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# Regiodivergent Iodocyclizations for the Highly Diastereoselective Synthesis of *syn*- and *anti*-Hydroxyl-Isochromanones and -Isobenzofuranones: Concise Synthesis of the Isochromanone Core of the Ajudazols

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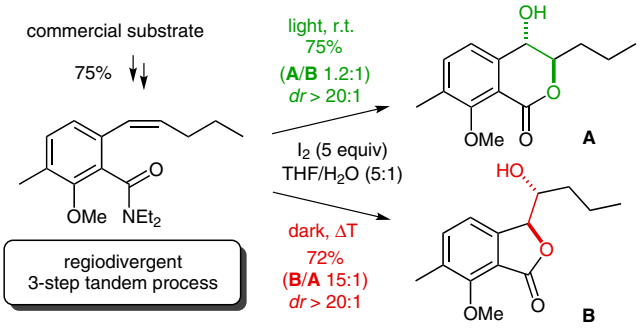


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**Abstract** An efficient synthetic strategy to access hydroxyl-isochromanone and -isobenzofurans from readily available joint alkene precursors by a regiodivergent one-pot iodocyclization–substitution tandem process is reported. The cyclizations proceed with excellent diastereoselectivities, with *E*-alkenes giving *syn*-configured products and *Z*-alkenes giving *anti*-products. A strong influence of light on the regioselectivity of the reaction was observed. High yields were also observed under radical conditions. The protective-group-free method enables a highly concise synthesis of the authentic isochromanone core of the ajudazols, which are highly potent inhibitors of the mitochondrial respiratory chain.

**Key words** natural products, asymmetric synthesis, iodocyclisation, tandem reaction, diastereoselectivity

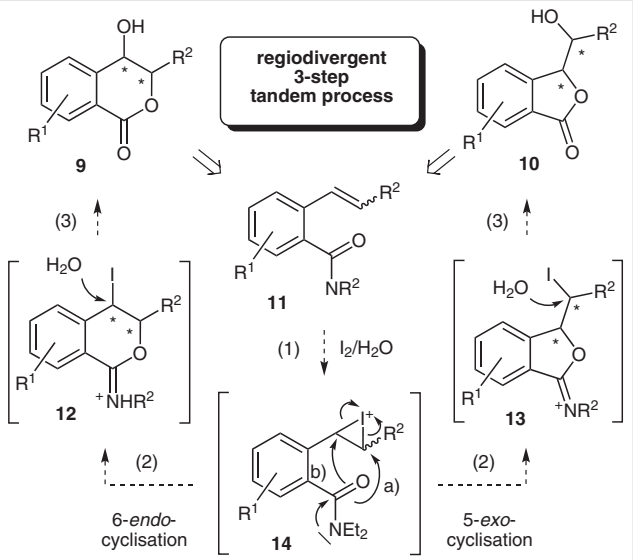
The ajudazols, which are structurally unique polyketides from the myxobacterium *Chondromyces crocatus*,[2–4] demonstrate extremely potent and selective inhibitory activities of the mitochondrial respiratory chain,[5] a key regulatory pathway for aerobic energy production that has been associated with various diseases,[6] including neuronal disorders.[7] As shown in Figure 1, a densely functionalized hydroxyl-isochromanone core constitutes one of the key structural elements of natural ajudazols A (**1**) and B (**2**), as well as a range of further bioactive natural products,[8,9] including the paecilomycins (**5**).[8b] However, only a few general synthetic methods to access this structural feature have been reported,[10] and these rely mainly on intramolecular Diels–Alder reactions (IMDA),[11] rearrangement reactions,[12] gold catalysis,[13] asymmetric oxylactonization reactions,[14] or asymmetric ortholithiation strategies.[4,15]

As exemplified by the paecilomycins/aigialomycin group of natural products (**5**, **7**)[9b,d] hydroxyl-isochromanones often co-occur with their corresponding hydroxyl-isobenzofuranone isomers. These heterocycles likewise constitute an important structural element in various bioactive natural products and medicinal compounds,[9,16] such as pestaphthalide A and B (**6**, **8**),[16c] with variable relative configurations. In addition, hydroxyl-isochromanones may also easily form the corresponding benzofuranones under basic conditions by translactonizations,[2,14c] and analogues of type **3** and **4** have also been postulated as more stable isomerization products for the ajudazols.[4] This renders the development of a flexible approach to access hydroxyl-isochromanone and –isobenzofuranone isomers by a modular synthetic route an attractive research goal.

As part of our efforts to develop novel one-pot procedures to generate complex polyketides,[17] we report herein a concise synthetic strategy to access all possible *syn*- and *anti*-hydroxyl-isochromanones and -isobenzofuranones. The approach involves a diversification strategy from readily available alkene precursors through a regiodivergent one-pot iodocyclization tandem process. The cyclizations proceed with excellent diastereoselectivity and enable an extremely short synthesis of the isochromanone and isobenzofuranone cores of the ajudazols and isoajudazols.

As shown in detail in Scheme 1, our modular synthetic strategy to access the target lactones of type **9** and **10** was based on iodocyclization of the same benzoic acid derived alkene **11**. After formation of an iodonium intermediate **14**, the amide or an analogous nucleophilic benzoic acid derivative may then undergo a formal 6-*endo*- or 5-*exo*-cyclization to access either **12** or **13**, which may then be substituted and hydrolyzed to the desired target heterocycles **9** or **10**.[18] We expected that a suitable choice of reaction conditions would lead to the desired regioisomeric product, whereas the double bond configuration may be used to control the diastereoselectivity. Reported precedence suggested that such a formal *endo*-pathway may indeed be possible for certain aromatic benzoic esters with *E*-alkenes,[14a,c] and related 5-*exo*-iodocyclizations without hydrolysis of the iodide have also been reported.[19,20]

To examine the feasibility of such a tandem process, we first studied the iodocyclization of various *E*-alkenes of type **19** to access hydroxyl-isochromanone **20** (Scheme 2). We envisioned that the functionalization of the benzoic acid derivative would have a critical influence on the reaction pathway. We were particularly interested in evaluating amides because they can be axially chiral,[4,21] which may




**Scheme 1** Proposed mechanism for a modular tandem process for the regiodivergent synthesis of hydroxyl-isochromanones and -isobenzofuranones

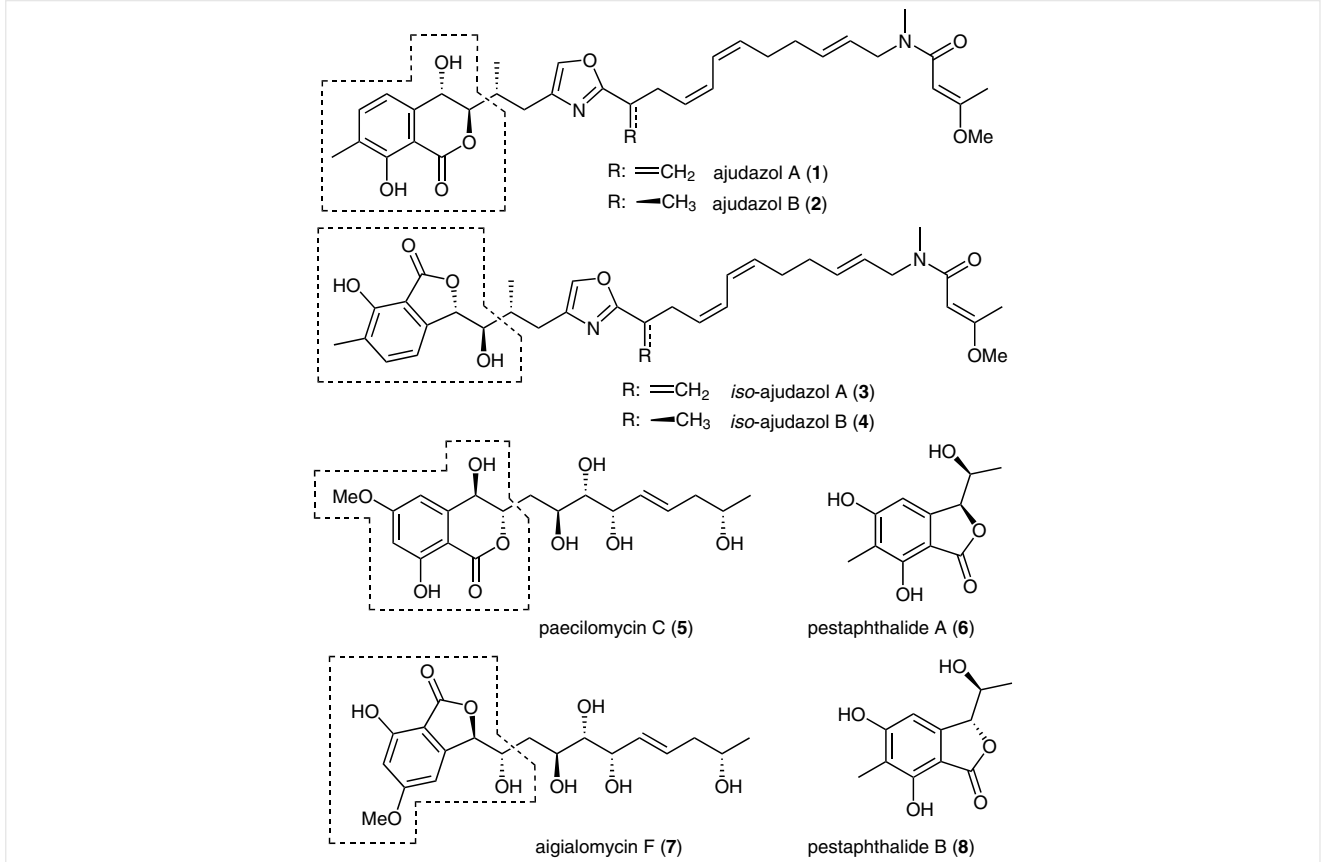
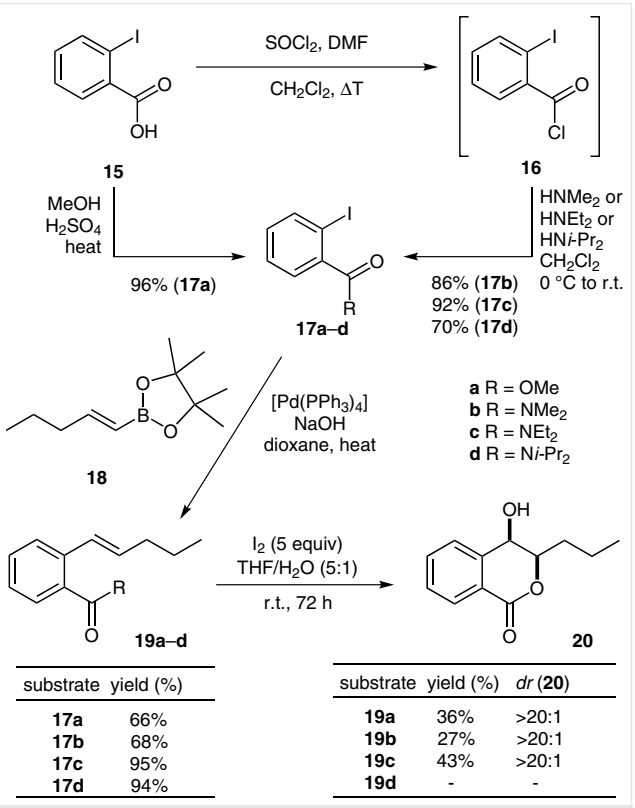



