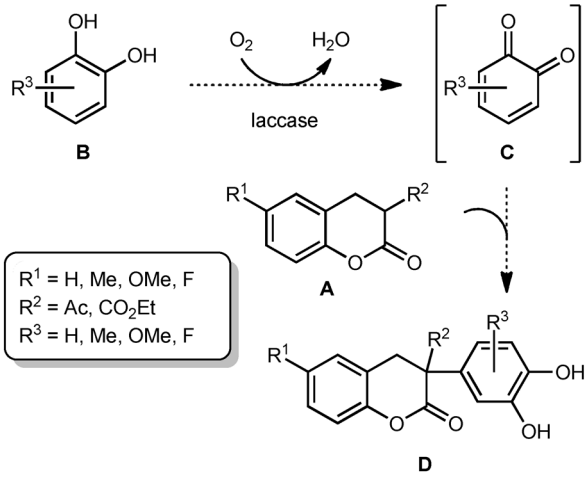


Figure 2. Natural arylated dihydro(iso)coumarins.

onic acids and coumarinyl halides, and Negishi,[32] starting with zincation at C-3, offer versatile methods for C–C cross-couplings. However, these vast developments require pre-functionalisation of the coumarin moieties, expensive, toxic and air sensitive ligands for the transition-metals as well as a challenging separation of products from the catalysts.[33] To the best of our knowledge, direct arylations of 3,4-dihydrocoumarins in 3-position have not been studied and investigated yet. As part of our on-going effort to utilise laccases in the synthesis of key-building blocks creating C–C bonds,[34] we thought to apply the method in the synthesis of this scaffold.



Scheme 1. Laccase-catalysed arylation of 3,4-dihydrocoumarins v*ia* an oxidation/Michael addition sequence.

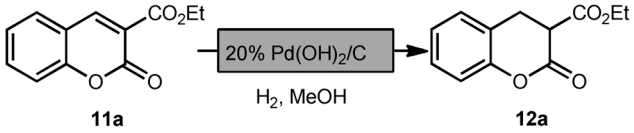
Laccases (benzenediol: oxygen oxidoreductase EC 1.10.3.2.) are blue multicopper oxidases that catalyse the oxidation of various substrates, for example, phenols, polyphenols or aromatic amines, using aerial oxygen as oxidising agent reducing it to water. The mild reaction conditions and the fact that these enzymes are readily commercially available, have also triggered a growing interest in synthetic applications.[35]

Since laccase-catalysed C–C bond forming reactions using catechols and hydroquinones in previous protocols were very promising,[36] our focus was now on the arylation of 3,4-dihydrocoumarins **A** leading to a new class of compounds bearing a stereogenic centre in the 3-position (Scheme 1). The process is supposed to start with a rapid laccase-catalysed oxidation of the catechol moiety **B** to the corresponding *ortho*-quinone **C** creating a Michael acceptor system. This system instantly undergoes a Michael addition with the nucleophilic C-3 carbon of the 3,4-dihydrocoumarins to form the 3-arylated 3,4-dihydrocoumarins **D**. Depending on the type and position of the residues on the catechol scaffold, regioisomers are possible.

Results and Discussion

We started our investigation by providing the starting materials for the laccase-catalysed coupling. First, hydrogenation of the commercially available ethyl 3-coumarincarboxylate (**11a**) (Table 1) was investigated. All hydrogenation reactions were carried out in a flow system (ThalesNano©). The H-Cube Pro™

Table 1. Optimisation of reaction conditions for the synthesis of dihydrocoumarin **12a** performing a continuous flow hydrogenation in the H-Cube Pro™.[38]



Entry	Press. [atm]	Temp. [°C]	H_2 [%]	Flow [mL min^{-1}]	Conc. [M]	Yield [%][a]
1	15	30	100	1.0	0.01	85
2	5	25	50	1.0	0.01	86
3	5	25	50	2.0	0.01	91
4	5	20	7	2.5	0.01	82[b]
5	3	20	25	2.5	0.01	93
6	**3**	**20**	**25**	**0.5**	**0.05**	**98[c]**
7	3	20	25	0.3	0.10	84[d]
8	3	20	25	0.3	0.23	68[e]

[a] Quantitative conversion.
[b] 92% conversion.
[c] Yield of isolated product.
[d] 89% conversion.
[e] 73% conversion. Yields calculated by ^{1}H NMR. In all cases, a side product was detected.

system offers tremendous advantages compared to established batch reactions. Besides improving safety issues by creating explosive hydrogen gas electrolytically from water in a closed system in low concentration, it offers short reaction times, fast optimisations of reaction conditions, exact reproduction, and automated procedures; ideally no further purification is necessary. The only requirement of this flow-system is the complete solubility of reagents. For best results, ThalesNano© recommend a concentration of 0.05 M. The dead volume of the system has to be considered. Commercially available cartridges (CatCarts®) with the most common catalysts were used.[37]

For our first example, we chose methanol as a solvent and Pearlman's catalyst[38] since under these conditions best results in previously performed batch reactions were achieved (84% yield). Our aim was a fast – albeit not completely rational – optimisation of the reduction conditions for the flow system with a special emphasis on mild reaction conditions (Table 1).

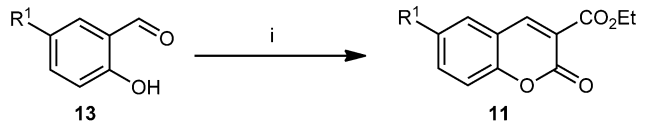
We started our investigation with a concentration of 0.01 M of coumarin **11a** in methanol, a system pressure of 15 atm, a hydrogen production set to the maximum of 100% and a flow rate of 1.0 mL min^{-1} at a temperature of 30 °C. Fortunately, we instantly obtained full conversion for the first attempt with a quite promising yield (85%, Table 1, entry 1). However, TLC analysis as well as the ^{1}H NMR data showed the presence of a known side product.[44] With signals of the same signal pattern for the ester group and the protons at C-3 and C-4 slightly shifted, the amount could exactly be determined. We then altered the conditions in order to suppress the forming of the side product, simultaneously improving the yield. Therefore, we decreased the hydrogen production to 50% as well as the pressure to 5 atm and the temperature to 25 °C (Table 1, entry 2). Since this set of conditions could not significantly improve the previous approach (86%, Table 1, entry 2), we increased the flow rate to decrease the residence time of the reagent in the cartridge (Table 1, entry 3). Again, we could slightly improve the yield reducing the amount of side product with full conversion of **11a** (91%; Table 1, entry 3). Increasing the flow rate to 2.5 mL min^{-1} while concomitantly decreasing the hydrogen production to 7% and the temperature to 20 °C, a reduced conversion rate of 92% and a yield of 82% was obtained (Table 1, entry 4). With the same flow rate of 2.5 mL min^{-1}, a system pressure of 3 atm and a hydrogen production of 25% we obtained the best result with full conversion using this concentration (93%; Table 1, entry 5). We then reduced the amount of solvent used and chose a concentration of 0.05 M as recommended by ThalesNano© for reductions carried out in flow. To our delight, full conversion with a nearly quantitative yield was achieved with this concentration (98%; Table 1, entry 6). The flow rate had to be adjusted to 0.5 mL min^{-1} due to a more concentrated solution of starting material **11a** in methanol. As we went on with increasing the concentration even to 0.10 M and 0.23 M under the same conditions except of reducing the flow rate to 0.3 mL min^{-1}, conversions of 89% and 73% with slightly lower yields were achieved (84 and 68%; Table 1, entries 7 and 8). Just traces of the side product were detected.

Furthermore, we could significantly improve the yield of this reaction compared to the batch approach and achieve the product in a secure and rapid way. Unfortunately, the forming of a side product could not be completely suppressed.

So after a few optimisations, 3,4-dihydrocoumarin **12a** was obtained in a nearly quantitative yield under mild reduction conditions (98%; Table 1, entry 6). The recommended concentration of 0.05 M was proved to be best. Moreover, we demonstrated good results even for more concentrated solutions. For all approaches the same catalyst cartridge was used.

In addition, coumarin derivatives with several substituents in the 6 position were synthesised for comparative studies. This was easily achieved in good yields applying a Knoevenagel condensation[39] starting from readily available salicylaldehydes **13** (Scheme 2). After filtering off the products **11b–d**, no further purification was required (yield: 67–83%).

With these compounds in hand, the H-Cube Pro™ protocol was utilised again for the reduction step. Due to a very poor solubility of the coumarins **11b**,



13 11

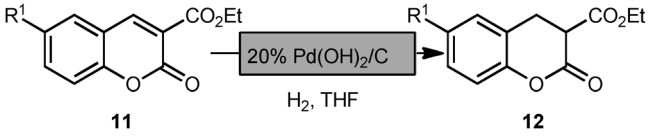
b, R^1 = Me (82%); **c**, R^1 = MeO (83%); **d**, R^1 = F (67%)

Scheme 2. Synthesis of coumarins **11b–d**. *Reagents and conditions:* (i) diethyl malonate (**14**), piperidine (cat.), AcOH (cat.), ethanol.

11c and **11d** in methanol (and in view of the side product formed), tetrahydrofuran was the solvent of choice for further approaches. The same catalyst cartridge was used for these reducing trials (Table 2).

For the first trial, the hydrogen production and system pressure were slightly increased compared to the successful previous approach in methanol to 30% and 5 atm, respectively (Table 2, entry 1). Fortunately, we obtained a nearly full conversion for dihydrocoumarin **12b** (97%; Table 2, entry 1). To our full satisfaction, increasing the pressure to 7 atm and hydrogen production to 35% with the same temperature (20 °C) led to a full conversion and an excellent yield (> 99%; Table 2, entry 2). The same was true for the dihydrocoumarin motifs **12a** and **12c** (>99%; Table 2, entries 3 and 6) where the syntheses proceeded in an excellent manner, too. In addition, no further purification step was needed to obtain pure 3,4-dihydrocoumarins **12a**, **b**, **c**. Even for coumarin **1a**, we were able to improve the yield from the first reduction approach where we used methanol as the solvent (>99%; Table 2, entry 6). For coumarin **11d**, no full conversion was detected using these conditions (99%;

Table 2. Optimisation of reaction conditions for the synthesis of chromanone **12** performing a continuous flow hydrogenation using the H-Cube Pro™ system with THF as solvent. Concentration set to 0.05 M.



