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Note

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Catalytic asymmetric cycloadditions between aldehydes and enolizable anhydrides: *cis*-selective dihydroisocoumarin formation

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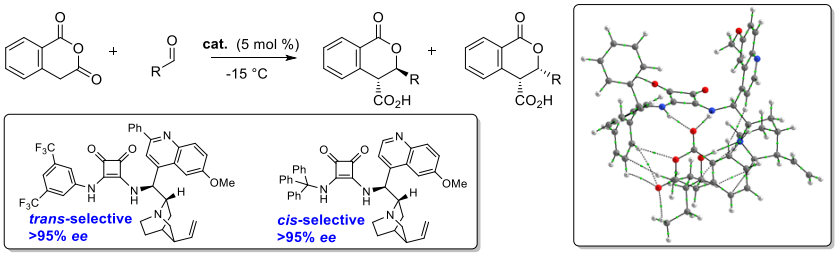
Supporting Information Placeholder



In the presence of a trityl-substituted cinchona alkaloid-based catalyst, homophthalic-, aryl succinic- and glutaconic anhydride derivatives reacted with aromatic and aliphatic aldehydes to produce *cis*-lactones in up to 90:10 dr and 99% *ee*. A DFT study has shown how the catalyst is uniquely able to bring about the opposite sense of diastereocontrol to that usually observed.

The reaction between enolizable cyclic anhydrides and aldehydes to form carboxy lactones is over a century old,[1,2,3,4,5] however a catalytic asymmetric variant of the process was not reported until 2012.[6] Since, the family of electrophiles amenable to these enantioselective reactions with anhydrides has been extended to include activated ketones,[7] Michael acceptors[8] and imines.[9]

In the first such asymmetric reaction, homophthalic anhydride (**1**) was shown – in the presence of a bifunctional squaramide-based cinchona alkaloid catalyst **3**[10] – to undergo cycloaddition with a range of aldehydes **2** to form *trans*-3,4-dihydroisocourmain (a structural unit present in numerous natural and synthetic molecules of medicinal and biological importance[11]) products of general type **4a,b** with excellent enantiocontrol and good-excellent diastereoselectivity favoring the formation of the *trans*-stereoisomer (Figure 1A). A short time later *α*-aryl succinic anhydrides **5** were reported to participate; providing access to arylated analogues of *trans*-paraconic acids **6a,b** with similar efficiency and stereochemical outcomes.[12,13] Calculations indicate that these reactions involve the catalyst deprotonating the anhydride and organizing the face-selective encounter between the squaramide-bound enolate and the ammonium ion-bound aldehyde in the stereocenter-forming step (*i.e.* **7**, Figure 1A).[14]

In 2011, Yeung and co-workers[15] reported an enantioselective approach to the synthesis of *trans*-3,4-dihydroisocoumarins such as **9a** *via* an elegant bromocyclization of a styrenyl carboxylic acid **8** promoted by thiocarbamate substituted cinchona alkaloid-

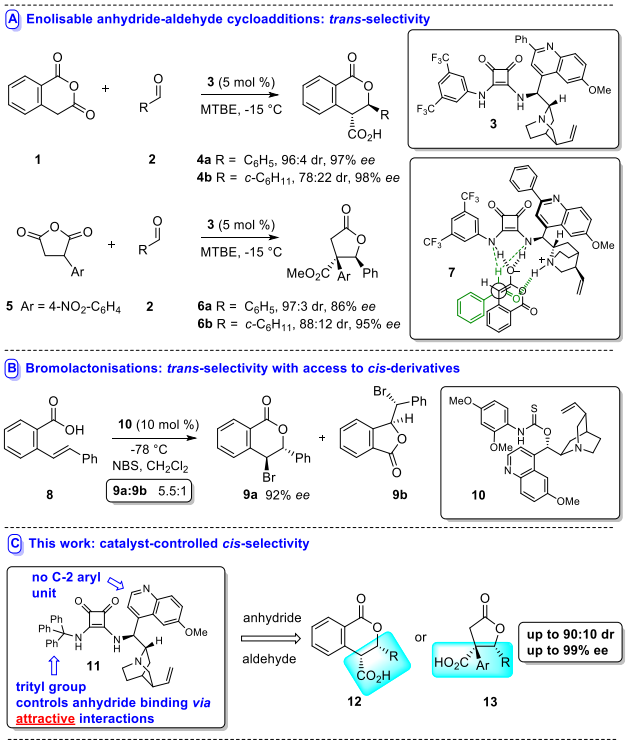


Figure 1. Organocatalytic formation of dihydroisocoumarins

derived catalyst **10** in excellent *ee*. These can be elaborated to *cis*-derivatives *via* S_N2 substitution. The competing formation of **9b**[16] and the requirements for a) very low temperatures, b) onward manipulation of the product to give a *cis*-diastereomer and c) the

presence of the styrenyl unit, make the development of a direct, broad-scope catalytic approach to *cis*-dihydroisocoumarins (especially in view of recent interest in these species following the isolation of the eurotuimide family of anti-fouling and antibacterial natural products[17]) an attractive goal.

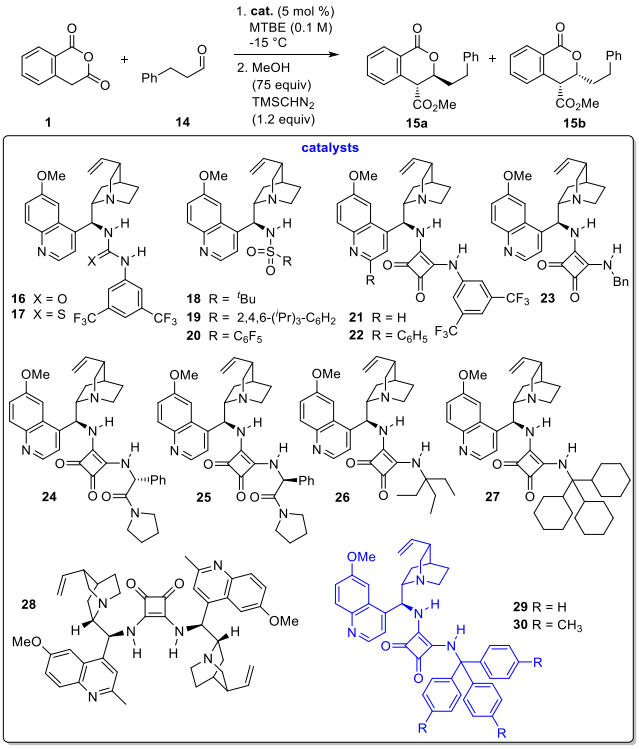
Herein we report the first such methodology involving the efficient *cis*-selective asymmetric cycloaddition of enolizable anhydrides and both aromatic and aliphatic aldehydes using a trityl-substituted squaramide catalyst; which controls the stereocenter forming event in an unusual and unexpected fashion.