**Figure 1** The ajudazols and related hydroxyl-isochromanone and hydroxyl-isobenzofuranone natural products

potentially be of use for asymmetric induction of the tandem process. Consequently, three different amides **17b**–**d** with variable steric demand were prepared together with ester **17a**. As shown in Scheme 2, their synthesis was accomplished by a diversification strategy from commercial iodobenzoic acid **15**. Synthesis of methyl ester **17a** was effected by acid-catalyzed esterification,[22] whereas dimethyl, diethyl, and diisopropyl amides **17b**–**d** were obtained by treatment of the acid chloride with the corresponding amines.[23] Suzuki coupling[24] of these iodides with *E*-boronate **18**[25] then gave access to the desired *E*-alkenes **19a**–**d** in high yields.[26]



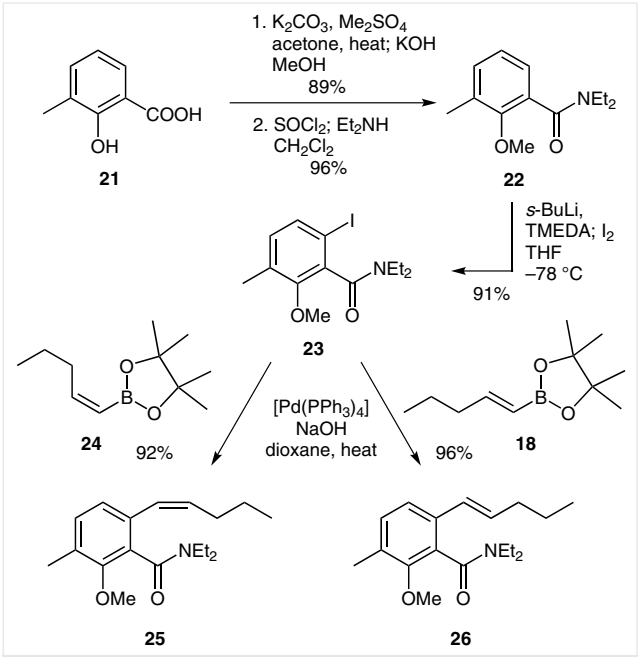

| substrate | yield (%) |
|---|---|
| **17a** | 66% |
| **17b** | 68% |
| **17c** | 95% |
| **17d** | 94% |

| substrate | yield (%) | *dr* (**20**) |
|---|---|---|
| **19a** | 36% | >20:1 |
| **19b** | 27% | >20:1 |
| **19c** | 43% | >20:1 |
| **19d** | - | - |

**Scheme 2** Concise synthesis of simplified hydroxyl-isochromanone **20** by one-pot iodocyclization-hydrolysis: evaluation of benzoic amides

These substrates were then submitted to various modifications of an iodocyclization protocol that was reported for a related cyclization.[27] Gratifyingly, using iodine (5 equiv) in a mixture of THF and water (5:1), the desired transformation into **20** could indeed be observed.[28,29] Higher yields were obtained for diethyl amide **19c** compared with dimethyl amide **19b** and methyl ester **19a**. In contrast, no product formation was observed for diisopropylamide **19d**, presumably for steric reasons. Importantly, in all cases, excellent *syn*-diastereoselectivities were observed, which suggests that this reaction proceeds by a highly conserved stereochemical transfer of the double bond configuration to the corresponding configuration of the hydroxyl-lactone.[17,18]

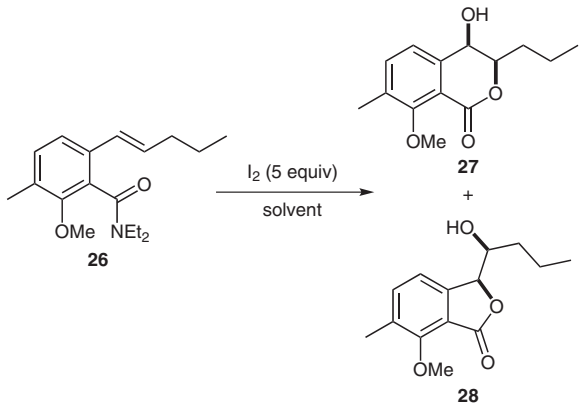
Having established the principal adaptability and the usefulness of ethyl amides, we then turned our attention to the authentic substitution pattern of the ajduzols and prepared the *ortho*-substituted *Z*- and *E*-alkenes **25** and **26**. As shown in Scheme 3, a joint synthesis was achieved by a diversification strategy involving iodo-compound **23**, which was coupled with either *Z*- or *E*-boronate **24**[30] and **18** to give the target compounds **25** and **26** in high yields. Iodo-compound **23** was readily available from commercial benzoic acid **21** by methylation,[11b] conversion into amide **22** via the acid chloride (not shown), and a high-yielding introduction of the iodide by an *ortho*-metalation strategy.




**Scheme 3** Concise synthesis of *E*- and *Z*-alkenes by a diversification strategy from joint intermediate **23**

With both **25** and **26** in hand, we studied our concept of a regiodivergent cyclization. We thus analyzed the tandem iodocyclization-hydrolysis of **26** to access both isochromanone **27** and isobenzofuranone **28**. As shown in Table 1, we first evaluated various solvent conditions. Gratifyingly, it quickly became apparent that both products could indeed be obtained in a regiodivergent fashion, proving our initial concept.[31] In agreement with our first study (Scheme 2), the *syn*-configured isochromanone was obtained, which was assigned from the small vicinal coupling constant between the two oxygen-bearing substituents ($J$ = 1.8 Hz), whereas the configuration of the isobenzofurane was unambiguously determined by X-ray crystallographic analysis (see Figure 2). In contrast to the reaction of the unsubstituted alkenes **19** (Scheme 2), the observed yields were only

**Table 1** Evaluation of Solvents for the Regiodivergent Cyclization of *E*-alkene **26** to *syn*-Products **27** and **28**[a]




| Entry | Solvent | Yield/rsm (%)[a] | | |
|---|---|---|---|---|
| | | **27** | **28** | **26** |
| 1[b] | THF | 13 | 17 | 0 |
| 2[b] | dioxane | 5 | 9 | 0 |
| 3[b] | acetone | 2 | 37 | 22 |
| 4[b] | DMF | 9 | 6 | 2 |
| 5[b] | DMSO | 18 | 13 | 29 |
| 6[b] | pyridine | 0 | 0 | 28 |
| 7[b] | $Et_2O$ | 1 | 6 | 33 |
| 8[b] | toluene | 0 | 0 | 73 |
| 9[b] | $CH_2Cl_2$ | 12 | 6 | 50 |
| 10[b] | EtOAc | 2 | 11 | 26 |
| 11[b] | cyclohexane | 0 | 2 | 43 |
| 12[b] | EtOH | 4 | 4 | 32 |
| 13 | $H_2O$ | 0 | 2 | 23 |
| 14[b] | MeCN | 0 | 11 | 18 |
| 15[c] | THF | 13 | 12 | 15 |
| 16[d] | THF | 0 | 0 | 100 |
| 17 | $H_2O$ | 0 | 2 | 23 |
| 18[e] | THF | 0 | 0 | 100 |
| 19[f] | THF | 8 | 21 | 0 |
| 20[g] | THF | 0 | 5 | 61 |
| 21[h] | THF | 0 | 11 | 70 |