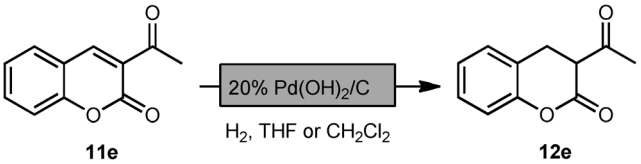
11 12

a, R^1 = H; **b**, R^1 = Me; **c**, R^1 = MeO; **d**, R^1 = F

Entry	R	Press. [atm]	Temp. [°C]	H_2 [%]	Flow [mL min^{-1}]	Yield [%]
1	Me	5	20	30	0.5	97[a]
2	Me	7	20	35	0.5	>99[b]
3	MeO	7	20	35	0.5	>99[b]
4	F	7	20	35	0.5	99[c]
5	F	7	22	40	0.4	>99[b]
6	H	7	20	35	0.5	>99[b]

[a] 97% conversion as calculated by ^{1}H NMR.[b] Quant. conversion. Yield of isolated product.[c] 99% conversion as calculated by ^{1}H NMR.

Table 3. Optimisation of reaction conditions for the synthesis of chromanone **12e** performing a continuous flow hydrogenation using the H-Cube Pro™ system. Concentration set to 0.05 M.



11e 12e

Entry	Press. [atm]	Temp. [°C]	H_2 [%]	Flow [mL min^{-1}]	Conv. [%][a]
1	2	15	15	0.5	11
2	2	20	20	0.5	16
3	2	15	25	0.5	46
4	2	25	22	0.5	64
5	**2**	**20**	**25**	**0.5**	**99[b]**
6	5	20	50	0.5	96
7	5	20	50	1.0	95
8	10	25	100	0.5	96
9	5	20	100	0.3	82[c]
10	30	20	100	0.5	96[c]
11	50	20	100	0.5	98[c]

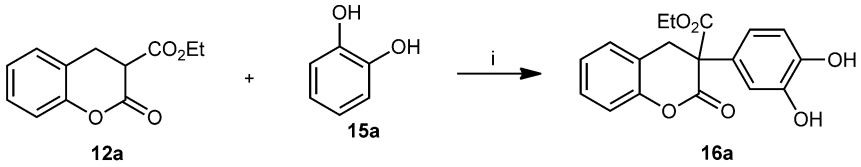
[a] Conversion determined by ^{1}H NMR.[b] 81% yield of isolated product.[c] Dichloromethane used as solvent. In all cases, side products were detected.

Table 2, entry 4). Therefore, we slightly increased the temperature to 22 °C and the hydrogen production to 40% while reducing the flow rate to 0.4 mL min^{-1}. Hence, we obtained full conversion and an excellent yield (>99%; Table 2, entry 5).

As a last coumarin derivative for our studies, we varied the residue in the 3 position from the ethyl ester group to an acetyl group using commercially available 3-acetylcoumarin (**11e**) as starting material to obtain 3-acetylchroman-2-one (**12e**). Again, continuous flow reductions were carried out using the flow system. $Pd(OH)_2/C$ was used as a catalyst here, too (Table 3). We started with very mild reduction conditions using 2 atm pressure, a flow rate of 0.5 mL min^{-1} as well as 15 °C temperature and 15% hydrogen production (11%; Table 3, entry 1) or 20 °C and 20% hydrogen production (16%; Table 3, entry 2). Obviously, both approaches led to very low conversions. Increasing the hydrogen production to 25% at a temperature of 15 °C gave rise to a significant improvement of conversion (46%; Table 3, entry 3). Using a higher temperature of 25 °C with a hydrogen production of 22% again increased the conversion (64%; Table 3, entry 4). The best result was obtained with a temperature of 20 °C and a hydrogen production of 25% with nearly full conversion and a good yield (81%; Table 3, entry 5).

In all cases, side products were detected. To suppress the formation of side products, we tried an in-

Table 4. Optimisation of reaction conditions for the laccase-catalysed synthesis of chromanone **16a**.[a]



Entry	Laccase from	Phosphate buffer/solvent [ratio]	Unit [U][b]	Yield [%][c]
1	*Pleurotus ostreatus*	Buffer/MeCN (2:1)	10	57[d]
2	*Agaricus bisporus*	Buffer/MeCN (2:1)	10	61[e]
3	***Agaricus bisporus***	**Buffer/MeCN (2:1)**	**15**	**71[f]**
4	*Agaricus bisporus*	Buffer/THF (2:1)	10	54[g]
5	*Agaricus bisporus*	Buffer/MeCN (1:1)	10	57[e]
6	*Agaricus bisporus*	Buffer/MeCN (2:1)	15	41[h]

[a] (i) *Reaction conditions:* 0.25 mmol **12a**, 1.2 equiv. **15a**, 3 mL solvent, 22 °C. Buffer: KH_2PO_4/K_2HPO_4, $c = 0.2$ M, pH 6.0.
[b] Activities as given by the supplier (8 U/mg for *A. bisporus*).
[c] Yields of isolated products.
[d] No full conversion after 24 h.
[e] Full conversion after 43 h.
[f] Full conversion after 18 h.
[g] Nearly full conversion after 43 h.
[h] Nearly full conversion after 28 h at 35 °C.

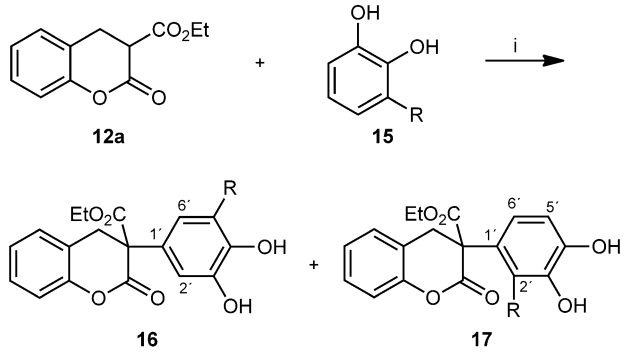
creased pressure of 5 atm with a hydrogen production of 50% (96%; Table 3, entry 6) and a higher flow rate of 1.0 mL min^{-1} (95%; Table 3, entry 7). In both cases a slightly lower conversion was obtained. Even with harsher conditions using 100% hydrogen production, 10 atm pressure and a temperature of 25 °C no significant influence on the conversion rate or the formation of side products was achieved (96%; Table 3, entry 8). Hence, we also tried dichloromethane as alternative. With this solvent, nearly the same conversions were received using harsh conditions with 50 atm and 100% hydrogen production (82–98%; Table 3, entries 9–11). However, we obtained 3,4-dihydrocoumarin **12e** in a good yield under mild reduction conditions (99% conversion, 81% yield; Table 3, entry 5). In total, all 3,4-dihydrocoumarins were synthesised with total yields between 66 and 99%. So far, just one purification step for compound **12e** was essential.

Next, we focused on the enzyme-catalysed arylation step. For this, we took the well-established reaction conditions from previous protocols as a starting point (Table 4, entry 1):[34] we had obtained best results using co-solvents like acetonitrile with phosphate buffer (pH 6.0) in a ratio of 1:2 (solvent/buffer) with commercially available laccase from *Pleurotus ostreatus* (10 U),[34b] a laccase that showed an outstanding tolerance towards organic co-solvents. As the model transformation, the reaction between ethyl 2-oxochroman-3-carboxylate (**12a**) and catechol (**15a**) was performed giving 3-arylated product **16a**.

With the established conditions, no full conversion of the substrate **12a** after 24 h was achieved using the laccase from *Pleurotus ostreatus*. Nevertheless, the desired product **16a** was instantly formed in a moderate yield (57%; Table 4, entry 1). After applying the laccase from *Agaricus bisporus* with the same amount of catalyst, we obtained a slightly higher yield. The reaction time for full conversion was about 43 h (61%; Table 4, entry 2). Hence, we slightly increased the catalyst loading to 15 U and observed full conversion and a good yield after 18 h at room temperature (22 °C) (71%; Table 4, entry 3). Besides, we could also show a co-solvent tolerance of the laccase from *Agaricus bisporus* towards tetrahydrofuran resulting in a moderate yield (54%; Table 4, entry 4). In addition, the fast formation of a previously negligible side product ($R_f = 0$) was observed, if the amount of enzyme was enhanced over 15 U; it is likely that the side product stems from the polymerisation of the *in situ* formed highly reactive *ortho*-quinone. Increasing the amount of co-solvent to a ratio of 1:1 buffer/acetonitrile (57%; Table 4, entry 5) or the temperature to 35 °C (41%; Table 4, entry 6) showed no positive effect on yield or reaction time. Moreover, no signs of decomposition or oxidation of dihydrocoumarin **12a** were detectable applying a slightly acidic pH value in an aqueous solution under oxidative conditions. As expected, the product was confirmed to be a racemic mixture by HPLC on a chiral stationary phase.

Both dihydrocoumarins **12** and catechols **15** were varied to evaluate the scope of the reaction. First, several mono-3-substituted catechols **15b–d** were reacted with ethyl 2-oxochroman-3-carboxylate (**12a**). Due to the additional residue R on the catechol scaffolds **15b–d**, the intermolecular 1,4-addition occurred either in the 4′ or 5′ position on the corresponding *ortho*-quinone and products **16** and **17** were isolated (Table 5).

Table 5. Laccase-catalysed reaction between dihydrocoumarin **12a** and catechols **15b–d**.[a]



b, R = MeO; **c**, R = Me; **d**, R = F

Entry	15	R	Time [h]	Product	Ratio[b] 16:17	Yield [%][c]
1	**b**	MeO	18	**16b**	–	80
2	**c**	Me	20	**16c**	–	70
3	**d**	F	19	**16d:17d**	78:22	64

[a] (i) *Reaction conditions:* 0.25 mmol **12a**, 1.2 equiv. **15b–d**, 15 U (8 U/mg) laccase from *Agaricus bisporus*, 3 mL solvent (buffer/MeCN 2:1), 22 °C. Buffer: KH_2PO_4/K_2HPO_4, $c = 0.2$ M, pH 6.0.