Our study began with a catalyst screen (Table 1). As substrates we chose the aliphatic hydrocinnamaldehyde **14** and homophthalic anhydride **1** under the conditions used in previous studies (0.1 M, MTBE, -15 °C). Crude reaction mixtures were esterified *in situ* to prevent retro-cycloaddition and facilitate analysis of the resulting esters by CSP-HPLC. The prototype (thio)urea-based cinchona alkaloid catalyst systems **16** and **17**[18] promoted the reaction with poor-moderate enantio- and diastereocontrol, favoring the *trans*-stereoisomer **15a** (entries 1-2). Sulfonamide-substituted analogues (**18-20**, entries 3-5) – regardless of their steric/electronic characteristics – fared little better, although their use did provide **15b** in higher (albeit unsatisfactory) *ee* than **15a**. Attention therefore returned to the squaramide-substituted alkaloid family of catalysts utilized in the original study. Specifically, we set out to vary the steric demand of the *N*-alkyl (*i.e.* non alkaloid-bound) substituent as much as possible, to probe its influence on diasterocontrol. The 3,5-*bis*(trifluoromethyl)phenyl substituted materials **21** and **22** performed as expected: leading to the generation of both **15a** and **15b** in excellent *ee*, but with 2:1 or 3:1 product ratios respectively, favoring the undesired **15a**. Interestingly, **21**, which is devoid of the C-2 phenyl unit at the catalyst's quinoline moiety, promoted the formation of greater levels of **15a** than its substituted variant **15b**, and so this (often beneficial) structural modification was not considered in all subsequent catalyst designs.[19]

Analogues of **21** in which the squaramide's aromatic ring has been exchanged for a benzyl- (*i.e.* **23**), D- or L-phenylglycinepyrrolidinamide (*i.e.* **24** and **25**) or triethylmethyl (*i.e.* **26**) substituent failed to perturb the levels of *trans*-diastereocontrol to an appreciable extent (entries 8-11). While the incorporation of a very large tricyclohexylmethyl (*i.e.* **27**) group led to the formation of a greater proportion of **15b**, enantioselectivity was poor (entry 12). The hindered, C-2 symmetric catalyst **28** also catalyzed the cycloaddition slowly with *ca.* 1:1 dr, but this reaction provided almost racemic **15b** (entry 13). Gratifyingly, the use of the *N*-trityl catalyst **29** led to a remarkable reversal of the trend; affording predominantly the *cis*-**15b** in 90% *ee*, with the minor *trans*-diastereomer also formed with excellent enantiocontrol (entry 14). Extending the reach of the trityl group through the installation of *p*-methyl moieties did not lead to further improvement (entry 15). A subsequent solvent and temperature screen identified THF as a superior medium; allowing the formation of **15b** with 71:29 dr and 99% *ee* (Table 1 entry 16)

With a catalyst and conditions leading to diastereo- and highly enantioselective formation of *cis*-dihydroisocoumarins in hand, we next wished to evaluate the substrate scope. A range of aliphatic aldehydes were evaluated as substrates for the process (Table 2). Lactones derived from straight chain- (*i.e.* products **31**-**32**), β-branched (*i.e.* product **33** – XRD structure shown in inset) and *α*-branched (*i.e.* **34**-**37**) aldehydes could be efficiently synthesized with good to high *cis*-diastereocontrol and excellent to outstanding levels of enantiomeric excess, with the latter class of substrate providing products with ≥ 80:20 dr and 98-99% *ee*. Cinnamaldehyde proved a more difficult substrate from a diastereocontrol standpoint, yet **38** was still formed with high *ee*.

Table 1. Catalyst evaluation



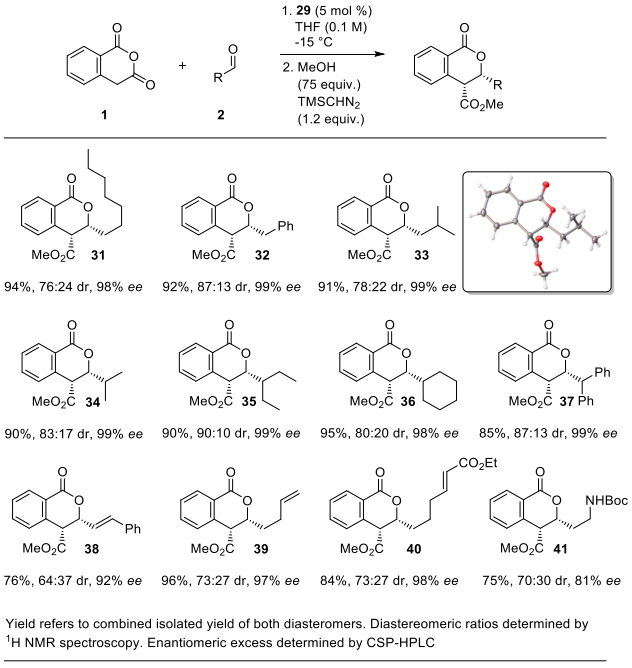
entry	cat.	T (h)	yield (%)[a]	15a:15b [a]	ee_{15a} (%)[b]	ee_{15b} (%)[b]
1	**16**	120	79	54:46	20	0
2	**17**	120	91	60:40	60	0
3	**18**	180	84	55:45	42	47
4	**19**	168	65	58:42	10	47
5	**20**	144	60	66:34	18	51
6	**21**	48	99	67:33	99	99
7	**22**	24	94	75:25	90	98
8	**23**	96	82	76:24	94	70
9	**24**	144	52	80:20	92	16
10	**25**	144	74	65:35	76	14
11	**26**	48	89	71:29	92	34
12	**27**	120	94	52:48	12	5
13	**28**	192	50	56:44	51	3
14	**29**	33	97	28:72	91	90
15	**30**	48	85	24:76	0	80
16[d]	**29**	48	99	29:71	92	99

[a]Combined yield of both diasteromers determined by ^{1}H NMR spectroscopy using 4-iodoanisole as an internal standard. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by CSP-HPLC. [d]THF solvent

Use of aldehydes incorporating non-conjugated olefin (*i.e.* product **39**) and Michael acceptor functionality were well tolerated by the catalyst – no competing Tamura cycloaddition[8] chemistry was observed during the formation of **40**. The only disappointing