[a] Reaction conditions (concn: 0.02 M): $I_2$ (5.0 equiv), r.t., 72 h; yield was determined by qNMR analysis of the crude product: see experimental part; rsm = recovered starting material.
[b] Solvent–$H_2O$, 5:1.
[c] Solvent–$H_2O$, 1:1.
[d] No water added.
[e] Concn: 0.002 M.
[f] Concn: 0.2 M.
[g] $H_2O$ (1.0 equiv) used.
[h] $H_2O$ (2.0 equiv) used.

low. Among the solvents evaluated, best yields were obtained for THF, acetone, and DMSO (entries 1, 3, and 5). We then studied the influence of the THF/water ratios (entries 15–21). As expected, no product was formed in the absence of water (entry 16). Increasing the water ratio was accompanied by a slight increase in the isochromanone/isobenzofuran ratio (entry 15), whereas the use of stoichiometric amounts of water lead to exclusive formation of the five-membered product, albeit in very low yields (entries 20 and 21). The low yield could not be further improved by increasing the concentration (entry 19), and dilution lead to decreased conversion (entry 18). In general, the degree of selectivity for product formation was affected by both the nature and the amount of solvent.

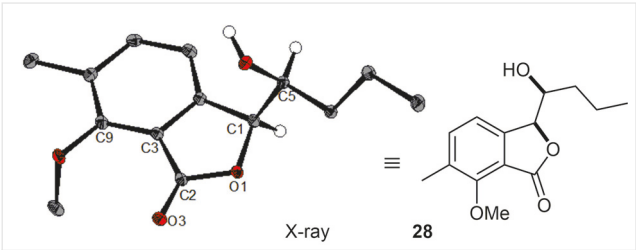
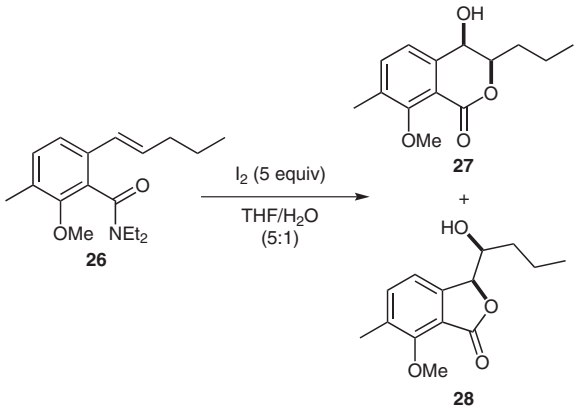



**Figure 2** X-ray crystal structure analysis of isobenzofuranone **28**

As shown in Table 2, we then evaluated alternative reaction parameters. Essentially no effect was observed by ultrasonicating the mixture (entries 1 and 2). However, the use of microwave irradiation accelerated the cyclization significantly, leading to useful levels of conversion (entry 4). Furthermore, irradiation with a 300 W Osram daylight lamp speeded up the reaction (entry 5). Importantly, a different preference for one of the regioisomers was observed under these conditions. Whereas microwave activation led to preferential formation of the five-membered lactone **28**, the six-membered ring **27** was obtained as the main product by irradiation with a daylight lamp.[32] During irradiation, a significant warming of the reaction to approximately 65 °C was observed. To analyze the thermal effect, we heated the reaction to this temperature, but excluded light (entry 6).[33] Again, higher yields were observed compared with those obtained by conducting the reaction at room temperature (Table 1, entry 1). However, the selectivity was switched and isobenzofuranone **28** was obtained as the main product. In contrast, only low levels of conversions were obtained upon irradiation and cooling (Table 2, entry 7) or upon lowering the reflux temperature (entry 8), demonstrating the important thermal effect. Carrying out the same reaction in the absence of light (entry 9) also led to a decreased yield, which again documents the importance of light for activation of the reaction. Importantly, no loss in the diastereoselectivity of the reaction was observed during irradiation (entries 5, 7, and 8).

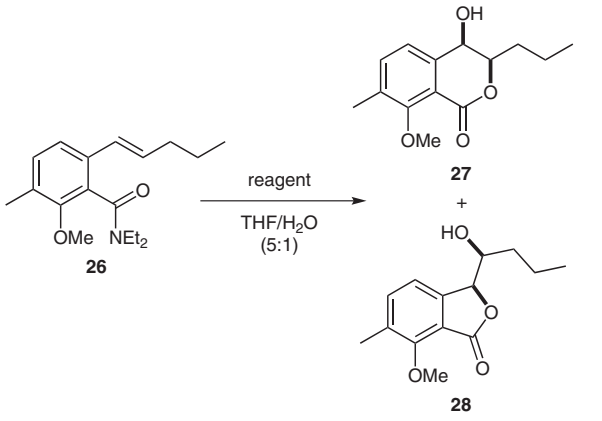
**Table 2** Evaluation of Microwave Conditions, Temperature, and Irradiation on the Regiodivergent Cyclization of *E*-Alkene **26** to *syn*-Products **27** and **28**[a]




| Entry | Conditions[a] | Yield/rsm (%)[b] | | |
|---|---|---|---|---|
| | | **27** | **28** | **26** |
| 1 | ultrasound, r.t., 4 h | 2 | 5 | 47 |
| 2 | ultrasound, r.t., 15 h | 5 | 14 | 0 |
| 3 | MW, 100 °C, 1 h | 7 | 24 | 43 |
| 4 | MW, 100 °C, 4 h | 12 | 40 | 0 |
| 5 | 300 W irradiation, reflux, 72 h | 34 | 29 | 5 |
| 6 | dark, 65 °C, 72 h | 22 | 42 | 6 |
| 7 | 300 W irradiation, 10 °C, cooling, 72 h | 2 | 5 | 49 |
| 8 | 300 W irradiation, reflux, $CH_2Cl_2$, 72 h | 14 | 15 | 40 |
| 9 | dark, r.t., 72 h | 9 | 12 | 27 |

[a] Reaction conditions (concn: 0.02 M): $I_2$ (5.0 equiv), THF–$H_2O$, 5:1.
[b] Yield was determined by qNMR analysis of the crude product: see experimental part; rsm = recovered starting material.

**Table 3** Evaluation of Iodine Reagents and Additives on the Regiodivergent Cyclization of *E*-Alkene **26** to *syn*-Products **27** and **28**[a]




| Entry | Conditions[a] | Yield/rsm (%)[b] | | |
|---|---|---|---|---|
| | | **27** | **28** | **26** |
| 1 | $I_2$ (1.1 equiv) | 2 | 3 | 47 |
| 2 | $I_2$ (20 equiv) | 16 | 19 | 0 |
| 3 | NIS (5 equiv) | 10 | 23 | 31 |
| 4 | ICl (5 equiv) | 12 | 15 | 49 |
| 5 | $I_2$ (5 equiv), HCl (5%) | 2 | 8 | 30 |
| 6 | $I_2$ (5 equiv), $H_2SO_4$ (5%) | 13 | 16 | 14 |
| 7 | $I_2$ (5 equiv), KOH (5%) | 6 | 17 | 15 |
| 8 | $I_2$ (5 eq), AIBN | 17 | 49 | 0 |
| 9 | $I_2$ (5 equiv), AIBN, irradiation (300 W) | 25 | 48 | 0 |

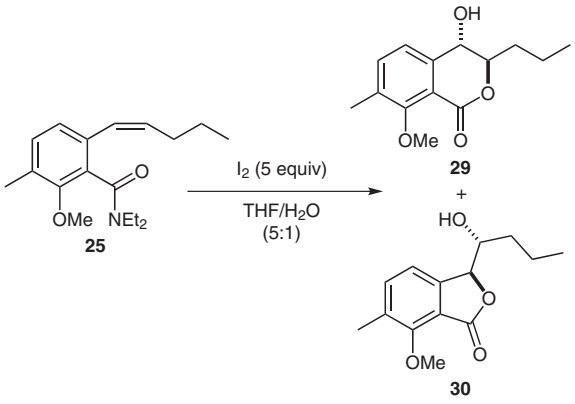
[a] Reaction conditions (concn: 0.02 M): stirring at r.t. for 72 h, THF–$H_2O$ (5:1).
[b] Yield was determined by qNMR analysis of the crude product: see experimental part; rsm = recovered starting material.

As shown in Table 3, we then studied the influence of the number of equivalents and the source of iodine, as well as alternative additives. Increasing the iodine concentration lead to a slight increase in yield (entry 2), whereas only very low yields were obtained with 1.1 equivalent of the halogen (entry 1). The use of either NIS or iodine chloride led to very similar yields (entries 3 and 4). Addition of acids or bases did not have a beneficial effect on the reaction (entries 5–7). As shown in Table 3, entries 8 and 9 this reaction can be carried out under radical conditions. In the presence of the radical initiator AIBN an increase of the conversion was observed (entries 8 and 9). In agreement with a slight decrease of diastereoselectivity (**28**: dr 7:1; entry 8) the reaction presumably proceeds through a radical pathway.