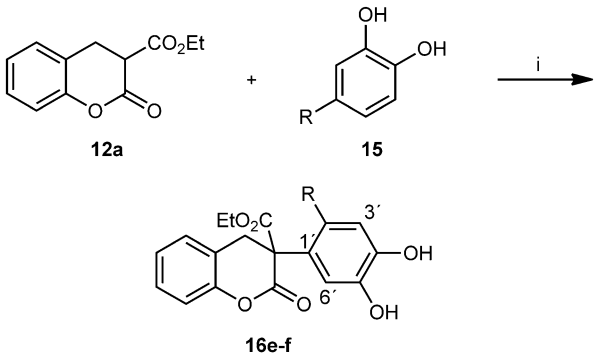
[b] Ratio was determined by ^{1}H NMR.

[c] Yields of isolated products.

For 3-methoxycatechol (**15b**) and 3-methylcatechol (**15c**), the isomers **16b** and **16c** are selectively formed in good yields of 80% and 70%, respectively (Table 5, entries 1 and 2). In contrast, the reaction of 3-fluorocatechol (**15d**) with dihydrocoumarin **12a** delivered both regioisomers **16d** and **17d** in a ratio of 78:22 in favour of compound **16d** (64%; Table 5, entry 3). Obviously, electron-withdrawing groups increase the electrophilicity at C-4 of the corresponding catechol **15**, while electron-donating groups renders this position less favourable. It should be noted that the regioisomers can be easily assigned *via* the characteristic coupling pattern in the ^{1}H NMR spectra for the protons 2′-H/6′-H (compounds **16**: $^4J_{2'\text{-H},6'\text{-H}} \sim 2.3$ Hz) and 5′-H/6′-H (compounds **17**: $^3J_{5'\text{-H},6'\text{-H}} \sim 8.5$ Hz), respectively.

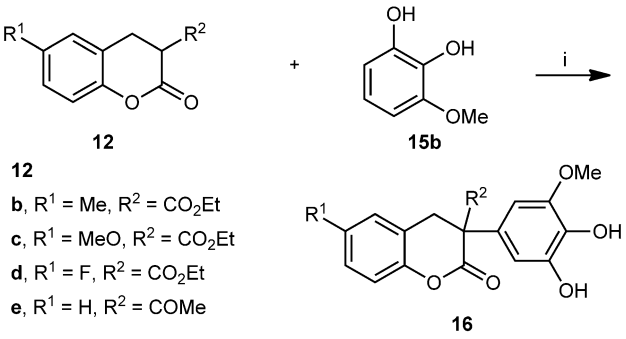
Next, 4-substituted catechols **15e**, **f** were also reacted with dihydrocoumarin **12a** (Scheme 3). As expected, in both cases of 4-methylcatechol (**15e**) and 4-chlorocatechol (**15f**), the addition occurred selectively in the 5′ position of the corresponding *ortho*-quinone providing 3-arylated dihydrocoumarins **16e** and **16f** in good yields of 68% and 63%, respectively.

Finally, we varied the coumarin scaffold using dihydrocoumarins **12b–e** with 3-methoxycatechol (**15b**) as arylation agent (Scheme 4). As expected, in all cases only one regioisomer **16g–j** was obtained. To our delight, an excellent yield was achieved in the case of



e, R = Me (68%; **16e**); **f**, R = Cl (63%; **16f**)

Scheme 3. Laccase-catalysed synthesis of **16e**, **f**. *Conditions:* (i) 0.25 mmol **12a**, 1.2 equiv. **15e**, **f**, 15 U (8 U/mg) laccase from *Agaricus bisporus*, 3 mL solvent (buffer/MeCN 2:1), 22 °C, 20 h. Buffer: KH_2PO_4/K_2HPO_4, $c = 0.2$ M, pH 6.0.



12

b, R^1 = Me, R^2 = CO_2Et

c, R^1 = MeO, R^2 = CO_2Et

d, R^1 = F, R^2 = CO_2Et

e, R^1 = H, R^2 = COMe

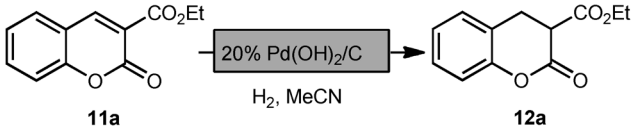
16

g, R^1 = Me, R^2 = CO_2Et	(94%; 24 h)
h, R^1 = MeO, R^2 = CO_2Et	(84%; 46 h)
i, R^1 = F, R^2 = CO_2Et	(77%; 18 h)
j, R^1 = H, R^2 = COMe	(63%; 18 h)

Scheme 4. Laccase-catalysed synthesis of **16g–j**. *Conditions:* (i) 0.25 mmol **12b–e**, 1.2 equiv. **15b**, 15 U (8 U/mg) of laccase from *Agaricus bisporus*, 3 mL solvent (buffer/MeCN 2:1), 22 °C. Buffer: KH_2PO_4/K_2HPO_4, $c = 0.2$ M, pH 6.0.

ethyl 6-methyl-2-oxochroman-3-carboxylate (**12b**) as substrate (94%). For the methoxy derivative **12c** the reaction time had to be extended to 46 h to reach full conversion (yield: 84%). Dihydrocoumarin **16i** was also obtained with full conversion in a good yield after 18 h (77%), while the arylation of acetyldihydrocoumarin **12e** took the same time to reach full conversion, albeit giving a lower yield (63%). Obviously, electron-donating groups on the dihydrocoumarin motif increase the reaction time: The increased electron density is decreasing the acidity at the C-3 rendering the position less nucleophilic. Again, no signs of decomposition or oxidation of the dihydrocoumarins **12b–e** under the slightly acidic conditions in an aqueous solution were detectable.

Table 6. Optimisation of reaction conditions for the synthesis of **12a** in acetonitrile performing a continuous flow hydrogenation using the H-Cube Pro™ system. Concentration set to 0.05 M.



11a **12a**

Entry	Press. [atm]	Temp. [°C]	H_2 [%]	Flow [mL min^{-1}]	Conv. [%][a]
1	3	20	25	0.5	51
2	5	20	50	0.3	96
3	10	20	100	0.3	88
4	**5**	**20**	**100**	**0.3**	**100[b]**

[a] Conversion determined by ^{1}H NMR.
[b] >99% yield of isolated product. No side products were detected.

Inspired by the recent findings of Mihovilovic and co-workers who demonstrated the successful combination of a continuous hydrogenation protocol with a biocatalytic oxygenation providing chiral lactones,[40] a similar approach was anticipated for the synthesis of 3-aryldihydrocoumarins **16**. While the established continuous flow hydrogenation of coumarins **11a–d** provided the corresponding dihydrocoumarins **12** in near quantitative yield without further purification steps, the solvent used was not compatible with the laccase-catalysed transformation. Hence, the solvent system needed to be adapted.

For this approach, the commercially available coumarin **11a** was used as well as the same catalyst cartridge from previous attempts containing 20% $Pd(OH)_2$/C. The starting point of the optimisation were the conditions shown to work best for methanol (Table 1, entry 6) and using acetonitrile instead. Unfortunately, only a moderate conversion was achieved (51%; Table 6, entry 1). Increasing the pressure to 5 atm and at the same time decreasing the flow rate to 0.3 mL min^{-1} when applying a hydrogen production of 50% gave an excellent conversion (96%; Table 6, entry 2), while further increasing the hydrogen production to a maximum of 100% and the system pressure (10 atm) led to a drop to 88% (Table 6, entry 3). Best results were found at a system pressure of 5 atm with a hydrogen production of 100% and a flow rate of 0.3 mL min^{-1} (>99%; Table 6, entry 4). No side products were detected and no further purification was necessary.

With optimal reduction conditions in acetonitrile at hand, the set-up for the approach was given (Figure 3): For this, the catechol **15b** was dissolved in acetonitrile, drawn up in a syringe and the injection rate of the syringe pump was adjusted to the flow rate of the H-Cube Pro™. Since the recommended concentration for the reduction in flow is 0.05 M, the laccase-catalysed arylation had to be carried out in a diluted manner (factor of six). Then, coumarin **11a** was reduced under the optimised reduction conditions while catechol **15b** was simultaneously injected into the reaction flask containing the enzyme in a buffer solution (Scheme 5). We were pleased to find that the overall yield was slightly increased compared to the two-step operation (82% *vs.* 80%); the reaction time was not influenced by higher dilution of the enzyme-catalysed step.

As acetonitrile is not recommended by ThalesNano© as a solvent and deactivation of the catalyst was observed, additional experiments were carried out using more suitable solvents. Since previous arylation