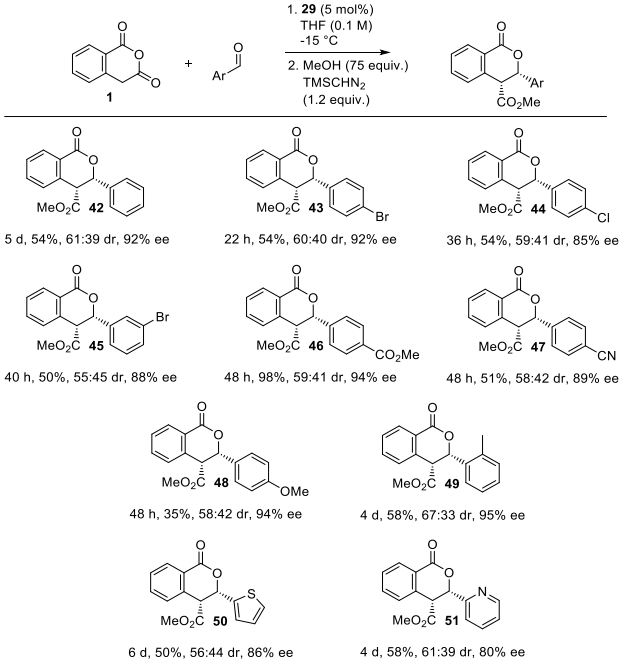
result occurred when an aldehyde incorporating a H-bond donating Boc-protected amine was utilized: in this case compound **41** was formed with a considerably lower *ee* of 81%.

Table 2. Substrate scope: aliphatic aldehydes



Yield refers to combined isolated yield of both diasteromers. Diastereomeric ratios determined by ^{1}H NMR spectroscopy. Enantiomeric excess determined by CSP-HPLC

Table 3. Substrate scope: aromatic aldehydes



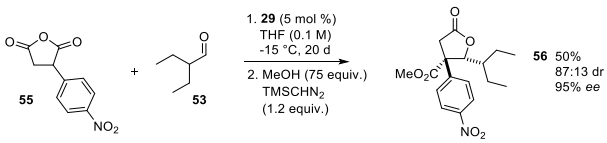
Yield refers to isolated yield of the *cis*-diastereomer. Diastereomeric ratios determined by ^{1}H NMR spectroscopy. Enantiomeric excess determined by CSP-HPLC.

Aromatic aldehydes were substrates which were shown earlier to be exceptionally well suited to the trans-selective cycloaddition reaction.[6] As expected, these were more difficult to coax into forming *cis*-dihydroisocoumarins (Table 3), however, catalyst **29** still promoted *cis*-selective cycloaddition in all cases involving a wide variety of functionalities. Esterified cycloadducts stemming from electron-neutral (*i.e.* **42**), electron-deficient (*i.e.* **43-47**) electron rich (*i.e.* **48**), hindered (*i.e.* **49**) and heterocyclic (*i.e.* **50-51**) aromatic aldehydes could be isolated with moderate diastereocontrol and good-excellent *ee*.

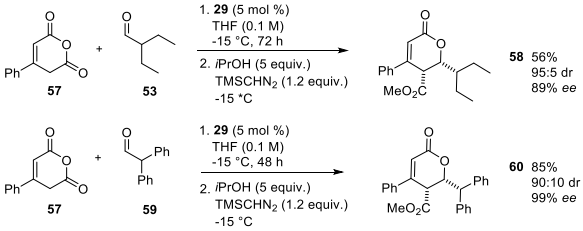
Scheme 1. Use of bromohomophthalic anhydride

The process is not restricted to homophthalic anhydride (**1**). A bromo-derivative (**52**, Scheme 1) could be reacted with the branched aldehyde **53** to yield ***cis*-54** in high dr and 98% *ee*. Gratifyingly, other enolizable anhydrides were also compatible: use of the *p*-nitrophenyl succinic anhydride **55** in the presence of **53** provided 50% yield of the very sterically congested lactone **56** with similar stereocontrol.

Scheme 2. Use of an enolizable succinic anhydride



Scheme 3. Use of a glutaconic anhydride derivative



A glutaconic anhydride derivative **57**[12] could also be utilized (Scheme 3). This reacted with **53** to generate the densely functionalized, highly malleable *cis*-ester derivative **58** in moderate isolated yield but excellent *ee*. This is the first time this anhydride class has been shown to react with aldehydes in an enantioselective process. Likewise, employment of α,α-diphenyl aldehyde **59** provided the corresponding lactone **60** in high isolated yield and 98% *ee*. This reaction was noteworthy in that the parent acid was formed as a single diastereomer, however a dr of 90:10 *cis*:*trans* was observed after esterification, despite careful experimentation and very mild conditions. This was not observed in any other case.[20]

In order to rationalize both the stereochemical outcome of the process and the key contribution of the catalyst's trityl unit, we carried out density functional theory (DFT) calculations on the reaction between **1** and **53** catalyzed by **29** (Figure 2). These were revealing – the catalyst deprotonates and binds the anhydride, directing the same face of the enolate towards the ammonium ion-bound aldehyde as seen before (*i.e.* **7**), however it does so in a very distinct fashion – *via* binding of the neutral (as drawn) carbonyl oxygen atom with the squaramide group. Further insight into this curious binding mode was provided by QTAIM theory (Figure 2, *right*): the unexpected binding mode is stabilized by

attractive interactions between the catalyst's *o*- and *m*-trityl protons and two of the enolate's oxygen atoms, thereby explaining why the trityl-substituted catalyst alone was capable of bringing about the formation of predominantly *cis*-products (for further discussion see the ESI). This gave us a salutary lesson regarding simplistic thinking in catalyst design: what was intended to be a repulsive steric interaction in fact influenced enolate binding by attractive means.

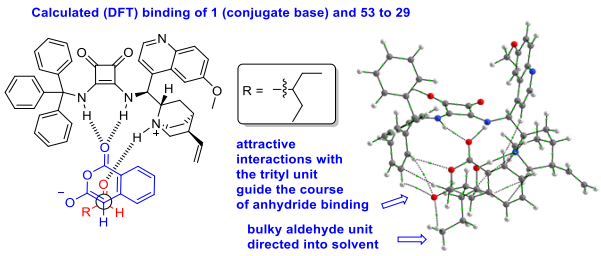


Figure 2. DFT-based stereochemical insight

In conclusion, we have developed the first enantioselective cycloaddition reaction between aldehydes and enolizable anhydrides which is *cis*-selective. Diastereocontrol up to 90:10 dr and enantiomeric excesses up to 99% are possible. The process is of broad scope: aliphatic aldehydes are superior substrates to aromatic analogues, however both are accepted by the catalyst. Homophthalic-, aryl succinic- and glutaconic anhydride derivatives are also compatible. DFT calculations have shown that the unique ability of **29** is due in part to an ability of the trityl aromatic protons to undergo attractive interactions with the catalyst-bound anhydride conjugate base.