Having established useful conditions to access both the *syn*-isochromanone **27** and -isobenzofuranone **28**, with excellent diastereoselectivities and useful regioselectivities (e.g., Table 2, entries 4–6), we then evaluated whether these results may also be applied to the corresponding *Z*-alkene **25** and evaluated the most efficient conditions for conversion of **25**. As shown in Table 4, both isochromanone **29** and isobenzofuranone **30** were obtained, which confirms the general proof of our divergent synthetic concept. Importantly, these two products were again observed as single isomers, but now with an *anti*-configuration. This demonstrates that the configuration of the double bond is reliably transferred to the relative configuration of the two new vicinal chiral centers. Consistent with the results obtained above, irradiation with light resulted in preparatively useful yields (entry 3), with the six-membered heterocycle formed as the main product. Heating the reaction led to dramatically improved yields (entry 2) and, consistent with the results obtained above, the regioselectivity was again switched in favor of the isobenzofuranone, and high regioselectivities (15:1) were obtained.

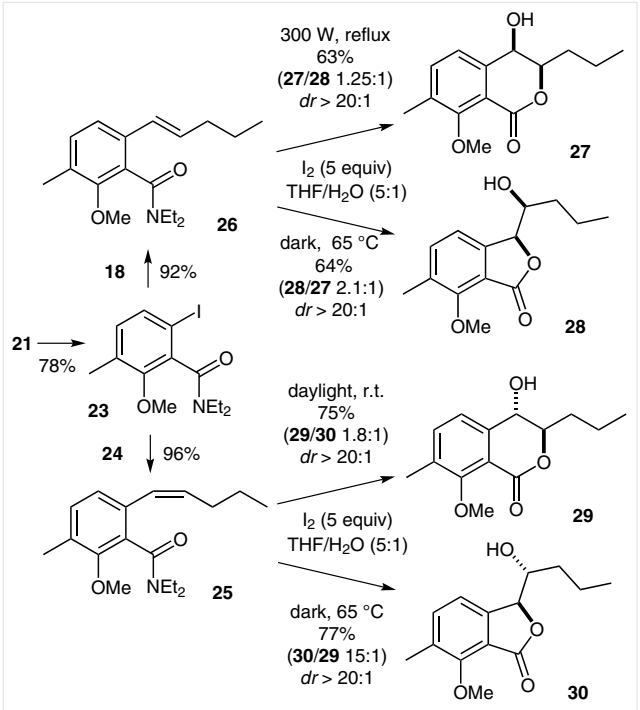
Importantly, the most effective conditions reported above were readily reproducible. As shown in Scheme 4 this enables rapid access to all *syn*- and *anti*-configured ajudazol type isochromanones and isobenzofuranones **27**–**30** in only two steps from iodo compound **23**, which, in turn, can be easily synthesized from commercial benzoic acid **21**.

**Table 4** Regiodivergent Cyclization of *Z*-Alkene **25** to *anti*-Products **29** and **30**[a]

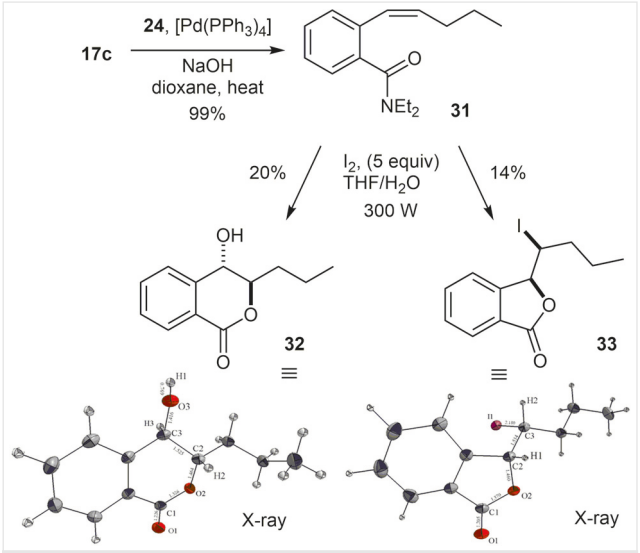



| Entry | Conditions[a] | Yield/rsm (%)[b] | | |
|---|---|---|---|---|
| | | **29** | **30** | **25** |
| 1 | daylight, r.t. | 48 | 27 | 0 |
| 2 | dark, 65 °C | 5 | 72 | 0 |
| 3 | 300 W irradiation, reflux | 34 | 28 | 0 |
| 4 | MW, 100 °C, 4 h | 33 | 26 | 0 |

[a] Reaction conditions (concn: 0.02 M): $I_2$ (5.0 equiv), THF–$H_2O$ (5:1), stirring for 72 h.
[b] Yield was determined by qNMR analysis of the crude product: see experimental part; rsm = recovered starting material.




**Scheme 4** Concise synthesis of all ajudazol type *syn*- and *anti*-hydroxyl-isochromanones and -isobenzofuranones by a diversification strategy from joint intermediate **23**



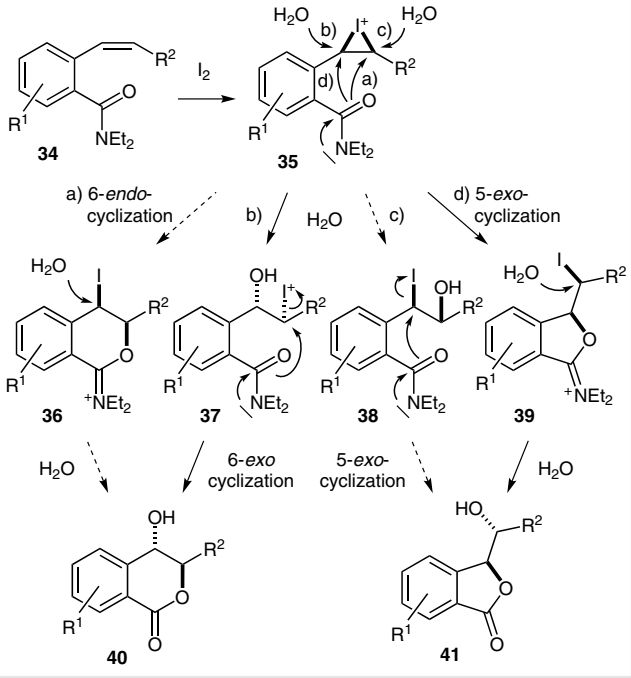

**Scheme 5** Synthesis and X-ray crystal structures of simplified *anti*-isochromanone **32** and iodo-isobenzofuranone **33**

All regio- and diastereomeric products can be obtained selectively in the tandem cyclization depending on the choice of reaction conditions. In all cases, high diastereoselectivities were obtained, with the *anti*-configured products being obtained from *Z*-alkenes and the *syn*-products deriving from *E*-alkenes.

To further understand the mechanism of this reaction, we then tried to isolate iodinated intermediates. This was successful in the cyclization of simplified *Z*-alkene **31**, which was readily obtained by coupling of iodide **17c** with *Z*-boronate **24** (Scheme 5). Both the *anti*-isochromanone **32** and the iodinated compound **33** could be obtained, and the structures of both heterocycles were unambiguously proven by X-ray crystallographic analysis.

Based on these results, a mechanism may be proposed for this iodocyclization/substitution reaction. As shown in Scheme 6 for the conversion of *Z*-alkene **34**, it is expected that the excellent diastereoselectivities are derived from two nucleophilic substitution reactions. Presumably, the reaction proceeds via iodonium intermediate **35**. Based on the isolation of iodolactone **33**, we assume that formation of isobenzofuranone **41** is initiated by a 5-*exo*-trig cyclization of the amide oxygen of **35** and subsequent substitution of intermediate **39**. This pathway should be favored over an alternative that would first involve intermolecular attack of water and subsequent 5-*exo*-cyclization of **38**. Presumably, formation of isochromanone **40** should proceed by a different sequence, involving direct intramolecular substitution of the reactive benzylic position as compared to a 6-*endo*-cyclization of **35** towards **36**.[34] Cyclization of the resulting benzylic alcohol **37** would then proceed in a much more favorable *exo*-fashion. This proposal is consistent with a pre-

vious proposal for a related conversion[14a] as well as with our own experimental results demonstrating that a decrease of the water concentration disfavors the six-membered-ring formation.




**Scheme 6** Proposed mechanism for the one-pot iodocyclization-substitution sequence: divergent pathway for isochromanone and isobenzofuranone synthesis

In summary, we have developed an efficient synthetic strategy with which to access all *syn*- and *anti*-configured hydroxyl-isochromanone and -isobenzofuranones with an ajudazol type substitution pattern from readily available joint alkene precursors. The protective-group-free[35] process is based on a one-pot iodocyclization–substitution tandem reaction and proceeds with excellent diastereoselectivities. Conversion of *E*-alkenes leads to stereoselective formation of *syn*-configured isochromanones and -isobenzofuranones, whereas *Z*-alkenes give rise to the *anti*-configured products. Depending on the reaction conditions, either six- or five-membered products may be obtained with good to preparatively useful selectivity. Both products are easily separable by column chromatography. Irradiation was shown to have a beneficial effect towards six-membered-ring formation, whereas carrying out the reaction under microwave or thermal conditions led to selective isobenzofurane lactones. An iodo-intermediate could be isolated for a related conversion, which further underlines a mechanistic proposal that suggests a different pathway for isochromanone and isobenzofuranone formation. The described method allows a highly concise synthesis of the authentic isochromanone and isobenzofurane fragments of the ajudazols and isoajudazols in only four steps from commercially available starting materials. The developed protocols may enable general applicable modular joint synthetic routes to hydroxyl-isochromanone and isobenzofuranone natural products and derived bioactive agents. Efforts will now be applied to develop an enantioselective variant of this reaction[36] and to further analyze the influence of light on this reaction. Furthermore, strategies will be pursued for further SAR studies of the ajudazols.