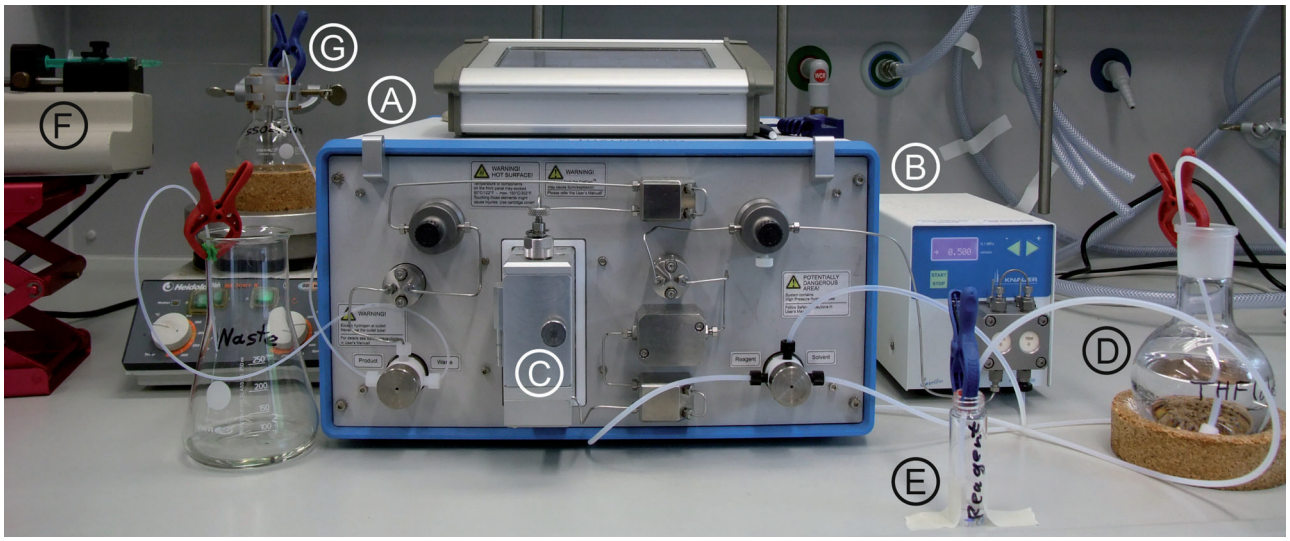
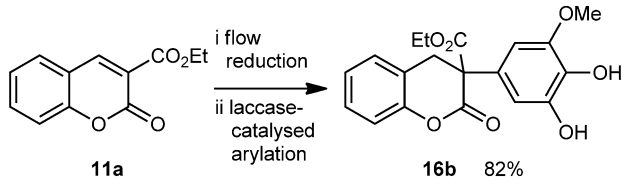
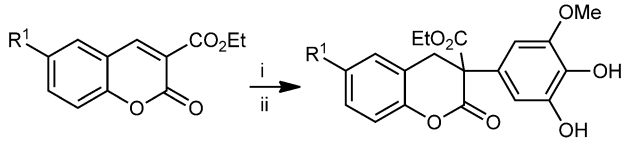


Figure 3. Set-up of the consecutive one-pot approach: **A** H-Cube Pro™ flow system, **B** HPLC pump, **C** catalyst cell, **D** solvent reservoir, **E** reagent, **F** syringe pump, **G** product line with reaction flask.



Scheme 5. Consecutive one-pot approach towards the synthesis of **16b**. *Reagents and Conditions:* (i) 5 atm, 20 °C, 20% $Pd(OH)_2/C$, 100% H_2, 0.3 mL min^{-1}, 0.23 mmol **11a**, 5 mL acetonitrile, 0.05 M; (ii) 1.2 equiv. **15b**, 1 mL acetonitrile (2 mL syringe, injection rate 4.32 mL h^{-1}), 15 U (8 U/mg) laccase from *Agaricus bisporus*, 12 mL buffer, 22 °C, 18 h. Buffer: KH_2PO_4/K_2HPO_4, $c = 0.2$ M, pH 6.0.



11	16	
a, R^1 = H	**b**, R^1 = H	68%
b, R^1 = Me	**g**, R^1 = Me	72%
c, R^1 = MeO	**h**, R^1 = MeO	62%
d, R^1 = F	**i**, R^1 = F	40%

Scheme 6. Consecutive one-pot approach towards the syntheses of **16b–i**. *Reagents and Conditions:* (i) 7 atm, 20 °C, 20% $Pd(OH)_2/C$, 35% H_2, 0.5 mL min^{-1} (for **11d**: 7 atm, 22 °C, 40% H_2, 0.4 mL min^{-1}), 0.25 mmol **11**, 5 mL tetrahydrofuran, 0.05 M; (ii) 1.2 equiv. **15b**, 1 mL tetrahydrofuran (2 mL syringe, injection rate 7.2 mL h^{-1}; for **11d**: 5.8 mL h^{-1}), 24 U (8 U/mg) laccase from *Agaricus bisporus*, 12 mL buffer, 22 °C. *Times:* **16b**: 23 h; **16g**: 22 h; **16h**: 27 h; **16i**: 20 h; Buffer: KH_2PO_4/K_2HPO_4, $c = 0.2$ M, pH 6.0.

approaches were successfully carried out using tetrahydrofuran (54%; Table 4, entry 4) and all coumarins **11a–d** being readily soluble in it, the following reactions were carried out using the established reduction conditions for tetrahydrofuran (Table 2, entries 2, 3 and 5, 6) with 3-methoxycatechol (**15b**) (Scheme 6). Fortunately, all following consecutive one-pot attempts were successful when using slightly more laccase (24 U) with yields ranging from 40–72% (Scheme 6). As expected, compared to the sequence in acetonitrile the achieved yields were lower, but the catalyst seemed to last considerably longer.

Conclusions

In summary, a convenient and efficient laccase-catalysed arylation of 3,4-dihydrocoumarins with various catechols leading to a new promising class of compound has been developed. These arylated dihydrocoumarins bearing an all-carbon quaternary centre in the 3 position were synthesised in moderate to excellent yields (63–94%): First, a quantitative and rapid continuous flow hydrogenation for the syntheses of several dihydrocoumarin scaffolds was established for different solvents. In almost every case, no further purification of the resulting dihydrocoumarins was required. For the second step, the enzyme-catalysed reactions were effectively carried out by a commercially available laccase under mild reaction conditions using aerial oxygen as the oxidising agent. The use of transition metals as well as co-factors or agents for rearomatisation could be avoided. Ultimately, an additional consecutive one-pot approach towards the arylation of dihydrocoumarins was successfully carried out with yields ranging between 40 and 82%.

Experimental Section

General Remarks

All chemicals being used were purchased from the companies Sigma–Aldrich/Fluka, TCI International, Alpha Aesar and VWR International/Merck. The laccase from *Agaricus bisporus* was also purchased from a commercial supplier (Sigma–Aldrich). Pure solvents were either purchased or distilled prior to use. Absolute solvents were either taken from a drying machine (MBraun (model MB SPS-800), or distilled. The pH value of the buffer was adjusted using a pH-meter 766 Calimatic®. Thin layer chromatography (TLC) was conducted on POLYGRAM® SIL G/UV254 plates with fluorescence indicator. Detection was either by UV absorption or treatment with ceric ammonium molybdate solution followed by heating. Preparative column chromatography was performed using silica gel 60, particle size 0.04–0.063 mm (230–240 mesh). NMR spectra were recorded on a Bruker-Advance/DRX 600 instrument (^{1}H at 600 MHz; ^{13}C at 151 MHz). Chemical shifts (δ) are reported relative to chloroform (^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm), methanol (^{1}H: 4.87 ppm; ^{13}C: 49.00 ppm) or tetrahydrofuran (^{1}H: 3.58 ppm; ^{13}C: 67.21 ppm). The multiplicities are reported with the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet. Higher order chemical shifts and J values are not corrected. Where it was necessary COSY, HSQC and HMBC spectra were recorded for structure elucidation. Infrared spectra were recorded using a PerkinElmer SpectrumOne IR-spectrometer. Melting points were determined using a Büchi B-540. HPLC measurements were performed on a chiral stationary phase using a Dionex machine with analytical column (Chiralpak IC) from Daicel. Substances were detected by UV at the wavelength of 205 nm. High-resolution mass spectra (HRMS) were measured by the Biospec group of the Research Centre Jülich. Measurements were recorded on a LTQ-FT Ultra machine from Thermo Fisher. Samples were ionized by ESI.

General Procedure for Syntheses of Coumarins[39]

2-Hydroxybenzaldehyde **13** (2.0 mmol) and diethyl malonate (**14**) (2.2 mmol) were dissolved in 4 mL ethanol (abs.). Piperidine (0.2 mmol) and acetic acid (0.02 mmol) were added

and the mixture was refluxed until full conversion was confirmed after 5–6 h (as judged by TLC). The hot solution was transferred to an Erlenmeyer flask, rinsed with 5 mL ethanol and diluted with 3 mL hot water. The mixture was stirred as it cooled down to room temperature and stored overnight in a refrigerator. The crystalline product **11** was collected by filtration, washed with cold ethanol/water (2:3) and dried under high vacuum.

Ethyl 6-methyl-2-oxo-2*H*-chromene-3-carboxylate (11b): Reaction of **13a** (300 mg, 2.2 mmol) and **14** (366 μL, 2.4 mmol) according to the general procedure gave **11b** as a pale yellow solid; yield: 419 mg (82%); mp 104 °C (lit.:[41] 105 °C); R_f = 0.19 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν = 3054, 2986, 2924, 1755, 1704, 1573, 1375, 1216, 1131, 979, 829, 796, 701 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.47 (s, 1H, 4-H), 7.46–7.44 (dd, ^3J = 8.5 Hz, ^4J = 1.9 Hz, 1H, 7-H), 7.39 (d, ^4J = 1.9 Hz, 1H, 5-H), 7.25 (d, ^3J = 8.5 Hz, 1H, 8-H), 4.42 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 2.43 (s, 3H, 6-CH_3), 1.41 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.25 (CO_2Et), 156.97 (C-2), 153.37 (C-8a), 148.61 (C-4), 135.46 (C-7), 134.62 (C-6), 129.07 (C-5), 118.19 (C-3), 117.65 (C-4a), 116.52 (C-8), 61.94 ($CO_2CH_2CH_3$), 20.70 (CH_3), 14.24 ($CO_2CH_2CH_3$); HR-MS (ESI): *m/z* = 233.0808 $[M+H]^+$, calculated for $C_{13}H_{13}O_4^+$: 233.0808, m/z = 255.0628 $[M+Na]^+$, calculated for $C_{13}H_{12}NaO_4^+$: 255.0628.

Ethyl 6-methoxy-2-oxo-2*H*-chromene-3-carboxylate (11c): Reaction of **13b** (246 μL, 2.0 mmol) and **14** (330 μL, 2.2 mmol) according to the general procedure gave **11c** as a yellow solid; yield: 407 mg (83%); mp 141 °C (lit.:[42] 137 °C); R_f = 0.15 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν = 3047, 2991, 2837, 1743, 1695, 1572, 1376, 1240, 1137, 981, 821, 791, 685 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.48 (s, 1H, 4-H), 7.30 (d, ^3J = 9.1 Hz, 1H, 8-H), 7.23 (dd, ^3J = 9.1 Hz, ^4J = 2.9 Hz, 1H, 7-H), 7.01 (d, ^4J = 2.9 Hz, 1H, 5-H), 4.42 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 3.86 (s, 3H, 6-OCH_3), 1.41 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.18 (CO_2Et), 156.92 (C-2), 156.26 (C-6), 149.76 (C-8a), 148.36 (C-4), 122.59 (C-8), 118.59 (C-3), 118.14 (C-4a), 117.89 (C-7), 110.63 (C-5), 61.98 ($CO_2CH_2CH_3$), 55.90 (OCH_3), 14.24 ($CO_2CH_2CH_3$); HR-MS (ESI): *m/z* = 249.0758 $[M+H]^+$, calculated for $C_{13}H_{13}O_5^+$: 249.0757.