EXPERIMENTAL SECTION

General information. Proton Nuclear Magnetic Resonance (NMR) spectra was recorded on Bruker DPX 400 MHz spectrometer using $CDCl_3$, DMSO-d_6 or D_2O as solvents and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or H_2O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (J) in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 and 202 MHz respectively). HSQC, HMBC, NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F254 slides, and visualized by UV irradiation or $KMnO_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument and are quoted in units of 10-1 deg cm^2 g^{-1}. Anhydrous tetrahydrofuran (THF), CH_2Cl_2 and Et_2O were obtained by using Pure Solv MD4EN Solvent Purification System. Methanol (MeOH) was dried over activated 3Å molecular sieves. Commercially available anhydrous t-butyl methyl ether (MTBE), 1,4-dioxane, 2-methyltetrahydrofuran (2-MeTHF), 1,2-dimethoxyethane, diisopropyl ether were used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, OD, OD-H, OJ-H (4.6 mm x 25 cm) and using ACQUITY UPC2, Trefoil CEL1, CEL2, 2.5µm (3.0 x 150 mm).

Procedure for the synthesis of catalyst 29. Synthesized according to the literature procedure as a white solid (3.85 g, 91%).[13] M.p. 156-158°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.61 (d, *J* = 4.5 Hz, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 7.56-7.46 (bs, 1H), 7.38 (dd, *J* = 2.3, 9.2 Hz, 1H), 7.20-7.09 (m, 9H), 7.07-6.91 (m, 6H), 6.55 (bs, 1H), 6.39 (bs, 1H), 5.91-5.71 (m, 2H), 5.06-4.96 (m, 2H), 3.90 (s, 3H), 3.69 (bs, 1H), 3.34-3.12 (m, 2H), 2.67-2.46 (m, 3H), 2.31-2.21 (m, 1H), 1.70-1.58 (m, 1H), 1.55-1.40 (m, 3H), 0.74-0.57 (m, 1H).

Procedure for the synthesis of compound 1.[6] A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with homophthalic acid (2.00 g, 11.1 mmol). Acetic anhydride (25 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 2 h. The excess acetic anhydride was removed *in vacuo* and the solid obtained was triturated with Et_2O (10 mL), filtered and dried to obtain homophthalic anhydride (**1**) as an off white solid (1.50 g, 85%). M.p. 141-142 °C (lit.,[6] m.p. 143-144 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 (d, *J* = 7.9 Hz, 1H), 7.75 (app. t, 1H), 7.52 (app. t, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 4.28 (s, 2H).

(E)-Ethyl-7-oxohept-2-enoate (***S1***). Synthesized according to the procedure developed by Singleton *et al*.[22] To an aqueous solution of glutaraldehyde (15 mL, 166 mmol, 25% *w/v* in water) in CH_2Cl_2 (3 mL) was added a solution of (carboethoxymethylene)triphenylphosphorane (5.78 g, 16.6 mmol) in CH_2Cl_2 (5 mL). The corresponding reaction mixture was allowed to stir at room temperature for 12 h, after which time EtOAc (30 mL) was added. The resulting solution was washed with water (20 mL) and then concentrated under reduced pressure. The crude product obtained was then purified by flash column chromatography eluting with 80:20 hexanes:EtOAc to furnish (*E*)-**S1** as a colourless oil (1.24 g, 44%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79-9.74 (t, *J* = 1.3 Hz, 1H), 6.93 (dt, *J* = 6.8, 15.7 Hz, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.50 (dt, *J* = 1.3, 13.2 Hz, 2H), 2.33-2.21 (m, 2H), 1.89-1.77 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); HRMS (ESI) m/z: $[M - H]^-$ Calcd. for $C_9H_{13}O_3$ 169.0867; Found 169.0865.

tert-butyl (2-aminoethyl)carbamate (***S2***). Synthesized according to the procedure developed by Guenter *et al*.[23] A 500 mL round-bottomed flask containing a magnetic stirring bar was charged with a solution of ethylenediamine (5.6 mL, 83.3 mmol) in CH_2Cl_2 (25 mL). A solution of di-*tert*-butyl dicarbonate (3.05 g, 14.0 mmol) in CH_2Cl_2 (200 mL) was then added dropwise over 3 h. The volatiles were removed *in vacuo* and the resulting oil was dissolved in a saturated aqueous solution of Na_2CO_3 (300 mL) and extracted with CH_2Cl_2 (2 x 150 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **S2** as colourless oil (1.59 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (bs, 1H), 3.13 (m, 2H), 2.76 (m, 2H), 1.41 (s, 9H), 1.22 (bs, 2H); HRMS (APCI) m/z: $[M + H]^+$ Calcd for $C_7H_{17}N_2O_2$ 161.1284; Found 161.1289.

tert-butyl (3-oxopropyl)carbamate (***S3***). Synthesized according to the procedure developed by Fujisawa *et al*.[24] An oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere, was charged with a solution of DMSO (3 mL, 32.3 mmol) in CH_2Cl_2 (57 mL), followed by oxalyl chloride (1.4 mL, 16.1 mmol) at -78 °C. The resultant mixture was stirred for 15 min and a solution of **S2** (1.71 g, 10.7 mmol) in CH_2Cl_2 (50 mL) was added dropwise. After 1 hour, triethylamine (7.5 mL, 53.8 mmol) was added at -78 °C and the corresponding solution was allowed to stir at room temperature for 30 min. The reaction mixture was then quenched with a 10% aqueous solution of HCl (100 mL) and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, then brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 70:30 hexanes:EtOAc, to afford **S3** as a yellow oil (1.50 g, 81%). TLC (hexanes:EtOAc 8:2, *v/v*): Rf = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1H), 4.73 (bs, 1H), 3.48-3.32 (m, 2H), 3.75-3.60 (m, 2H), 1.42 (s, 9H); HRMS (APCI) m/z: $[M + Na]^+$ Calcd. for $C_8H_{15}NO_3Na$ 196.0944; Found 196.0936.

Bromoisochroman-1,3-dione (***52***). Synthesized according to the literature procedure as an off white solid (800 mg, 85%).[25]. M.p. 176-177 °C (lit.[25] 171-173 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 2.0 Hz, 1H), 7.94 (dd, *J* = 2.0, 8.3 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 4.23 (s, 2H).

3-(4-Nitrophenyl)dihydrofuran-2,5-dione (***55***). Synthesized according to the literature procedure as a white solid (1.20 g, 68%).[12] M.p. 66-68 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.22 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 4.84 (dd, *J* = 8.3, 10.2 Hz, 1H), 3.44 (dd, *J* = 10.2, 18.3 Hz, 1H), 3.32 (dd, *J* = 8.3, 18.3 Hz, 1H).