All reactions in anhydrous solvents were performed under an atmosphere of argon in flame-dried glassware. All flasks were equipped with rubber septa and reactants were handled by using standard Schlenk techniques. Reactions were monitored by TLC on silica gel 60 $F_{254}$ precoated plates (0.2 mm $SiO_2$, Machery–Nagel) and visualized using UV light and/or staining with a solution of $KMnO_4$ (1.5 g $KMnO_4$, 10 g $K_2CO_3$, 1.25 mL 10% NaOH in 200 mL $H_2O$) and subsequent heating. For column chromatography, silica gel (pore size 60 Å, 40–63 µm) was used. $^1H$ and $^{13}C$ NMR spectra were recorded with Bruker AC-300, DRX-300, DPX-300, DPX-400, and DRX-500 spectrometers. Chemical shifts (δ) are reported in ppm, coupling constants (*J*) in hertz (Hz). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br. (broad). High-resolution mass spectra (HRMS) were recorded with Bruker ICR APEX-QE, Vacuum Generators ZAB-2F, Finnigan MAT TSQ 700, JEOL JMS-700, Bruker Daltonics micrOTOF-Q and a Thermo Finnigan MAT 95 XL. The X-ray crystallographic data collection of **28** was performed with a Bruker X8 KappaApex-II diffractometer (CCD) at 100(2) K; those of **32** and **33** were obtained with a STOE IPDS-2T diffractometer at 123(2) K. The diffractometers were equipped with a low-temperature device (Kryoflex I, Bruker AXS GmbH or Cryostream 700er series, Oxford Cryosystems) and used graphite monochromated Mo-$K_\alpha$ radiation ($\lambda$ = 0.71073 Å). Details of the X-ray structure determinations are given in the Supporting Information. The structures have been deposited with the Cambridge Crystallographic Data Centre as CCDC-1428336 (**28**), CCDC-1428337 (**32**), and CCDC-1428338 (**33**), and can be obtained free of charge via www.ccdc.cam.ac.uk.

**Methyl 2-Iodobenzoate (17a)**[37]

2-Iodobenzoic acid (7.50 g, 30.2 mmol, 1 equiv) was dissolved in MeOH (150 mL), then concentrated sulfuric acid (20 mL) was added slowly. The mixture was stirred and heated at reflux for 3 h. After cooling to r.t., the reaction mixture was diluted with $Et_2O$ (150 mL), the layers were separated, and the organic phase was washed with $H_2O$ (2 × 150 mL), sat. aq $NaHCO_3$ (200 mL) and sat. aq NaCl (200 mL). After drying over $MgSO_4$, the solvent was removed in vacuo to give the product.

Yield: 7.59 g (29.0 mmol, 96%); colorless oil.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 7.14 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1 H), 7.39 (ddd, *J* = 7.7, 7.5, 1.2 Hz, 1 H), 7.79 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.99 (dd, *J* = 8.0, 1.2 Hz, 1 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 52.5, 94.0, 127.9, 130.9, 132.6, 135.1, 141.3, 166.9.

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_8H_6IO_2$: 260.9412; found: 260.9407.

**Amides 17b–d; General Procedure 1 (GP1)**

Freshly distilled thionyl chloride (5 equiv) and DMF (0.1 mL, cat.) were added to a solution of 2-iodobenzoic acid (**15**; 1 equiv) in $CH_2Cl_2$ (75 mL) under an argon atmosphere. The resulting mixture was stirred and heated at reflux for 5 h. Excess thionyl chloride was removed in vacuo and the residue was dissolved in $CH_2Cl_2$ (50 mL) and cooled to 0 °C. The amine (5 equiv) was slowly added to the solution. The mixture was stirred overnight at r.t. and then diluted with EtOAc (150 mL) and washed with sat. aq $NH_4Cl$ (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with sat. aq NaCl (100 mL) and dried over $MgSO_4$. After removing the solvent in vacuo, flash chromatography (silica gel) afforded the product.

**2-Iodo-*N*,*N*-dimethylbenzamide (17b)**[38]

Thionyl chloride (12.0 g, 101 mmol, 5 equiv) and DMF (0.1 mL, cat.) were added to a solution of 2-iodobenzoic acid (5.00 g, 20.2 mmol, 1 equiv). Dimethylamine hydrochloride (1.81 g, 22.2 mmol, 5 equiv) was added after 5 h, as described in GP1 for the preparation of 2-iodobenzamides. After work-up of the crude product, flash chromatography (silica gel; cyclohexane–$Et_2O$, 3:1) afforded the product.

Yield: 4.74 g (17.3 mmol, 86%); colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.84 (s, 3 H), 3.13 (s, 3 H), 7.06 (ddd, *J* = 8.0, 7.5, 1.6 Hz, 1 H), 7.20 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.38 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1 H), 7.81 (dd, *J* = 8.0, 1.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 34.7, 38.4, 92.4, 127.0, 128.4, 130.0, 139.0, 142.8, 170.1.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{10}INONa$: 297.9705; found: 297.9711.

***N*,*N*-Diethyl-2-iodobenzamide (17c)**[39]

Thionyl chloride (30.5 g, 256 mmol, 5 equiv), DMF (0.1 mL, cat.) and 2-iodobenzoic acid (12.7 g, 51.2 mmol, 1 equiv) were reacted with diethylamine (18.7 g, 256 mmol, 5 equiv) by following GP1 for the preparation of 2-iodobenzamides. Purification of the crude product by flash chromatography (silica gel; cyclohexane–$Et_2O$, 2:1) afforded the product.

Yield: 14.29 g (47.13 mmol, 92%); light-yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 3.02–3.22 (m, 2 H), 3.22–3.39 (m, 1 H), 3.78–3.93 (m, 1 H), 7.04 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1 H), 7.19 (ddd, *J* = 7.5, 1.7, 0.4 Hz, 1 H), 7.36 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1 H), 7.80 (ddd, *J* = 8.0, 1.1, 0.4 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 13.9, 38.9, 42.7, 92.7, 126.8, 128.2, 129.8, 139.1, 142.8, 170.0.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}INONa$: 326.0012; found: 326.0012.

**2-Iodo-*N*,*N*-diisopropylbenzamide (17d)**

The reaction was carried out as described in GP1. Thionyl chloride (18.0 g, 151 mmol, 5 equiv) and DMF (0.1 mL, cat.) were added to 2-iodobenzoic acid (7.50 g, 30.2 mmol, 1 equiv). After 5 h, diisopropylamine (15.3 g, 151 mmol, 5 equiv) was added slowly. The crude product was purified by flash chromatography (silica gel; cyclohexane–$Et_2O$, 3:1) to afford a pale-yellow solid. Recrystallization from $CH_2Cl_2$/*n*-hexane (dissolved at 40 °C, then cooled to –28 °C) gave the product.

Yield: 7.04 g (21.3 mmol, 70%); colorless crystals.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.7 Hz, 3 H), 1.27 (d, *J* = 6.7 Hz, 3 H), 1.56 (d, *J* = 6.7 Hz, 3 H), 1.60 (d, *J* = 6.7 Hz, 3 H), 3.55 (d.sept, *J* = 25.6, 6.7 Hz, 2 H), 7.02 (ddd, *J* = 7.9, 7.6, 1.6 Hz, 1 H), 7.13 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.35 (ddd, *J* = 7.6, 7.5, 1.1 Hz, 1 H), 7.81 (dd, *J* = 7.9, 1.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 20.0 (2C), 20.6, 20.7, 46.0, 51.2, 92.3, 125.8, 128.2, 129.4, 139.3, 144.2, 169.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}INOH$: 332.0506; found: 332.0507.

**Suzuki Coupling Reaction for the Synthesis of 19a–d; General Procedure 2 (GP2)**

Substituted 2-iodobenzamide or methyl 2-iodobenzoate (1 equiv) was dissolved in dioxane (30 mL), then boronic acid pinacol ester (1 equiv), tetrakis(triphenylphosphine)palladium(0) (5 mol%) and NaOH (2 N in $H_2O$, 2 equiv) were added successively. The reaction mixture was stirred and heated at reflux for 3 h, then the reaction was quenched with $H_2O$ (50 mL) and the mixture was extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed with sat. aq NaCl (50 mL) and dried over $MgSO_4$. After removing the solvent in vacuo, flash chromatography (silica gel) afforded the product.