Ethyl 6-fluoro-2-oxo-2*H*-chromene-3-carboxylate (11d): Reaction of **13c** (300 mg, 2.1 mmol) and **14** (358 μL, 2.4 mmol) according to the general procedure gave **11d** as a white solid; yield: 338 mg (67%); mp 112 °C; R_f = 0.31 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν = 3060, 2996, 1746, 1686, 1569, 1292, 1243, 1157, 980, 834, 791, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.45 (s, 1H, 4-H), 7.39–7.33 (m, 2H, 5-H, 7-H), 7.30 (dd, ^3J = 7.5 Hz, ^4J = 2.6 Hz, 1H, 8-H), 4.42 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 1.41 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.76 (CO_2Et), 157.93 (C-2), 157.90 (d, ^1J = 252 Hz, C-6), 151.33 (d, ^5J = 1.9 Hz, C-8a), 147.34 (d, ^5J = 2.8 Hz, C-4), 121.81 (d, ^3J = 24.6 Hz, C-5), 119.57 (C-3), 118.48 (d, ^4J = 8.2 Hz, C-8), 118.43 (d, ^4J = 8.6 Hz, C-4a), 114.35 (d, ^3J = 24.0 Hz, C-7), 62.20 ($CO_2CH_2CH_3$), 14.20 ($CO_2CH_2CH_3$); HR-MS (ESI): *m/z* = 237.0558 $[M+H]^+$, calculated for $C_{12}H_{10}FO_4^+$: 237.0558, *m/z* = 259.0378 $[M+Na]^+$, calculated for $C_{12}H_9FNaO_4^+$: 259.0377.

General Procedure for the Continuous Flow Hydrogenation towards the Syntheses of 3,4-Dihydrocoumarins

The H-Cube Pro™ flow system by ThalesNano© was equipped with the catalyst cartridge 20% $Pd(OH)_2/C$ (30 mm) and the relevant solvent (absolute). The corresponding reduction conditions were entered. Ethyl 3-coumarincarboxylate **11** was dissolved in the relevant solvent (absolute, 0.05 M). After the flow system had stabilised at the desired conditions, the reduction was started. The dead volumes of the system (1.59 mL) as well as of the catalyst cartridge (0.19 mL) had to be considered. The product solution was evaporated und dried in high vacuum. Where necessary the crude products were purified using flash chromatography.

Ethyl 2-oxochroman-3-carboxylate (12a): Conditions: 7 atm, 20 °C, 35% H_2, 0.5 mL min^{-1}. Reduction of **11a** (55 mg, 0.25 mmol) in tetrahydrofuran (5.5 mL) according to the general procedure gave **12a** as a white solid; yield: 55 mg (99%); mp 53 °C (lit.:[43] 50–55 °C); R_f = 0.35 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν = 2985, 2936, 1758, 1724, 1257, 1136, 1019, 916, 754, 688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (td, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1H, 7-H), 7.22 (dd, ^3J = 7.5 Hz, ^4J = 1.7 Hz, 1H, 5-H), 7.12 (td, ^3J = 7.5 Hz, ^4J = 1.1 Hz, 1H, 6-H), 7.08 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, 8-H), 4.26–4.16 (m, 2H, OCH_2CH_3), 3.76 (dd, ^3J = 8.6 Hz, ^3J = 6.0 Hz, 1H, 3-H), 3.42 (dd, ^2J = 15.9 Hz, ^3J = 8.6 Hz, 1H, 4-H), 3.18 (dd, ^2J = 15.9 Hz, ^3J = 6.0 Hz, 1H, 4-H), 1.21 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.49 (CO_2Et), 164.80 (C-2), 151.40 (C-8a), 128.70 (C-7), 128.25 (C-5), 124.80 (C-6), 120.71 (C-4a), 116.82 (C-8), 62.18 ($CO_2CH_2CH_3$), 46.37 (C-3), 27.32 (C-4), 13.94 ($CO_2CH_2CH_3$); HR-MS (ESI): *m/z* = 219.0661 $[M-H]^+$, calculated for $C_{12}H_{11}O_4^-$: 219.0663.

Ethyl 6-methyl-2-oxochroman-3-carboxylate (12b): Conditions: 7 atm, 20 °C, 35% H_2, 0.5 mL min^{-1}. Reduction of **11b** (90 mg, 0.39 mmol) in tetrahydrofuran (7.8 mL) according to the general procedure gave **12b** as a white solid; yield: 90 mg (99%); mp 88 °C; R_f = 0.35 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν = 3001, 2983, 2938, 1764, 1736, 1492, 1375, 1207, 1130, 1020, 817, 768, 655 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.06 (dd, ^3J = 8.3 Hz, ^4J = 2.0 Hz, 1H, 7-H), 7.00 (d, ^4J = 2.0 Hz, 1H, 5-H), 6.95 (d, ^3J = 8.3 Hz, 1H, 8-H), 4.26–4.15 (m, 2H, OCH_2CH_3), 3.73 (dd, ^3J = 8.5, ^3J = 6.0 Hz, 1H, 3-H), 3.37 (dd, ^2J = 15.9 Hz, ^3J = 8.5 Hz, 1H, 4-H), 3.12 (dd, ^2J = 15.9 Hz, ^3J = 6.0 Hz, 1H, 4-H), 2.31 (s, 3H, 6-CH_3), 1.22 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.61 (CO_2Et), 165.02 (C-2), 149.30 (C-8a), 134.46 (C-6), 129.15 (C-5), 128.64 (C-7), 120.32 (C-4a), 116.50 (C-8), 62.14 ($CO_2CH_2CH_3$), 46.44 (C-3), 27.28 (C-4), 20.71 (CH_3), 13.95 ($CO_2CH_2CH_3$); HR-MS (ESI): *m/z* = 233.0818 $[M-H]^+$, calculated for $C_{13}H_{13}O_4^-$: 233.0819.

Ethyl 6-methoxy-2-oxochroman-3-carboxylate (12c): Conditions: 7 atm, 20 °C, 35% H_2, 0.5 mL min^{-1}. Reduction of **11c** (100 mg, 0.40 mmol) in tetrahydrofuran (8.1 mL) according to the general procedure gave **12c** as a white solid; yield: 100.5 mg (99%); mp 97 °C; R_f = 0.25 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν = 2984, 2925, 2841, 1752, 1732, 1494, 1370, 1206, 1133, 1018, 807, 784, 654 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.06 (dd, ^3J = 8.3 Hz, ^4J = 2.0 Hz, 1H, 7-H), 7.00 (d, ^4J = 2.0 Hz, 1H, 5-H), 6.95 (d, ^3J =

8.3 Hz, 1H, 8-H), 4.26–4.15 (m, 2H, OCH_2CH$_3$), 3.73 (dd, ^3J=8.5, ^3J=6.0 Hz, 1H, 3-H), 3.37 (dd, ^2J=15.9 Hz, ^3J=8.5 Hz, 1H, 4-H), 3.12 (dd, ^2J=15.9 Hz, ^3J=6.0 Hz, 1H, 4-H), 2.31 (s, 3H, 6-CH_3), 1.22 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, CDCl$_3$): δ=167.54 (*C*O$_2$Et), 164.97 (C-2), 156.39 (C-6), 145.29 (C-8a), 121.66 (C-4a), 117.60 (C-8), 113.77 (C-5), 113.22 (C-7), 62.17 (CO$_2$*C*H$_2$CH$_3$), 55.67 (O*C*H$_3$), 46.32 (C-3), 27.57 (C-4), 13.97 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=249.0764 [M−H]$^+$, calculated for C$_{13}$H$_{13}$O$_5^-$: 249.0768.

Ethyl 6-fluoro-2-oxochroman-3-carboxylate (12d): Conditions: 7 atm, 22 °C, 40% H$_2$, 0.4 mL min^{-1}. Reduction of **11d** (100 mg, 0.42 mmol) in tetrahydrofuran (8.5 mL) according to the general procedure gave **12d** as a white solid; yield: 100.4 mg (99%); mp 91 °C; R_f=0.36 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν=3085, 2927, 1747, 1729, 1493, 1377, 1195, 1142, 1018, 873, 655 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ=7.04 (dd, ^3J=8.9 Hz, ^4J=4.6 Hz, 1H, 5-H), 6.98 (ddd, ^3J=8.9 Hz, ^3J=8.2 Hz, ^4J=3.0 Hz, 1H, 7-H), 6.94 (dd, ^3J=8.2 Hz, ^4J=3.0 Hz, 1H, 8-H), 4.26–4.16 (m, 2H, OCH_2CH$_3$), 3.76 (dd, ^3J=8.2, ^3J=6.0 Hz, 1H, 3-H), 3.41 (dd, ^2J=16.1 Hz, ^3J=8.2 Hz, 1H, 4-H), 3.17 (dd, ^2J=16.1 Hz, ^3J=6.0 Hz, 1H, 4-H), 1.22 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, CDCl$_3$): δ=167.17 (*C*O$_2$Et), 164.31 (C-2), 159.14 (d, ^1J=244 Hz, C-6), 147.38 (d, ^4J=2.7 Hz, C-8a), 122.39 (d, ^3J=8.3 Hz, C-4a), 118.16 (d, ^3J=8.6 Hz, C-8), 115.43 (d, ^2J=23.7 Hz, C-5), 114.93 (d, ^2J=24.2 Hz, C-7), 62.34 (CO$_2$*C*H$_2$CH$_3$), 45.92 (C-3), 27.32 (d, ^4J=1.6 Hz, C-4), 13.95 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=237.0567 [M−H]$^+$, calculated for C$_{12}$H$_{10}$FO$_4^-$: 237.0568.