Phenyl-2H-pyran-2,6(3H)-dione (***57***). Synthesized according to the literature procedure as a white solid (118 mg, 51%).[8] M.p. 195-197 °C (lit.[8] m.p. 193-195 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.79 (d, *J* = 6.7 Hz, 2H), 7.55-7.41 (m, 3H), 6.78 (s, 1H), 4.15 (s, 2H).

General procedure A for the racemic synthesis of dihydroisocoumarins and *γ*-butyrolactones (Table 1 entry 16, Tables 2 and 3). An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with the relevant anhydride (1 equiv.) and anhydrous THF (2.5 mL, 0.1 M). The relevant aldehyde (1 equiv.) followed by *N*,*N*-diisopropylethylamine (8.6 µL, 0.0492 mmol - 20 mol%) were then added *via* syringe and the resulting mixture was allowed to stir for 20 h at room temperature. To the corresponding solution of carboxylic acids in THF (2.5 mL, 0.1 M), were added *via* syringe anhydrous MeOH (750 µL, 18.5 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography to afford both diastereomers.

General procedure B for the enantioselective synthesis of dihydroisocoumarins and *γ*-butyrolactones (Table 1 entry 16, Tables 2 and 3). An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with the relevant anhydride (1.0 equiv.), catalyst **29** (8.13 mg, 0.0123 mmol - 5 mol%) and anhydrous THF (0.1 M). The resulting mixture was cooled to -15 °C and the relevant aldehyde (1 equiv.) was added *via* syringe. The reaction was allowed to stir at -15 °C and for a time indicated in the relative Table. The yield and diastereomeric ratio of the carboxylic acids were determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (10 mL) and extracted with a 10% aqueous solution of $NaHCO_3$ (15 mL). The combined aqueous phases were acidified with an aqueous solution of HCl (2.0 N, 5 mL) and the mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish the diastereomeric mixture of carboxylic acids. To a solution of the carboxylic acid products in dry THF (0.1 M) were added *via* syringe anhydrous MeOH (750 µL, 18.5 mmol) followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) and the reaction was allowed to stir for 20 min. The solvent was then evaporated *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, to isolated both diastereomers – the enantiomeric excesses of which were determined by CSP-HPLC.

General procedure C for the racemic synthesis of kavalactones derivatives (Scheme 3). An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with phenyl glutaconic anhydride (**57**, 46.3 mg, 0.246 mmol) and anhydrous THF (2.5 mL, 0.1 M). The relevant aldehyde (1 equiv.) was then added to the reaction followed by equal amounts of catalyst **18** (14.2 mg, 0.0246 mmol - 10 mol%) and its pseudoenantiomer catalyst *epi*-**18** (14.2 mg, 0.0246 mmol - 10 mol%) and the resulting mixture was allowed to stir for 20 h at room temperature. The corresponding solution of carboxylic acids in dry THF (2.5 mL, 0.1 M) was then cooled to -15 °C and anhydrous *i*PrOH (94 µL, 1.23 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) were added *via* syringe. The reaction was allowed to stir for 20 min at -15 °C, after which time the solvent was removed *in vacuo.* The resultant crude mixture of diastereomeric esters was then purified by flash column chromatography to furnish both diastereomers.

General procedure D for the enantioselective synthesis of kavalactones (Scheme 3) An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with phenyl glutaconic anhydride (**57**, 46.3 mg, 0.246 mmol), catalyst **29** (8.13 mg, 0.0123 mmol - 5 mol%) and anhydrous THF (0.1 M). The resulting mixture was cooled to -15 °C and the relevant aldehyde (1 equiv.) was added *via* syringe. The reaction was allowed to stir at -15 °C and for a time indicated in the relative Table. The yield and diastereomeric ratio of the carboxylic acids were determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (10 mL) and extracted with a 10% aqueous solution of $NaHCO_3$ (15 mL). The combined aqueous phases were acidified with an aqueous solution of HCl (2.0 N, 5 mL) and the mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish the diastereomeric mixture of carboxylic acids. To a solution of the corresponding carboxylic acids in dry THF (0.1 M) cooled to -15 °C, anhydrous *i*PrOH (94 µL, 1.23 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) were added *via* syringe and the reac-

tion was allowed to stir for 20 minutes. The solvent was then evaporated under reduced pressure and the crude mixture of diastereomeric esters was purified by flash column chromatography to furnish both diastereomers. The enantiomeric excesses of the products were determined by CSP-HPLC using the conditions indicated for each case.

Methyl-1-oxo-3-((E)-styryl)isochromane-4-carboxylate (***15a, 15b***). Prepared according to general procedure B, using freshly distilled hydrocinnamaldehyde (**14**, 32.0 μL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 33 h to give a diastereomeric mixture of carboxylic acids in a 71:29 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**15b** and *trans*-**15a** were isolated combined as a pale yellow oil (74.0 mg, 99%). CSP-HPLC analysis: Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 70/30, 0.3 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**15b** 70.4 min (major enantiomer) and 105.9 min (minor enantiomer); *trans*-**15a** 60.6 min (major enantiomer) and 79.2 min (minor enantiomer). Spectral data for this compound were consistent with those in the literature.[6] TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.34; *cis*-**15b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.9 Hz, 1H), 7.56 (app. t, 1H), 7.48 (app. t, 1H), 7.32-7.24 (m, 2H), 7.25-7.14 (m, 4H), 4.60-4.52 (m, 1H), 3.83 (d, *J* = 3.2 Hz, 1H), 3.67 (s, 3H), 3.05-2.90 (m, 1H), 2.90-2.83 (m, 1H), 2.31-2.18 (m, 1H), 2.14-2.02 (m, 1H); *trans*-**15a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.7 Hz, 1H), 7.57 (app. t, 1H), 7.47 (app. t, 1H), 7.32-7.24 (m, 3H), 7.25-7.14 (m, 3H), 4.90-4.82 (m, 1H), 3.92 (d, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 3.05-2.90 (m, 1H), 2.83-2.75 (m, 1H), 2.15-2.01 (m, 1H), 1.99-1.84 (m, 1H); HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{19}H_{19}O_4$ 311.1277; Found 311.1284.