**(*E*)-Methyl 2-(Pent-1-enyl)benzoate (19a)**

(*E*)-4,4,5,5-Tetramethyl-2-(pent-1-enyl)-1,3,2-dioxaborolane (**18**; 1.10 g, 5.60 mmol, 1 equiv), palladium(0) catalyst (324 mg, 0.28 mmol, 5 mol%), and NaOH (2 N solution, 5.60 mL, 11.20 mmol, 2 equiv) were added to methyl 2-iodobenzoate (**17a**; 1.47 g, 5.60 mmol, 1 equiv) in dioxane by following GP2. Flash chromatography (silica gel; cyclohexane–$Et_2O$, 50:1) gave the product.

Yield: 0.76 g (3.71 mmol, 66%); pale-yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3 H), 1.52 (sext, *J* = 7.3 Hz, 2 H), 2.23 (dq, *J* = 7.3, 1.6 Hz, 2 H), 3.90 (s, 3 H), 6.14 (dt, *J* = 15.7, 7.3 Hz, 1 H), 7.13 (dt, *J* = 15.7, 1.6 Hz, 1 H), 7.25 (ddd, *J* = 7.8, 7.5, 1.2 Hz, 1 H), 7.43 (ddd, *J* = 7.9, 7.5, 1.5 Hz, 1 H), 7.52–7.56 (m, 1 H), 7.84 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.7, 22.4, 35.2, 52.0, 126.4, 127.2, 128.1, 128.5, 130.2, 131.9, 133.8, 139.7, 168.1.

HRMS (ESI+): *m*/*z* [M]$^+$ calcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1151.

**(*E*)-*N*,*N*-Dimethyl-2-(pent-1-enyl)benzamide (19b)**

2-Iodo-*N*,*N*-dimethylbenzamide (**17b**; 2.27 g, 8.24 mmol, 1 equiv) was reacted with (*E*)-4,4,5,5-tetramethyl-2-(pent-1-enyl)-1,3,2-dioxaborolane (**18**; 1.61 g, 8.24 mmol, 1 equiv), tetrakis(triphenylphosphine)palladium(0) (476 mg, 0.41 mmol, 5 mol%) and NaOH (2 N solution, 8.24 mL, 16.5 mmol, 2 equiv) according to GP2. Flash chromatography (silica gel; cyclohexane–$Et_2O$, 4:1 and 5 vol% $Et_3N$) gave the product.

Yield: 1.22 g (5.63 mmol, 68%); yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 1.47 (sext, *J* = 7.4 Hz, 2 H), 2.12–2.21 (m, 2 H), 2.77 (br. s, 3 H), 3.13 (br. s, 3 H), 6.21 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.34 (dt, *J* = 15.8, 1.4 Hz, 1 H), 7.17 (ddd, *J* = 7.5, 1.7, 0.6 Hz, 1 H), 7.21 (ddd, *J* = 7.5, 7.4, 1.5 Hz, 1 H), 7.29 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1 H), 7.47–7.51 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.7, 22.4, 34.7, 35.2, 38.4, 125.5, 126.3, 126.5, 126.9, 128.8, 133.7, 134.4, 135.0, 171.3.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{19}NONa$: 240.1359; found: 240.1357.

**(*E*)-*N*,*N*-Diethyl-2-(pent-1-enyl)benzamide (19c)**

*N*,*N*-Diethyl-2-iodobenzamide (**17c**; 2.70 g, 8.91 mmol, 1 equiv) was dissolved in dioxane as described in the GP2. (*E*)-4,4,5,5-Tetramethyl-2-(pent-1-enyl)-1,3,2-dioxaborolane (**18**; 1.75 g, 8.91 mmol, 1 equiv), tetrakis(triphenylphosphine)palladium(0) (515 mg, 0.45 mmol, 5 mol%) and NaOH (2 N solution, 8.91 mL, 17.8 mmol, 2 equiv) were added and the reaction is allowed to run. After work-up, the crude product was purified by flash chromatography (silica gel; cyclohexane–$Et_2O$, 4:1).

Yield: 2.07 g (8.46 mmol, 95%); brown oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 0.99 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.47 (sext, *J* = 7.4 Hz, 2 H), 2.11–2.20 (m, 2 H), 3.08 (q, *J* = 7.1 Hz, 2 H), 3.29–3.89 (m, 2 H), 6.21 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.37 (dt, *J* = 15.8, 1.4 Hz, 1 H), 7.14–7.24 (m, 2 H), 7.27–7.32 (m, 1 H), 7.45–7.53 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.8, 13.7, 13.9, 22.3, 35.2, 38.7, 42.7, 125.3, 125.9, 126.5, 126.7, 128.5, 133.4, 134.2, 135.5, 170.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{23}NONa$: 268.1672; found: 268.1672.

**(*E*)-*N*,*N*-Diisopropyl-2-(pent-1-enyl)benzamide (19d)**

2-Iodo-*N*,*N*-diisopropylbenzamide (**17d**; 1.88 g, 5.69 mmol, 1 equiv) was dissolved in dioxane. (*E*)-4,4,5,5-Tetramethyl-2-(pent-1-enyl)-1,3,2-dioxaborolane (**18**; 1.12 g, 5.69 mmol, 1 equiv), the palladium(0) catalyst (324 mg, 0.28 mmol, 5 mol%) and NaOH (2 N solution, 5.69 mL, 11.4 mmol, 2 equiv) were added in accordance with GP2. Flash chromatography (silica gel; cyclohexane–$Et_2O$, 8:1) gave the product.

Yield: 1.45 g (5.37 mmol, 94%); orange oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H), 1.08 (d, *J* = 6.7 Hz, 3 H), 1.48 (sext, *J* = 7.4 Hz, 2 H), 1.58 (d, *J* = 6.8 Hz, 3 H), 1.59 (d, *J* = 6.8 Hz, 3 H), 2.16 (ddt, *J* = 7.4, 6.6, 1.4 Hz, 2 H), 3.50 (sept, *J* = 6.8 Hz, 1 H), 3.60 (sept, *J* = 6.7 Hz, 1 H), 6.23 (dt, *J* = 15.8, 6.6 Hz, 1 H), 6.43 (dt, *J* = 15.8, 1.4 Hz, 1 H), 7.10 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.19 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1 H), 7.27 (ddd, *J* = 7.7, 7.5, 1.4 Hz, 1 H), 7.50 (dd, *J* = 7.7, 1.3 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = –13.8, 20.3, 20.5, 20.7, 20.7, 22.3, 35.3, 45.8, 50.9, 125.1, 125.3, 126.6, 126.8, 128.2, 133.0, 133.9, 136.8, 170.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}NONa$: 296.1985; found: 296.1982.

**Iodolactonization; General Procedure 3 (GP3)**

2-Alkenylbenzamide or 2-alkenylmethyl benzoate was dissolved in THF–$H_2O$ (5:1, 5 mL), then $I_2$ (5 equiv) was added and the reaction mixture was protected from light and stirred at r.t. for three days. The reaction was then quenched by addition of sat. aq sodium thiosulfate (10 mL) and the aqueous phase was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with sat. aq NaCl (10 mL) and dried over $MgSO_4$. The product was obtained by flash chromatography after removing the solvent in vacuo.

***syn*-4-Hydroxy-3-propylisochroman-1-one (20) from 19c**

(*E*)-*N*,*N*-Diethyl-2-(pent-1-enyl)benzamide (**19c**; 0.23 g, 1.12 mmol, 1 equiv) was reacted with $I_2$ (1.43 g, 5.62 mmol, 5 equiv) according to GP3, except the reaction was exposed to light while stirring. Flash chromatography (silica gel; cyclohexane–$Et_2O$, 4:1) afforded the product.

Yield: 0.13 g (0.65 mmol, 58%, dr > 20:1); pale milky oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3 H), 1.45–1.56 (m, 1 H), 1.58–1.69 (m, 1 H), 1.78–1.90 (m, 1 H), 1.93–2.06 (m, 1 H), 2.14–2.46 (br. m, 1 H), 4.47 (ddd, *J* = 8.1, 5.5, 2.1 Hz, 1 H), 4.62 (d, *J* = 2.1 Hz, 1 H), 7.46 (dd, *J* = 7.6, 1.1 Hz, 1 H), 7.48–7.54 (m, 1 H), 7.64 (ddd, *J* = 7.6, 7.5, 1.1 Hz, 1 H), 8.09 (dd, *J* = 7.6, 1.4 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.9, 18.3, 32.3, 66.6, 80.9, 124.2, 127.8, 129.8, 130.4, 134.3, 140.3, 165.0.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}O_3Na$: 229.0835; found: 229.0842.

***N*,*N*-Diethyl-2-methoxy-3-methylbenzamide (22)**

To a solution of 2-methoxy-3-methylbenzoic acid (5 g, 30 mmol, 1.0 equiv) in anhydrous $CH_2Cl_2$ (300 mL), freshly distilled thionyl chloride (11.0 mL, 150 mmol, 5.0 equiv) was added. The reaction mixture was heated at reflux vigorously (oil bath temperature 100 °C) for 5 h. After cooling to r.t., all volatiles were removed in vacuo, the residue was dissolved in anhydrous $CH_2Cl_2$ (150 mL) under an atmosphere of argon and cooled to 0 °C. Maintaining the internal temperature below 5 °C a solution of diethylamine (15.5 mL, 150 mmol, 5.0 equiv) in anhydrous $CH_2Cl_2$ (50 mL) was added dropwise. When the addition was complete, the reaction mixture was slowly warmed to r.t., and stirred overnight to complete the reaction. $H_2O$ (100 mL) was added, the organic phase was separated and the aqueous phase was extracted with $Et_2O$ (3 × 150 mL). The combined organic phases were washed with HCl (2 N, 2 × 25 mL), aq NaOH (2 N, 2 × 25 mL), $H_2O$ (25 mL), and sat. aq NaCl (25 mL). After drying over $MgSO_4$ the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 3:1) to give **22**.