3-Acetylchroman-2-one (12e): Conditions: 2 atm, 20 °C, 25% H$_2$, 0.5 mL min^{-1}. Reduction of **11e** (50 mg, 0.27 mmol) in tetrahydrofuran (6.5 mL) according to the general procedure gave **12e** as a white solid; yield: 40.7 mg (81%); mp 76 °C (lit.:[43] 75–76 °C); R_f=0.36 (petroleum ether/ethyl acetate 80/20); IR (ATR): ν=2920, 2850, 1757, 1712, 1587, 1454, 1261, 1181, 1107, 952, 864, 748, 714 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ=13.39 (s, 1H, OH)*, 7.21 (td, ^3J=8.1 Hz, ^4J=1.6 Hz, 1H, 7-H), 7.17 (dd, ^3J=7.6 Hz, ^4J=1.6 Hz, 1H, 5-H), 7.09 (td, ^3J=7.6 Hz, ^4J=1.2 Hz, 1H, 6-H), 7.03 (dd, ^3J=8.1 Hz, ^4J=1.2 Hz, 1H, 8-H), 3.78 (dd, ^3J=9.4, ^3J=6.2 Hz, 1H, 3-H), 3.69 (s, 2H, 4-H)*, 3.38 (dd, ^2J=16.1 Hz, ^3J=9.4 Hz, 1H, 4-H), 3.05 (dd, ^2J=16.1 Hz, ^3J=6.2 Hz, 1H, 4-H), 2.39 (s, 3H, CH_3C=O), 2.13 (d, ^4J=0.8 Hz, 3H, CH_3COH)*; ^{13}C NMR (151 MHz, CDCl$_3$): δ=200.92 (CH$_3$*C*=O), 177.25 (CH$_3$*C*OH)*, 169.01 (C-2)*, 165.75 (C-2), 151.06 (C-8a), 150.26 (C-8a)*, 128.54 (C-7), 128.44 (C-7)*, 128.27 (C-5), 127.97 (C-5)*, 124.89 (C-6), 124.55 (C-6)*, 121.18 (C-4a), 119.96 (C-4a)*, 116.93 (C-8)*, 116.71 (C-8), 90.57 (C-3)*, 52.44 (C-3), 29.60 (*C*H$_3$C=O), 26.04 (C-4)*, 25.71 (C-4), 19.18 (*C*H$_3$COH)* (*signals from the corresponding enol form); HR-MS (ESI): *m/z*=189.0556 [M−H]$^+$, calculated for C$_{11}$H$_9$O$_3^-$: 189.0557.

General Procedure for the Laccase-Catalysed Arylation of 3,4-Dihydrocoumarins

3,4-Dihydrocoumarin **12** (0.25 mmol) and catechol **15** (0.30 mmol) were dissolved in 1 mL acetonitrile and 1 mL KP$_i$-buffer (KH$_2$PO$_4$/K$_2$HPO$_4$, *c*=0.2 M, pH 6.0). A solution of laccase from *Agaricus bisporus* (15 U=1.875 mg; 8 U/mg) in 1 mL of phosphate buffer was added successively. The mixture was stirred vigorously under air at room temperature (22 °C) for 18–46 h. The reaction mixture was quenched with 5 mL water and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine and dried over MgSO$_4$. After filtration and removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography on silica gel. For the separation of the regioisomers **16d** and **17d** HPLC on a chiral stationary phase was used. The pure products **16** and **17** were obtained after 'drying' the sample on a high vacuum line.

Ethyl 3-(3,4-dihydroxyphenyl)-2-oxochroman-3-carboxylate (16a): Reaction of **12a** (55 mg, 0.25 mmol) and **15a** (33 mg, 0.30 mmol) according to the general procedure after 18 h gave **16a** as a white solid; yield: 58.4 mg (71%); mp 150 °C; R_f=0.23 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3404, 2970, 2922, 1755, 1725, 1459, 1231, 1139, 1120, 1109, 1037, 919, 755, 662 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ=7.24 (dd, ^3J=7.7 Hz, ^4J=1.6 Hz, 1H, 5-H), 7.22 (td, ^3J=8.1 Hz, ^4J=1.6 Hz, 1H, 7-H), 7.09 (td, ^3J=7.7 Hz, ^4J=1.1 Hz, 1H, 6-H), 7.02 (dd, ^3J=8.1 Hz, ^4J=1.1 Hz, 1H, 8-H), 6.85 (d, ^4J=2.3 Hz, 1H, 2′-H), 6.74 (d, ^3J=8.3 Hz, 1H, 5′-H), 6.70 (dd, ^3J=8.3 Hz, ^4J=2.3 Hz, 1H, 6′-H), 4.12 (q, ^3J=7.1 Hz, 2H, OCH_2CH$_3$), 3.70 (d, ^2J=15.7 Hz, 1H, 4-H), 3.54 (d, ^2J=15.7 Hz, 1H, 4-H), 1.05 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, THF-d_8): δ=169.69 (*C*O$_2$Et), 166.22 (C-2), 152.30 (C-8a), 146.15 (C-3′), 145.76 (C-4′), 129.09 (C-8), 128.81 (C-7), 126.52 (C-1′), 124.73 (C-6), 123.23 (C-4a), 119.12 (C-6′), 116.54 (C-5), 115.88 (C-2′), 115.28 (C-5′), 62.20 (CO$_2$*C*H$_2$CH$_3$), 58.35 (C-3), 33.78 (C-4), 13.91 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=327.0874 [M−H]$^+$, calculated for C$_{18}$H$_{15}$O$_6^-$: 327.0874.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-2-oxochroman-3-carboxylate (16b): Reaction of **12a** (56 mg, 0.25 mmol) and **15b** (43 mg, 0.30 mmol) according to the general procedure after 18 h gave **16b** as a pale brown solid; yield: 72.8 mg (80%); mp 48–52 °C; R_f=0.16 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3407, 2937, 2849, 1774, 1720, 1522, 1458, 1230, 1202, 1136, 1084, 918, 759, 661 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ=7.26–7.21 (m, 2H, 5-H, 7-H), 7.09 (td, ^3J=7.5 Hz, ^4J=1.1 Hz, 1H, 6-H), 7.04 (dd, ^3J=8.1 Hz, ^4J=1.1 Hz, 1H, 8-H), 6.60 (d, ^4J=2.1 Hz, 1H, 2'-H), 6.48 (d, ^4J=2.1 Hz, 1H, 6'-H), 5.39 (s, 1H, 3′-OH), 5.26 (br s, 1H, 4'-OH), 4.13 (q, ^3J=7.1 Hz, 2H, OCH_2CH$_3$), 3.86 (s, 3H, 5′-OCH_3), 3.75 (d, ^2J=15.6 Hz, 1H, 4-H), 3.54 (d, ^2J=15.6 Hz, 1H, 4-H), 1.08 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, CDCl$_3$): δ=168.98 (*C*O$_2$Et), 166.64 (C-2), 150.94 (C-5′), 146.84 (C-8a), 143.75 (C-3′), 132.62 (C-4′), 128.61 (C-7), 128.28 (C-5), 125.84 (C-1′), 124.70 (C-6), 121.41 (C-4a), 116.29 (C-8), 108.17 (C-2′), 103.19 (C-6′), 62.48 (CO$_2$*C*H$_2$CH$_3$), 57.97 (C-3), 56.15 (C-5′O*C*H$_3$), 33.42 (C-4), 13.70 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=357.0980 [M−H]$^+$, calculated for C$_{19}$H$_{17}$O$_7^-$: 357.0980.

Ethyl 3-(3,4-dihydroxy-5-methylphenyl)-2-oxochroman-3-carboxylate (16c): Reaction of **12a** (38 mg, 0.17 mmol) and **15c** (25 mg, 0.20 mmol) according to the general procedure after 20 h gave **16c** as a waxy yellow solid; yield: 40.6 mg (70%); mp 43–45 °C; R_f=0.24 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3428, 2981, 1757, 1724, 1459, 1231, 1188, 1136, 1096, 919, 756, 660 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ=7.24 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, 5-H), 7.22 (td, ^3J=8.1 Hz, ^4J=1.5 Hz, 1H, 7-H), 7.09 (td,

^3J=7.5 Hz, ^4J=0.9 Hz, 1H, 6-H), 7.02 (dd, ^3J=8.1 Hz, ^4J=0.9 Hz, 1H, 8-H), 6.70 (d, ^4J=2.2 Hz, 1H, 2′-H), 6.62 (d, ^4J=2.2 Hz, 1H, 6′-H), 6.23 (s, 1H, 3′-OH), 5.54 (s, 1H, 4′-OH), 4.11 (q, ^3J=7.1 Hz, 2H, OCH_2CH$_3$), 3.69 (d, ^2J=15.7 Hz, 1H, 4-H), 3.55 (d, ^2J=15.7 Hz, 1H, 4-H), 2.18 (s, 3H, 5′-CH_3), 1.05 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, CDCl$_3$): δ=169.43 (*C*O$_2$Et), 167.63 (C-2), 150.92 (C-8a), 143.16 (C-3′), 142.71 (C-4′), 128.68 (C-8), 128.33 (C-7), 125.36 (C-4a), 124.85 (C-6), 124.51 (C-1′), 121.54 (C-5′), 121.29 (C-6′), 116.40 (C-5), 112.55 (C-2′), 62.67 (CO$_2$*C*H$_2$CH$_3$), 58.00 (C-3), 33.44 (C-4), 15.73 (C-5′*C*H$_3$), 13.70 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=341.1030 [M−H]$^+$, calculated for C$_{19}$H$_{17}$O$_6^-$: 341.1030.

Ethyl 3-(3,4-dihydroxy-5-fluorophenyl)-2-oxochroman-3-carboxylate (16d) and ethyl 3-(2-fluoro-3,4-dihydroxyphenyl)-2-oxochroman-3-carboxylate (17d): Reaction of **12a** (55 mg, 0.25 mmol) and **15d** (40 mg, 0.30 mmol) according to the general procedure after 19 h gave **16d** and **17d** as a 78:22 mixture of regioisomers; yield: 55.4 mg (64%); R_f 0.15 (petroleum ether/ethyl acetate 70/30); HR-MS (ESI): *m/z*=345.0780 [M−H]$^+$, calculated for C$_{18}$H$_{14}$FO$_6^-$: 345.0780.