Methyl-3-heptyl-1-oxoisochromane-4-carboxylate (*cis*-**31**, *trans*-**31**). Prepared according to general procedure B, using freshly distilled octanal (38.4 μL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 76:24 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 90:10 hexanes:EtOAc, *cis*-**31** and *trans*-**31** were isolated combined as a white solid (70.4 mg, 94%). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 221 nm, retention times: *cis*-**31** 48.4 min (minor enantiomer) and 62.1 min (major enantiomer); *trans*-**31** 33.4 min (minor enantiomer) and 35.6 min (major enantiomer). M.p. 50-55 ºC; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.61; $[\alpha]_D^{20}$ = -3.2 (*c* = 0.05, $CHCl_3$);**cis*-**31**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 7.8 Hz, 1H), 7.61 (app. t, 1H), 7.50 (app. t, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 4.63-4.59 (m, 1H), 3.88 (d, *J* = 3.2 Hz, 1H), 3.69 (s, 3H), 1.92-1.82 (m, 1H), 1.84-1.73 (m, 1H), 1.66-1.61 (m, 1H), 1.52-1.47 (m, 1H), 1.47-1.32 (m, 8H), 0.92-0.86 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.3, 164.8, 136.8, 133.7, 130.7, 129.0, 127.2, 125.5, 78.7, 52.6, 47.9, 32.8, 31.73, 29.2, 29.04, 25.2, 22.7, 14.1; *trans*-**31**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.0 Hz, 1H), 7.58 (app. t, 1H), 7.48 (app. t, 1H), 7.23 (d, *J* 7.4 Hz, 1H), 4.63 (ddd, *J* = 3.8, 6.5, 12.5 Hz, 1H), 3.92 (d, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 1.83-1.74 (m, 1H), 1.66-1.61 (m, 2H), 1.52-1.47 (m, 1H), 1.47-1.32 (m, 8H), 0.92-0.86 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.7, 163.9, 135.9, 134.0, 130.5, 128.6, 127.3, 124.7, 79.1, 52.7, 48.4, 33.7, 31.7, 29.1, 29.08, 25.0, 22.6, 14.0; IR (neat): 3133, 3025, 1730, 1680, 1580, 1467, 1156, 1125, 1096, 1012, 790, 685, 705; HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{18}H_{25}O_4$ 305.1747; Found 305.1760.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**31**:*trans*-**31** in a 79:21 ratio

Methyl-3-benzyl-1-oxoisochromane-4-carboxylate (*cis*-***32***, *trans*-***32***). Prepared according to general procedure B, using freshly distilled phenylacetaldehyde (27.4 μL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 h to furnish a diastereomeric mixture of carboxylic acids in a 87:13 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**32** and *trans*-**32** were isolated combined as a white solid (67.1 mg, 92%). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), *n*-hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**32** 40.3 min (minor enantiomer) and 48.0 min (major enantiomer); *trans*-**32** 15.4 min (major enantiomer) and 21.6 min (minor enantiomer). M.p. 68-70 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.41, $[\alpha]_D^{20}$ = -4.5 (*c* = 0.04, $CHCl_3$);**cis*-**32**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 6.5 Hz, 1H), 7.56 (app. t, 1H), 7.49 (app. t, 1H), 7.45-7.36 (m, 5H), 7.35 (d, *J* = 6.9 Hz, 1H), 4.81 (ddd, *J* = 2.9, 6.7, 7.8 Hz, 1H), 3.84 (d, *J* = 2.9 Hz, 1H), 3.73 (s, 3H), 3.30 (dd, *J* = 6.7, 14.2 Hz, 1H), 3.16 (dd, *J* = 7.8, 14.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.2, 164.6, 136.7, 135.8, 133.7, 130.7, 129.5, 129.1, 128.8, 127.4, 127.2, 125.4, 79.7, 52.7, 46.7, 38.9; *trans*-**32**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 6.4 Hz, 1H), 7.64 (app. t, 1H), 7.49 (app. t, 1H), 7.45-7.36 (m, 5H), 7.17 (d, *J* = 6.3 Hz, 1H), 5.22-5.17 (m, 1H), 3.86 (d, *J* = 5.2 Hz, 1H), 3.72 (s, 3H), 3.17 (dd, *J* = 6.3, 14.1 Hz, 1H), 2.89 (dd, *J* = 7.8, 14.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.4, 163.5, 135.5, 135.2, 134.3, 130.5, 129.5, 128.87, 128.82, 127.9, 127.3, 124.7, 79.4, 52.8, 46.5, 39.6; IR (neat): 3030, 2952, 1724, 1658, 1453, 1434, 1376, 1261, 1158, 1119, 1030, 979, 738, 698; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{18}H_{16}O_4Na$ 319.0940; Found 319.0945.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**32**:*trans*-**32** in a 84:16 ratio

Methyl-3-isopropyl-1-oxoisochromane-4-carboxylate (*cis*-***33***, *trans*-***33***). Prepared according to general procedure B, using freshly distilled isovaleraldehyde (26.9 μL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 78:22 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**33** and *trans*-**33** were isolated combined as a white solid (58.7 mg, 91%). CSP-HPLC analysis: Chiralcel ODH (4.6 mm x 25 cm), *n*-hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: *cis*-**33** 16.8 min; *trans*-**33** 11.2 min. M.p. 95-97 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.27; $[\alpha]_D^{20}$ = -6.3 (*c* = 0.04, $CHCl_3$);* *cis*-**33**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 7.8 Hz, 1H), 7.59 (app. t, 1H), 7.51 (app. t, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 4.72 (ddd, *J* = 3.3, 4.5, 9.2 Hz, 1H), 3.83 (d, *J* = 3.3 Hz, 1H), 3.70 (s, 3H), 2.10-2.01 (m, 1H), 1.88 (ddd, *J* = 5.9, 9.2, 14.6 Hz, 1H), 1.58 (ddd, *J* = 4.5, 8.4, 14.6 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H);$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 169.3, 164.8, 136.8, 133.7, 130.7, 129.0, 127.2, 125.4, 76.8, 52.6, 48.3, 41.5, 24.1, 22.9, 21.9; *trans*-**33**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.4 Hz, 1H), 7.63-7.59 (m, 1H), 7.49-7.45 (m, 1H), 7.24 (d, *J* = 7.3 Hz, 1H), 4.96 (ddd, *J* = 4.5, 6.1, 9.2 Hz, 1H), 3.87 (d, *J* = 6.1 Hz, 1H,), 3.80 (s, 3H), 2.01-1.94 (m, 1H), 1.85 (ddd, *J* = 5.9, 9.2, 14.6 Hz, 1H), 1.55 (ddd, *J* = 4.5, 8.4, 14.6 Hz, 1H),

0.97 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.7, 163.8, 135.8, 134.1, 130.4, 128.7, 127.4, 124.7, 77.4, 52.8, 48.8, 42.8, 24.2, 23.1, 21.5; IR (neat): 2956, 1719, 1605, 1459, 1311, 1264, 1163, 1113, 1087, 993, 948, 827, 711, 606, 567; HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{15}H_{19}O_4$ 263.1277; Found 263.1273.