Yield: 6.4 g (29 mmol, 96%); colorless oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 2.29 (s, 3 H), 3.05–3.23 (m, 2 H), 3.27–3.44 (m, 2 H), 3.79 (s, 3 H), 7.00–7.08 (m, 2 H), 7.15–7.21 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.9, 14.1, 16.1, 39.0, 43.1, 61.5, 124.2, 125.4, 131.5, 131.6, 131.8, 154.2, 169.3.

HRMS (ESI+): *m*/*z* [M + 2H]$^+$ calcd for $C_{13}H_{21}NO_2$: 223.1522; found: 223.1524.

***N*,*N*-Diethyl-6-Iodo-2-methoxy-3-methylbenzamide (23)**

*N*,*N*-Diethyl-2-methoxy-3-methylbenzamide (**22**; 2.6 g, 12 mmol, 1.0 equiv) and tetramethylethylenediamine (1.6 g, 14 mmol, 1.2 equiv) were dissolved in anhydrous THF and cooled to –78 °C. *s*-BuLi (1.4 M in hexanes; 10 mL, 14 mmol) was added dropwise and the reaction mixture was stirred for 30 min at –78 °C. A solution of iodine (3.5 g, 14 mmol, 1.2 equiv) in THF (30 mL) was added dropwise by using a dropping funnel, keeping the internal temperature below –70 °C. The reaction mixture was stirred for 1 h at –78 °C then warmed slowly to r.t. The reaction was quenched by adding sat. aq sodium thiosulfate (50 mL), the organic phase was separated, and the aqueous phase was extracted with $Et_2O$ (3 × 100 mL). The combined organic phases were washed with $H_2O$ (50 mL) and sat. aq NaCl (50 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 4:1) to give **23**.

Yield: 3.7 g (11 mmol, 91%); pale-yellow oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 2.23 (s, 3 H), 2.99–3.19 (m, 2 H), 3.43–3.72 (m, 2 H), 3.76 (s, 3 H), 6.87 (d, *J* = 7.9 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 13.7, 15.7, 38.9, 42.9, 61.7, 89.7, 131.8, 132.5, 134.5, 137.3, 154.9, 168.0.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}INO_2$: 348.0455; found: 348.0457.

### (*Z*)-4,4,5,5-Tetramethyl-2-(pent-1-enyl)-1,3,2-dioxaborolane (24)

The reaction was carried out under argon atmosphere. The reaction vessel was charged with chloro(1,5-cyclooctadiene)rhodium(I) dimer (280 mg, 0.06 mmol, 3 mol%), then cyclohexane (100 mL), triisopropylphosphine (384 mg, 2.40 mmol, 6 mol%), $Et_3N$ (4.05 g, 40.0 mmol, 1.0 equiv) and catecholborane (4.80 g, 40.0 mmol, 1.0 equiv) were added consecutively. The resulting reaction mixture was stirred at r.t. for 2 h, then a solution of pinacol (7.09 g, 60 mmol, 1.5 equiv) in cyclohexane (60 mL) was added and the mixture was stirred under argon atmosphere at r.t. overnight. The solvent was removed in vacuo and the residue was purified by flash chromatography (silica gel; cyclohexane–$Et_2O$, 40:1) to give **24**.

Yield: 4.42 g (22.5 mmol, 56%); yellowish brown liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3 H), 1.26 (s, 12 H), 1.41 (sext, *J* = 7.4 Hz, 2 H), 2.37 (qd, *J* = 7.4, 1.3 Hz, 2 H), 5.34 (dt, *J* = 14.0, 1.3 Hz, 1 H), 6.42 (dt, *J* = 14.0, 7.4 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.6, 24.8 (4C), 26.9, 34.2, 82.8 (2C), 154.9 (the olefinic C next to boron was not detected).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{21}BO_2$: 196.1744; found: 196.17242.

### (*Z*)-*N*,*N*-Diethyl-2-methoxy-3-methyl-6-(pent-1-en-1-yl)benzamide (25)

*N*,*N*-Diethyl-6-iodo-2-methoxy-3-methylbenzamide (**23**; 0.95 g, 2.73 mmol, 1.00 equiv), (*Z*)-4,4,5,5-tetramethyl-2-(pent-1-en-1-yl)-1,3,2-dioxaborolane (**24**; 0.64 g, 3.28 mmol, 1.20 equiv) and aq NaOH (2 N, 2.7 mL, 5.40 mmol, 2.00 equiv) were dissolved in 1,4-dioxane (15 mL). The mixture was degassed by bubbling argon gas through the solvent for 15 min, then tetrakis(triphenylphosphine)palladium(0) (0.19 g, 0.16 mmol, 0.06 equiv) was added. The reaction mixture was heated at reflux (oil bath temperature 105 °C) for 3 h under argon atmosphere, then the reaction was quenched with $H_2O$ (20 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed with sat. aq NaCl (25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 3:1) to give **25**.

Yield: 0.73 g (2.5 mmol, 92%); green-brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.36–1.50 (m, 2 H), 2.14–2.27 (m, 2 H), 2.28 (s, 3 H), 2.99–3.09 (m, 2 H), 3.46–3.66 (m, 2 H), 3.77 (s, 3 H), 5.65 (dt, *J* = 11.7, 7.3 Hz, 1 H), 6.31 (d, *J* = 11.7 Hz, 1 H), 7.00 (d, *J* = 7.9 Hz, 1 H), 7.11 (d, *J* = 7.9 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.6, 13.7, 13.9, 15.8, 23.1, 30.8, 38.6, 42.9, 61.5, 124.9, 125.5, 129.6, 130.5, 131.2, 133.3, 133.9, 154.1, 168.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115; found: 290.2113.

### (*E*)-*N*,*N*-Diethyl-2-methoxy-3-methyl-6-(pent-1-en-1-yl)benzamide (26)

*N*,*N*-Diethyl-6-iodo-2-methoxy-3-methylbenzamide (**23**; 1.25 g, 3.6 mmol, 1.00 equiv), (*E*)-4,4,5,5-tetramethyl-2-(pent-1-en-1-yl)-1,3,2-dioxaborolane (0.85 g, 4.3 mmol, 1.20 equiv) and aq NaOH (2 N, 3.6 mL, 7.2 mmol, 2.00 equiv) were dissolved in 1,4-dioxane (20 mL). The mixture was degassed by bubbling argon gas through the solvent for 15 min before tetrakis(triphenylphosphine)palladium(0) (0.25 g, 0.2 mmol, 0.06 equiv) was added. The reaction mixture was heated at reflux (oil bath temperature 105 °C) for 3 h under argon atmosphere then the reaction was quenched with $H_2O$ (25 mL) and the mixture was extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed with sat. aq NaCl (25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 3:1) to give **26**.

Yield: 1.00 g (3.5 mmol, 96%); brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.45 (sext, *J* = 7.3 Hz, 2 H), 2.07–2.18 (m, 2 H), 2.26 (s, 3 H), 2.97–3.15 (m, 2 H), 3.49–3.70 (m, 2 H), 3.77 (s, 3 H), 6.16 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.28 (d, *J* = 15.8 Hz, 1 H), 7.08 (d, *J* = 7.9 Hz, 1 H), 7.19 (d, *J* = 7.9 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.7, 13.7 (2 C), 15.7, 22.4, 35.2, 38.8, 42.9, 61.5, 120.8, 126.3, 129.5, 130.0, 131.1, 132.7, 133.8, 154.2, 168.2.

HRMS (ESI+): *m*/*z* [M]$^+$ calcd for $C_{18}H_{27}NO_2$: 289.2042; found: 289.2041.

### General Procedure for qNMR Studies

The crude product that was obtained after the iodolactonization reaction was dissolved in $CDCl_3$ (0.5 mL) and transferred into an NMR tube. An accurately measured amount (0.1 mL) of a precisely prepared stock solution of dimethyl terephthalate in $CDCl_3$ was added and the mixture was homogenized. The amount of each product was determined by relating the proton integral of the ester functions of dimethyl terephthalate (3.9 ppm, 6 H) to the signals of the products.[40]

### *syn*-4-Hydroxy-8-methoxy-7-methyl-3-propylisochroman-1-one (27)

(*E*)-*N*,*N*-Diethyl-2-methoxy-3-methyl-6-(pent-1-en-1-yl)benzamide (**26**; 39 mg, 135 µmol, 1.0 equiv), was dissolved in THF (5 mL) then $H_2O$ (1 mL) and $I_2$ (170 mg, 675 µmol, 5.0 equiv) were added. The reaction mixture was irradiated with a 300 W daylight lamp held approximately 10 cm from the reaction vessel. A cooling finger was attached to the reaction flask and the mixture was stirred for three days. The reaction was quenched by addition of sat. aq sodium thiosulfate solution (5 mL), the organic phase was separated, and the aqueous phase was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with sat. aq NaCl (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 5:1) to give **27** (12 mg, 47 µmol, 34%; mp 93 °C) as a white solid as well as **28** (9.7 mg, 42.3 µmol, 29%).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.3 Hz, 3 H), 1.44–1.69 (m, 2 H), 1.72–2.03 (br. s m, 3 H), 2.33 (s, 3 H), 3.88 (s, 3 H), 4.38 (ddd, *J* = 8.1, 6.0, 1.8 Hz, 1 H), 4.60 (d, *J* = 1.7 Hz, 1 H), 7.10 (d, *J* = 7.7 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 16.2, 18.3, 32.2, 61.5, 67.3, 80.0, 116.8, 122.8, 134.6, 136.5, 140.2, 160.5, 162.0.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_4Na$: 273.1097; found: 273.1095.