Major isomer 16d: pale yellow solid; mp 43–47 °C; IR (ATR): ν=3386, 2961, 2526, 1753, 1721, 1524, 1236, 1138, 1017, 919, 755, 661 cm^{-1}; ^{1}H NMR (600 MHz, MeOH-d_4): δ=7.31 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, 5-H), 7.28 (td, ^3J=7.8 Hz, ^4J=1.6 Hz, 1H, 7-H), 7.13 (td, ^3J=7.5 Hz, ^4J=1.2 Hz, 1H, 6-H), 7.02 (dd, ^3J=8.2 Hz, ^4J=1.2 Hz, 1H, 8-H), 6.62 (d, $^4J_{H,H}$=2.3 Hz, 1H, 2'-H), 6.61 (dd, $^3J_{6'\text{-H,F}}$=15.1 Hz, $^4J_{H,H}$=2.3 Hz, 1H, 6'-H), 4.10 (q, ^3J=7.1 Hz, 2H, OCH_2CH$_3$), 3.69 (d, ^2J=15.8 Hz, 1H, 4-H), 3.66 (d, ^2J=15.8 Hz, 1H, 4-H), 1.06 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, MeOH-d_4): δ=170.49 (*C*O$_2$Et), 168.10 (C-2), 153.11 (d, ^1J=238 Hz, C-5′), 152.52 (C-8a), 148.46 (d, ^3J=5.8 Hz, C-3′), 134.56 (d, ^2J=15.0 Hz, C-4′), 129.75 (C-7), 126.60 (d, ^3J=8.4 Hz, C-1′), 125.89 (C-5), 123.30 (C-6), 117.14 (C-4a), 112.01 (d, ^4J=1.7 Hz, C-2′), 107.45 (d, ^2J=21.7 Hz, C-6′), 102.60 (C-8), 63.50 (CO$_2$*C*H$_2$CH$_3$), 59.29 (C-3), 34.13 (C-4), 14.08 (CO$_2$CH$_2$*C*H$_3$).

Minor isomer 17d: white solid; mp 53–57 °C; IR (ATR): ν=3386, 2928, 2531, 1759, 1728, 1460, 1231, 1140, 1022, 919, 756, 665 cm^{-1}; ^{1}H NMR (600 MHz, MeOH-d_4): δ=7.29 (td, ^3J=7.9 Hz, ^4J=1.6 Hz, 1H, 7-H), 7.24 (dd, ^3J=7.6 Hz, ^4J=1.6 Hz, 1H, 5-H), 7.11 (td, ^3J=7.5 Hz, ^4J=1.2 Hz, 1H, 6-H), 7.06 (dd, ^3J=8.2 Hz, ^4J=1.2 Hz, 1H, 8-H), 6.52 (dd, $^3J_{H,H}$=8.5 Hz, $^5J_{5'\text{-H,F}}$=1.4 Hz, 1H, 5′-H), 6.48 (dd, $^4J_{6'\text{-H,F}}$=7.9 Hz, $^3J_{H,H}$=8.5 Hz, 1H, 6′-H), 4.13 (m, 2H, OCH_2CH$_3$), 3.74 (d, ^2J=15.7 Hz, 1H, 4-H), 3.61 (d, ^2J=15.7 Hz, 1H, 4-H), 1.07 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, MeOH-d_4): δ=170.43 (*C*O$_2$Et), 167.52 (C-2), 166.26 (d, ^1J=244 Hz, C-2′), 152.80 (C-8a), 149.23 (^3J=5.1 Hz, C-4′), 143.44 (^2J=13.8 Hz, C-3′), 129.77 (C-8a), 129.78 (C-5), 129.59 (C-7), 125.89 (^4J=4.4 Hz, C-6′), 125.92 (C-6), 122.91 (C-4a), 118.15 (^3J=5.1 Hz, C-6′), 117.11 (C-8), 111.18 (^5J=1.8 Hz, C-5′), 110.59 (^2J=21.5 Hz, C-1′), 63.50 (CO$_2$*C*H$_2$CH$_3$), 57.75 (C-3), 34.63 (C-4), 14.07 (CO$_2$CH$_2$*C*H$_3$).

Ethyl 3-(2-methyl-4,5-dihydroxyphenyl)-2-oxochroman-3-carboxylate (16e): Reaction of **12a** (55 mg, 0.25 mmol) and **15e** (37 mg, 0.30 mmol) according to the general procedure after 20 h gave **16e** as a yellow solid; yield: 58.0 mg (68%); mp 52–55 °C; R_f=0.17 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3414, 2976, 1757, 1728, 1459, 1231, 1182, 1140, 1023, 918, 867, 756 cm^{-1}; ^{1}H NMR (600 MHz, MeOH-d_4): δ=7.27 (td, ^3J=8.1 Hz, ^4J=1.7 Hz, 1H, 7-H), 7.21 (dd, ^3J=7.4 Hz, ^4J=1.7 Hz, 1H, 5-H), 7.09 (td, ^3J=7.4 Hz, ^4J=1.2 Hz, 1H, 6-H), 7.05 (dd, ^3J=8.1 Hz, ^4J=1.2 Hz, 1H, 8-H), 6.60 (s, 2H, 3′-H, 6′-H), 4.12 (m, 2H, OCH_2CH$_3$), 3.72 (d, ^2J=15.8 Hz, 1H, 4-H), 3.64 (d, ^2J=15.8 Hz, 1H, 4-H), 3.32 (m, 2H, 4′-OH, 5′-OH), 2.13 (s, 3H, 2′-CH_3), 1.07 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, MeOH-d_4): δ=171.48 (*C*O$_2$Et), 168.45 (C-2), 152.76 (C-8a), 145.78 (C-5′), 143.78 (C-4'), 129.67 (C-7), 129.45 (C-5), 129.39 (C-1′), 125.83 (C-6), 125.79 (C-2′), 123.04 (C-4a), 120.33 (C-6′), 116.90 (C-8), 116.19 (C-3′), 63.38 (CO$_2$*C*H$_2$CH$_3$), 59.76 (C-3), 35.08 (C-4), 20.46 (C-2′*C*H$_3$), 14.04 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=341.1030 [M−H]$^+$, calculated for C$_{19}$H$_{17}$O$_6^-$: 341.1030.

Ethyl 3-(2-chloro-4,5-dihydroxyphenyl)-2-oxochroman-3-carboxylate (16f): Reaction of **12a** (55 mg, 0.25 mmol) and **15f** (40 mg, 0.30 mmol) according to the general procedure after 20 h gave **16f** as a yellow solid; yield: 57.0 mg (63%); mp 48–52 °C; R_f=0.18 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3385, 2917, 1765, 1735, 1489, 1459, 1231, 1142, 1019, 918, 863, 756 cm^{-1}; ^{1}H NMR (600 MHz, MeOH-d_4): δ=7.27 (td, ^3J=7.8 Hz, ^4J=1.6 Hz, 1H, 7-H), 7.17 (dd, ^3J=7.4 Hz, ^4J=1.5 Hz, 1H, 5-H), 7.08 (m, 2H, 6-H, 8-H), 6.78 (s, 1H, 3′-H), 6.58 (s, 1H, 6′-H), 4.21 (m, 2H, OCH_2CH$_3$), 3.99 (d, ^2J=16.0 Hz, 1H, 4-H), 3.69 (d, ^2J=16.0 Hz, 1H, 4-H), 1.16 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, MeOH-d_4): δ=170.40 (*C*O$_2$Et), 167.57 (C-2), 152.45 (C-8a), 147.12 (C-4′), 145.35 (C-5′), 129.66 (C-7), 129.53 (C-5), 126.05 (C-6), 124.71 (C-2′), 123.89 (C-1′), 122.90 (C-4a), 118.95 (C-6′), 117.20 (C-3′), 116.99 (C-8), 63.63 (CO$_2$*C*H$_2$CH$_3$), 60.34 (C-3), 34.06 (C-4), 14.10 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=361.0484 [M−H]$^+$, calculated for C$_{18}$H$_{14}$ClO$_6^-$: 361.0484.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-6-methyl-2-oxochroman-3-carboxylate (16g): Reaction of **12b** (58 mg, 0.25 mmol) and **15b** (42 mg, 0.30 mmol) according to the general procedure after 24 h gave **16g** as a brown solid; yield: 86.5 mg (94%); mp 50–57 °C; R_f=0.18 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3438, 2937, 1754, 1728, 1615, 1521, 1463, 1258, 1201, 1138, 1085, 815, 692 cm^{-1}; ^{1}H NMR (600 MHz, MeOH-d_4): δ=7.12 (d, ^4J=2.0 Hz, 1H, 5-H), 7.07 (dd, ^3J=8.3 Hz, ^4J=2.0 Hz, 1H, 7-H), 6.89 (d, ^3J=8.3 Hz, 1H, 8-H), 6.47 (d, ^4J=2.2 Hz, 1H, 2'-H), 6.46 (d, ^4J=2.2 Hz, 1H, 6'-H), 4.12 (m, 2H, OCH_2CH$_3$), 3.80 (s, 3H, 5′-OCH_3), 3.65 (s, 2H, 4-H), 2.30 (s, 3H, 6-CH_3), 1.09 (t, ^3J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (151 MHz, MeOH-d_4): δ=170.89 (*C*O$_2$Et), 168.73 (C-2), 150.46 (C-5′), 149.42 (C-8a), 146.45 (C-3′), 135.72 (C-6), 135.40 (C-4′), 130.03 (C-5), 130.02 (C-7), 126.46 (C-1′), 123.19 (C-4a), 116.82 (C-8), 109.83 (C-2′), 104.43 (C-6′), 63.33 (CO$_2$*C*H$_2$CH$_3$), 59.69 (C-3), 56.73 (C-5′O*C*H$_3$), 34.29 (C-4), 20.73 (C-6 *C*H$_3$), 14.15 (CO$_2$CH$_2$*C*H$_3$); HR-MS (ESI): *m/z*=371.1136 [M−H]$^+$, calculated for C$_{20}$H$_{19}$O$_7^-$: 371.1136.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-6-methoxy-2-oxochroman-3-carboxylate (16h): Reaction of **12c** (62 mg, 0.25 mmol) and **15b** (42 mg, 0.30 mmol) according to the general procedure after 46 h gave **16h** as a pale brown solid; yield: 81.0 mg (84%); mp 48–53 °C; R_f 0.08 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3430, 2939, 2843, 1754, 1728, 1614, 1521, 1494, 1198, 1139, 1086, 1019, 811, 693 cm^{-1}; ^{1}H NMR (600 MHz, MeOH-d_4): δ=6.93 (d, ^3J=