*$[\alpha]_D^{20}$ refers to *cis*-**33** which was isolated after trituration of the diastereomeric mixture with isopropanol

Methyl-3-isopropyl-1-oxoisochromane-4-carboxylate (*cis*-***34***, *trans*-***34***). Prepared according to general procedure B, using freshly distilled isobutyraldehyde (22.4 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 84:16 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtAOc, *cis*-**34** and *trans*-**34** were isolated combined as a white solid (54.9 mg, 90%). CSP-HPLC analysis: Chiralcel ODH (4.6 mm x 25 cm), *n*-hexane/IPA: 85/15, 0.5 mL min^{-1}, RT, UV detection at 221 nm, retention times: *cis*-**34** 20.3 (minor enantiomer) and 21.8 min (major enantiomer); *trans*-**34** 15.2 min (major enantiomer) and 17.2 (minor enantiomer). M.p. 69-72 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.26; $[\alpha]_D^{20}$ = -5.1 (*c* = 0.05, $CHCl_3$);* *cis*-**34**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 7.5 Hz, 1H), 7.56 (app. t, 1H), 7.50 (app. t, 1H), 7.31 (d, J = 7.5 Hz, 1H), 4.15 (dd, J = 3.0, 9.9 Hz, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.65 (s, 3H), 2.13-2.03 (m, 1H), 1.17 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): 169.4, 164.9, 137.1, 133.7, 130.7, 129.0, 127.3, 125.6, 84.4, 52.6, 46.2, 31.1, 18.5, 19.4; *trans*-**34**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 7.8 Hz, 1H), 7.58 (app. t, 1H), 7.48 (app. t, 1H), 7.21 (d, J = 7.4 Hz, 1H), 4.64-4.60 (m, 1H), 4.04 (d, J = 6.4 Hz, 1H), 3.77 (s, 3H), 1.88-1.77 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 165.6, 136.1, 134.1, 130.3, 128.6, 127.3, 125.6, 83.9, 52.8, 46.3, 30.9, 19.3, 17.2; IR (neat): 2973, 1718, 1604, 1436, 1263, 1210, 1168, 1109, 1084, 983, 768, 714, 642; HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{14}H_{17}O_4$ 249.1121; Found 249.1122.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**34**:*trans*-**34** in a 84:16 ratio

Methyl-1-oxo-3-(pentan-3-yl)isochromane-4-carboxylate (*cis*-***35***, *trans*-***35***). Prepared according to general procedure B, using freshly distilled 2-ethylbutyraldehyde (30.3 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 6 days to give a diastereomeric mixture of carboxylic acids in a 88:12 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 95:5 hexanes:EtOAc, *cis*-**35** and *trans*-**35** were isolated combined as a white solid (61.2 mg, 90%). CSP-HPLC analysis: ACQUITY UPC², Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: *cis*-**35** 2.05 min; *trans*-**35** 2.02 min. M.p. 45-47 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.64; $[\alpha]_D^{20}$ = -3.9 (*c* = 0.04, $CHCl_3$);* *cis*-**35**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 7.7 Hz, 1H), 7.58 (app. t, 1H), 7.50 (app. t, 1H), 7.34 (d, J = 7.7 Hz, 1H), 4.45 (dd, J = 2.9, 9.8 Hz, 1H), 4.01 (d, J = 2.9 Hz, 1H), 3.68 (s, 3H), 1.90-1.77 (m, 3H), 1.70-1.59 (m, 1H), 1.55-1.42 (m, 1H), 0.94-0.88 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.5, 165.0, 137.2, 133.6, 130.7, 129.0, 127.3, 125.6, 80.6, 52.6, 46.1, 41.7, 20.0, 19.7, 9.8, 9.6; *trans*-**35**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 5.8 Hz, 1H), 7.61 (app. t, 1H), 7.50 (app. t, 1H), 7.23 (d, J = 7.6 Hz, 1H), 4.90-4.84 (m, 1H), 4.14 (d, J = 6.7 Hz, 1H), 3.80 (s, 3H), 1.90-1.77 (m, 3H), 1.70-1.59 (m, 1H), 1.55-1.42 (m, 1H), 0.94-0.88 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.9, 164.2, 137.2, 134.0, 130.4, 128.6, 127.2, 125.6, 80.7, 52.7, 46.2, 43.2, 21.9, 20.9, 11.2, 10.8; IR (neat): 2963, 2878, 1724, 1604, 1458, 1264,1226, 1158, 1110, 1085, 997, 717, 691; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{16}H_{20}O_4Na$ 299.1259; Found 299.1279.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**35**:*trans*-**35** in a 90:10 ratio.

Methyl-3-cyclohexyl-1-oxoisochroman-4-carboxylate (*cis*-***36*** *trans*-***36***). Prepared according to general procedure B, using freshly distilled cyclohexanecarboxyaldehyde (29.8 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 24 h to give a diastereomeric mixture of carboxylic acids in a 80:20 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 90:10 hexanes:EtOAc, *cis*-**36** and *trans*-**36** were isolated combined as a pale yellow oil (67.4 mg, 95%). Spectral data for this compound were consistent with those in the literature.[6] CSP-HPLC analysis: Chiralcel ODH (4.6 mm x 25 cm), *n*-hexane/IPA: 60/40, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**36** 59.5 min (minor enantiomer) and 65.1 min (major enantiomer); *trans*-**36** 51.8 min (major enantiomer) and 62.3 min (minor enantiomer). *cis*-**36**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 7.6 Hz, 1H), 7.58 (app. t, 1H), 7.50 (app. t, 1H), 7.33 (d, J = 7.6 Hz, 1H), 4.26 (dd, J = 3.0, 9.9 Hz, 1H), 4.03 (d, J = 3.0 Hz, 1H), 3.69 (s, 3H), 2.41-2.23 (m, 1H), 2.03-1.08 (m, 8H), 1.08-0.95 (m, 2H); *trans*-**36**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 7.9 Hz, 1H), 7.58 (app. t, 1H), 7.46 (app. t, 1H), 7.22 (d, J = 7.6 Hz, 1H), 4.66 (m, 1H), 4.06 (d, J = 5.7 Hz, 1H), 3.77 (s, 3H), 1.97-1.88 (m, 1H), 1.87-1.08 (m, 10 H); HRMS (APCI) m/z: $[M- H]^-$ Calcd. for $C_{17}H_{19}O_4$ 287.1288; Found 287.1277.