### *syn*-(1-Hydroxybutyl)-7-methoxy-6-methylisobenzofuran-1(3*H*)-one (28)

(*E*)-*N*,*N*-Diethyl-2-methoxy-3-methyl-6-(pent-1-en-1-yl)benzamide (**26**; 33 mg, 114 µmol, 1.0 equiv), was dissolved in THF (5 mL), then $H_2O$ (1 mL) and $I_2$ (145 mg, 570 µmol, 5.0 equiv) were added. The reaction mixture was heated at reflux for three days protected from

light. The reaction was quenched by addition of sat. aq sodium thiosulfate (5 mL), the organic phase was separated, and the aqueous phase was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with sat. aq NaCl (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 5:1) to give **28** (12 mg, 48 µmol, 42%; mp 103 °C) as an off-white solid, as well as **27** (5.7 mg, 22.9 µmol, 20%).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 1 H), 1.44–1.72 (m, 5 H), 2.33 (s, 3 H), 3.89–4.00 (m, 1 H), 4.09 (s, 3 H), 5.29 (d, *J* = 3.5 Hz, 1 H), 7.09 (d, *J* = 7.7 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.6, 18.8, 35.1, 62.2, 72.3, 82.1, 116.6, 117.6, 132.1, 137.6, 147.3, 157.6, 168.2.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_4Na$: 273.1097; found: 273.1102.

### *anti*-4-Hydroxy-8-methoxy-7-methyl-3-propylisochroman-1-one (29)

(*Z*)-*N*,*N*-Diethyl-2-methoxy-3-methyl-6-(pent-1-en-1-yl)benzamide (**25**; 29.0 mg, 100 µmol, 1.0 equiv), was dissolved in THF (4.2 mL), then $H_2O$ (0.8 mL) and $I_2$ (125 mg, 500 µmol, 5.0 equiv) were added. The reaction mixture was stirred at r.t. for three days, then the reaction was quenched by addition of sat. aq sodium thiosulfate (5 mL). The organic phase was separated and the aqueous phase was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with sat. aq NaCl (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 5:1) to give **29**.

Yield: 12.1 mg (48 µmol, 48%); white solid; mp 129 °C.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H),1.42–1.86 (m, 5 H), 2.30 (s, 3 H), 3.86 (s, 3 H), 4.29 (td, *J* = 8.0, 3.6 Hz, 1 H), 4.57–4.63 (m, 1 H), 7.22 (d, *J* = 7.7 Hz, 1 H), 7.43 (d, *J* = 7.7 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.8, 16.0, 18.1, 33.6, 61.5, 68.2, 81.8, 116.3, 120.4, 133.3, 136.6, 141.4, 160.1, 161.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_4Na$: 273.1097; found: 273.1095.

### *anti*-(1-Hydroxybutyl)-7-methoxy-6-methylisobenzofuran-1(3*H*)-one (30)

(*Z*)-*N*,*N*-Diethyl-2-methoxy-3-methyl-6-(pent-1-en-1-yl)benzamide (**25**; 37 mg, 128 µmol, 1.0 equiv), was dissolved in THF (5 mL), then $H_2O$ (1 mL) and $I_2$ (162 mg, 640 µmol, 5.0 equiv) were added. The reaction mixture was heated at reflux for three days protected from light. The reaction was quenched by addition of sat. aq sodium thiosulfate (5 mL), the organic phase was separated, and the aqueous phase was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with sat. aq NaCl (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 5:1) to give **30** (23.0 mg, 92.0 µmol, 72%) as a colorless oil, and **29** (1.6 mg, 6.40 µmol, 5%).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.87–1.03 (m, 3 H), 1.38–1.70 (m, 5 H), 2.31 (s, 3 H), 3.84–4.01 (m, 1 H), 4.06 (s, 3 H), 5.29 (d, *J* = 4.4 Hz, 1 H), 7.13 (d, *J* = 7.7 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.8, 15.5, 18.7, 34.0, 62.2, 72.7, 82.5, 116.6, 117.4, 132.1, 137.4, 147.0, 157.3, 168.2.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_4Na$: 273.1097; found: 273.1095.

### (*Z*)-*N*,*N*-Diethyl-2-(pent-1-enyl)benzamide (31)

By following GP2, *N*,*N*-diethyl-2-iodobenzamide (**17c**; 1.70 g, 5.61 mmol, 1 equiv) was reacted with (*Z*)-4,4,5,5-tetramethyl-2-(pent-1-enyl)-1,3,2-dioxaborolane (**24**; 1.10 g, 5.61 mmol, 1 equiv), palladium(0) catalyst (324 mg, 0.28 mmol, 5 mol%), and NaOH (2 N, 5.61 mL, 11.22 mmol, 2 equiv). After work-up of the reaction, flash chromatography (silica gel; cyclohexene–$Et_2O$, 4:1) afforded the product.

Yield: 1.36 g (5.53 mmol, 99%); orange oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3 H), 0.99 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.45 (sext, *J* = 7.5 Hz, 2 H), 2.19–2.28 (m, 2 H), 3.06 (q, *J* = 7.1 Hz, 2 H), 3.24–3.87 (m, 2 H), 5.71 (dt, *J* = 11.6, 7.3 Hz, 1 H), 6.39 (dt, *J* = 11.6, 1.8 Hz, 1 H), 7.15–7.34 (m, 4 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.8, 13.9, 14.0, 23.0, 30.7, 38.6, 42.6, 125.7, 125.8, 126.7, 128.0, 129.3, 134.0, 134.4, 136.9, 170.4.

HRMS (ESI+): *m*/*z* [M]$^+$ calcd for $C_{16}H_{23}NO$: 245.1780; found: 245.1783.

### *anti*-4-Hydroxy-3-propylisochroman-1-one (32) and *syn*-(1-Iodobutyl)isobenzofuran-1(3*H*)-one (33)

(*Z*)-*N*,*N*-Diethyl-2-(pent-1-en-1-yl)benzamide (51 mg, 0.21 mmol, 1.0 equiv), was dissolved in THF (5 mL), then $H_2O$ (1 mL) and $I_2$ (264 mg, 1.05 mmol, 5.0 equiv) were added. The reaction mixture was irradiated with a 300 W daylight lamp held approximately 10 cm from the reaction vessel. A cooling finger was attached to the reaction flask and the mixture was stirred for 60 min. The reaction was quenched by addition of sat. aq sodium thiosulfate (5 mL), the organic phase was separated, and the aqueous phase was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with sat. aq NaCl (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 4:1) to give **32** (8.1 mg, 40.6 µmol, 20%) as a colorless oil and **33** (9.0 mg, 32.9 µmol, 14%) as a yellow oil.

### *anti*-4-Hydroxy-3-propylisochroman-1-one (32)

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H), 1.43–1.55 (m, 1 H), 1.60–1.77 (m, 2 H), 1.77–1.89 (m, 1 H), 2.20–2.91 (br. s, 1 H), 4.42 (ddd, *J* = 8.5, 7.6, 3.6 Hz, 1 H), 4.73 (d, *J* = 7.6 Hz, 1 H), 7.47 (ddd, *J* = 7.6, 7.5, 1.3 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.65 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1 H), 8.06 (dd, *J* = 7.6, 1.3 Hz, 1 H).

$^{13}$C (100 MHz, $CDCl_3$): δ = 13.8, 18.1, 33.9, 67.9, 82.6, 123.7, 125.5, 128.8, 130.2, 134.3, 141.4, 164.4.

HRMS (ESI+): *m*/*z* [M]$^+$ calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0942.

### *syn*-(1-Iodobutyl)isobenzofuran-1(3*H*)-one (33)

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 1.39–1.54 (m, 1 H), 1.58–1.72 (m, 1 H), 1.72–1.81 (m, 1 H), 1.82–1.94 (m, 1 H), 4.49 (ddd, *J* = 9.9, 4.7, 2.5 Hz, 1 H), 5.32 (d, *J* = 2.5 Hz, 1 H), 7.58 (ddd, *J* = 7.7, 7.6, 1.3 Hz, 1 H), 7.64 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.70 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1 H), 7.92 (dd, *J* = 7.6, 1.3 Hz, 1 H).

$^{13}$C (100 MHz, $CDCl_3$): δ = 13.1, 22.9, 35.3, 38.0, 82.3, 122.2, 125.7, 126.9, 129.8, 134.2, 148.3, 169.6.

HRMS (ESI+): *m*/*z* [M]$^{+\bullet}$ calcd for $C_{12}H_{14}O_3$: 315.9960; found: 315.9961.

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## Supporting Information

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