8.9 Hz, 1H, 8-H), 6.87 (d, ^4J=3.0 Hz, 1H, 5-H), 6.81 (dd, ^3J=8.9 Hz, ^4J=3.0 Hz, 1H, 7-H), 6.48 (d, ^4J=2.2 Hz, 1H, 2′-H), 6.47 (d, ^4J=2.2 Hz, 1H, 6′-H), 4.13 (m, 2H, OCH_2CH_3), 3.81 (s, 3H, 5′-OCH_3), 3.77 (s, 3H, 6-OCH_3), 3.67 (s, 2H, 4-H), 1.11 (t, ^3J=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (151 MHz, MeOH-d_4): δ=170.87 (CO_2Et), 168.76 (C-2), 158.03 (C-5′), 149.43 (C-3′), 146.45 (C-6), 146.35 (C-8a), 135.40 (C-4′), 126.39 (C-1′), 124.55 (C-4a), 117.91 (C-8), 114.75 (C-7), 114.56 (C-5), 109.84 (C-2′), 104.42 (C-6′), 63.36 ($CO_2CH_2CH_3$), 59.61 (C-3), 56.74 (C-5′OCH_3), 56.12 (C-6 OCH_3), 34.49 (C-4), 14.18 ($CO_2CH_2CH_3$); HR-MS (ESI): m/z=387.1086 $[M-H]^+$, calculated for $C_{20}H_{19}O_8^-$: 387.1085.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-6-fluoro-2-oxochroman-3-carboxylate (16i): Reaction of **12d** (59 mg, 0.25 mmol) and **15b** (42 mg, 0.30 mmol) according to the general procedure after 22 h gave **16i** as a pale brown solid; yield: 71.4 mg (77%); mp 142 °C; R_f=0.14 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3419, 2985, 2854, 1769, 1713, 1607, 1520, 1492, 1191, 1145, 1080, 1022, 821, 718, 692 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.00 (ddd, $^3J_{H,F}$=8.2 Hz, ^4J=4.6 Hz, ^5J=1.0 Hz, 1H, 5-H), 6.94 (dd, ^3J=8.1 Hz, $^4J_{H,F}$=2.4 Hz, 1H, 8-H), 6.93 (m, 1H, 7-H), 6.57 (d, ^4J=2.2 Hz, 1H, 2′-H), 6.45 (d, ^4J=2.2 Hz, 1H, 6′-H), 5.47 (s, 1H, 3′-OH), 5.37 (s, 1H, 4′-OH), 4.16 (q, ^3J=7.1 Hz, 2H, OCH_2CH_3), 3.85 (s, 3H, 5′-OCH_3), 3.73 (d, ^2J=15.8 Hz, 1H, 4-H), 3.51 (d, ^2J=15.8 Hz, 1H, 4-H), 1.12 (t, ^3J=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ=168.67 (CO_2Et), 166.13 (C-2), 159.11 (d, ^1J=244 Hz, C-6), 147.02 (d, ^4J=2.6 Hz, C-8a), 146.80 (C-5′), 143.76 (C-3′), 132.57 (C-4′), 125.72 (C-1′), 123.22 (d, ^3J=8.3 Hz, C-4a), 117.74 (d, ^3J=8.5 Hz, C-8), 115.41 (d, ^2J=23.6 Hz, C-5), 114.98 (d, ^2J=24.1 Hz, C-7), 108.02 (C-2′), 103.01 (C-6′), 62.67 ($CO_2CH_2CH_3$), 57.68 (C-3), 56.23 (C-5′OCH_3), 33.61 (C-4), 13.83 ($CO_2CH_2CH_3$); HR-MS (ESI): m/z=375.0885 $[M-H]^+$, calculated for $C_{19}H_{16}FO_7^-$: 375.0885.

3-Acetyl-3-(3,4-dihydroxy-5-methoxyphenyl)-chroman-2-one (16j): Reaction of **12e** (50 mg, 0.26 mmol) and **15b** (44 mg, 0.32 mmol) according to the general procedure after 18 h gave **16j** as a pale brown solid; yield: 54.5 mg (63%); mp 65 °C; R_f=0.19 (petroleum ether/ethyl acetate 70/30); IR (ATR): ν=3532, 3390, 2919, 2849, 1753, 1687, 1611, 1539, 1454, 1302, 1233, 1142, 1082, 1026, 847, 757, 655 cm^{-1}; ^{1}H NMR (600 MHz, MeOH-d_4): δ=7.27 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, 5-H), 7.23 (td, ^3J=7.8 Hz, ^4J=1.6 Hz, 1H, 7-H), 7.07 (td, ^3J=7.5 Hz, ^4J=1.2 Hz, 1H, 6-H), 6.98 (dd, ^3J=7.8 Hz, ^4J=1.2 Hz, 1H, 8-H), 6.42 (d, ^4J=2.2 Hz, 1H, 2′-H), 6.37 (d, ^4J=2.2 Hz, 1H, 6'-H), 3.79 (s, 3H, 5′-OCH_3), 3.70 (d, ^2J=16.2 Hz, 1H, 4-H), 3.55 (d, ^2J=16.2 Hz, 1H, 4-H), 2.08 (s, 3H, $COCH_3$); ^{13}C NMR (151 MHz, MeOH-d_4): δ=205.12 ($COCH_3$), 169.32 (C-2), 152.47 (C-5′), 149.99 (C-8a), 147.09 (C-3′), 135.67 (C-4′), 129.60 (C-7), 129.50 (C-8), 125.81 (C-1′), 125.69 (C-6), 123.42 (C-4a), 116.87 (C-5), 109.57 (C-2′), 103.89 (C-6′), 64.24 (C-3), 56.75 (C-5′OCH_3), 32.79 (C-4), 27.22 ($COCH_3$); HR-MS (ESI): m/z=327.0873 $[M-H]^+$, calculated for $C_{18}H_{15}O_6^-$: 327.0874.

General Procedure for the Laccase-Catalysed Arylation of 3,4-Dihydrocoumarins in a Consecutive One-Pot Approach

The H-Cube Pro™ flow system was prepared according to the general procedure of the flow hydrogenation. Coumarin **11** (0.25 mmol) was dissolved in the relevant solvent (absolue, 0.05 M). The catechol **15b** (0.30 mmol) was dissolved in 1 mL of the relevant solvent and drawn into a 2 mL syringe. This syringe was placed on a syringe pump. A solution of laccase from *Agaricus bisporus* (15 U=1.875 mg; 24 U=3.0 mg; 8 U/mg) in 12 mL of phosphate buffer (KH_2PO_4/K_2HPO_4, c=0.2 M, pH 6.0) was placed in the reaction flask. The injection rate of the syringe pump was adjusted to the flow rate of the reduction system. With stirring of the enzyme solution both reagents were added successively. The mixture was stirred vigorously under air at room temperature (22 °C) for 18–27 h. The reaction mixture was quenched with 10 mL water and extracted with ethyl acetate (3× 30 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the crude products were purified by flash column chromatography on silica gel. The pure products **16** were afforded after drying in high vacuum.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-2-oxochroman-3-carboxylate (16b): Conditions: 5 atm, 20 °C, 100% H_2, 0.3 mL min^{-1}, 4.32 mL h^{-1} injection rate. Reaction of **11a** (50 mg, 0.23 mmol) and **15b** (39 mg, 0.28 mmol) in acetonitrile with 15 U of laccase according to the general procedure gave **16b** after 18 h as a pale brown solid; yield: 67.6 mg (82%). The spectroscopic data corresponded to those previously measured.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-2-oxochroman-3-carboxylate (16b): Conditions: 7 atm, 20 °C, 35% H_2, 0.5 mL min^{-1}, 7.20 mL h^{-1} injection rate. Reaction of **11a** (55 mg, 0.25 mmol) and **15b** (42 mg, 0.30 mmol) in tetrahydrofuran with 24 U of laccase according to the general procedure gave **16b** after 23 h as a pale brown solid; yield: 61.0 mg, (68%). The spectroscopic data corresponded to those previously measured.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-6-methyl-2-oxochroman-3-carboxylate (16g): Conditions: 7 atm, 20 °C, 35% H_2, 0.5 mL min^{-1}, 7.20 mL h^{-1} injection rate. Reaction of **11b** (57 mg, 0.25 mmol) and **15b** (41 mg, 0.29 mmol) in tetrahydrofuran with 24 U of laccase according to the general procedure gave **16g** after 22 h as a brown solid; yield: 66.0 mg (72%). The spectroscopic data corresponded to those previously measured.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-6-methoxy-2-oxochroman-3-carboxylate (16h): Conditions: 7 atm, 20 °C, 35% H_2, 0.5 mL min^{-1}, 7.20 mL h^{-1} injection rate. Reaction of **11c** (62 mg, 0.25 mmol) and **15b** (42 mg, 0.30 mmol) in tetrahydrofuran with 24 U of laccase according to the general procedure gave **16h** after 27 h as a pale brown solid; yield: 60.3 mg (62%). The spectroscopic data corresponded to those previously measured.

Ethyl 3-(3,4-dihydroxy-5-methoxyphenyl)-6-fluoro-2-oxochroman-3-carboxylate (16i): Conditions: 7 atm, 22 °C, 40% H_2, 0.4 mL min^{-1}, 5.76 mL h^{-1} injection rate. Reaction of **11d** (59 mg, 0.25 mmol) and **15b** (42 mg, 0.30 mmol) in tetrahydrofuran with 24 U of laccase according to the general procedure gave **16i** after 20 h as a pale brown solid; yield: 37.2 mg (40%). The spectroscopic data corresponded to those previously measured.

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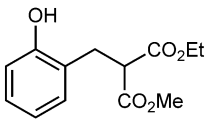

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