(3R,4R)-Methyl-3-benzhydryl-1-oxoisochromane-4-carboxylate (*cis*-***37***, *trans*-***37***). Prepared according to general procedure B, using freshly distilled diphenylacetaldehyde (43.6 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 hours to give a diastereomeric mixture of carboxylic acids in a 87:13 ratio (*cis:trans*). After esterification, the crude mixture was purified by flash column chromatography to give **37** (a chromatographically inseparable mixture of diastereomers with retention of *dr*) as a white solid (78.1 mg, 85%). Full characterisation of *cis*-**37** was made possible by trituration of the diastereomeric mixture with IPA in which *trans*-**37** is completely soluble. Full characterisation of *trans*-**37** was complicated due to the partial solubility of *cis*-**37** in IPA. CSP-HPLC analysis: ACQUITY UPC², Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, *cis*-**37** 3.38 min (minor enantiomer) and 3.58 min (major enantiomer); *trans*-**37** 3.69 min (major enantiomer) and 3.85 min (minor enantiomer). M.p. 174-176. ºC; TLC (hexanes:EtOAc, 8/2 *v/v*): R_f = 0.67; $[\alpha]^{20}{}_D$ = -2.9 (c = 0.04, $CHCl_3$);* *cis*-**37**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 7.7 Hz, 1H), 7.56 (app. t, 1H), 7.50 (app. t, 1H), 7.43-7.38 (m, 2H), 7.38-7.25 (m, 8H), 7.22 (t, J =7.3 Hz, 1H,), 5.39 (dd, J = 2.4, 10.9 Hz, 1H), 4.59 (d, J = 10.9 Hz, 1H), 3.75 (d, J = 2.4 Hz, 1H), 3.66 (s, 3H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): δ = 168.9, 164.4, 140.2, 140.1, 136.9, 133.7, 130.7, 129.1, 129.0, 128.6 (C x 2), 128.1, 127.6, 127.5, 126.8, 125.3, 79.9, 53.6, 52.4, 45.8; IR (neat): 3029, 1734, 1724, 1600, 1494, 1452, 1251, 1221, 1157, 1107, 1085, 996, 973,

749, 695, 592; HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{24}H_{21}O_4$ 373.1434; Found 373.1434.

*$[\alpha]_D^{20}$ refers to *cis*-**37** which was isolated after trituration of the diastereomeric mixture with isopropanol

Methyl-1-oxo-3-((E)-styryl)isochromane-4-carboxylate (*cis*-***38***, *trans*-***38***). Prepared according to general procedure B, using freshly distilled cinnamaldehyde (31.0 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 63:37 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**38** and *trans*-**38** were isolated combined as a pale yellow oil (57.6 mg, 76%). CSP-HPLC analysis: ACQUITY UPC², Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: *cis*-**38** 3.0 min (minor enantiomer) and 3.3 min (major enantiomer); *trans*-**38** 3.4 min (major enantiomer) and 3.7 min (minor enantiomer). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.42; $[\alpha]_D^{20}$ = -6.0 (*c* = 0.03, $CHCl_3$);**cis*-**38**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 7.7 Hz, 1H,), 7.63 (app. t, 1H), 7.54 (app. t, 1H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.42-7.29 (m, 4H), 6.91 (d, *J* = 16.0 Hz, 1H), 6.38 (dd, *J* = 6.1, 16.0 Hz, 1H), 5.36 (ddd, *J* = 1.4, 3.5, 6.1 Hz, 1H,), 4.08 (d, *J* = 3.5 Hz, 1H), 3.68 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.9, 164.3, 136.3, 135.7, 134.0, 133.9, 130.8, 129.2, 128.7, 128.5, 127.55, 126.88, 125.2, 123.1, 78.4, 52.6, 48.9; *trans*-**38**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.9 Hz, 1H), 7.63 (app. t, 1H), 7.51 (app. t, 1H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.42-7.29 (m, 4H), 6.79 (d, *J* = 15.9 Hz, 1H), 6.20 (dd, *J* = 6.8, 15.9 Hz, 1H), 5.60-5.54 (m, 1H), 4.11 (d, *J* = 6.3 Hz, 1H), 3.80 (s, 3H). $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): δ = 170.1, 163.7, 135.5, 135.4, 135.2, 134.3, 130.5 128.9, 128.69, 128.6, 127.51, 126.85, 124.7, 123.9, 79.4, 52.9, 49.1; IR (neat): 2954, 1732, 1713, 1606, 1439, 1311, 1266, 1230, 1164, 1154, 1117, 710, 690, 607; HRMS (APCI) m/z: $[M + Na]^+$ Calcd. for $C_{19}H_{16}O_4Na$ 331.0940; Found 331.0943.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**38**:*trans*-**38** in a 66:34 ratio

Methyl-3-(but-3-en-1-yl)-1-oxoisochromane-4-carboxylate (*cis*-***39***, *trans*-**39**). Prepared according to general procedure B, using freshly distilled 4-pentenal (26.0 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 74:26 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, *cis*-**39** and *trans*-**39** were isolated combined as a pale yellow oil (61.4 mg, 96%). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), *n*-hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**39** 8.4 min (minor enantiomer) and 13.4 min (major enantiomer).); *trans*-**39** 9.2 min (major enantiomer) and 10.7 min (minor enantiomer). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.47; $[\alpha]_D^{20}$ = -5.9 (*c* = 0.07, $CHCl_3$);* *cis*-**39**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 7.3 Hz, 1H), 7.59 (app. t, 1H), 7.50 (app. t, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 5.90-5.76 (m, 1H), 5.12 (dd, *J* = 1.5, 17.1 Hz, 1H), 5.04 (dd, *J* = 1.5, 10.1 Hz, 1H), 4.68 (ddd, *J* = 3.3, 4.8, 8.7 Hz, 1H), 3.87 (d, *J* = 3.3 Hz, 1H), 3.69 (s, 3H), 2.49-2.25 (m, 2H), 2.13-1.97 (m, 1H), 1.95-1.81 (m, 1H). $^{13}C\{^1H\}$ NMR100 MHz, $CDCl_3$): δ = 169.2, 164.7, 136.7, 133.7, 130.7, 129.0, 127.3, 125.4, 116.1, 77.7, 52.6, 47.8, 31.8, 29.2; *trans*-**39**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.6 Hz, 1H), 7.61 (app. t, 1H), 7.49 (app. t, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 5.85-5.74 (m, 1H), 5.09 (dd, *J* = 1.6, 17.3 Hz, 1H), 5.03 (dd, *J* = 1.6 Hz, 1H), 4.95 (ddd, *J* = 4.0, 6.6 Hz, 1H), 3.94 (d, *J* = 6.6 Hz, 1H), 3.81 (s, 3H), 2.43-2.20 (m, 2H), 1.96-1.82 (m, 1H), 1.77-1.64 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.6, 163.8, 136.6, 135.8, 134.1, 130.5, 128.7, 126.6, 124.6, 116.0, 78.3, 52.8, 48.4, 32.9, 29.1; IR (neat): 2951, 1720, 1640, 1604, 1458, 1435, 1240, 1159, 1116, 1086, 1030, 996, 916, 768, 709. HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{15}H_{17}O_4$ 261.1121; Found 261.1116.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**39**: *trans*-**39** in a 74:26 ratio

*Methyl-3-((E)-6-ethoxy-6-oxohex-4-en-1-yl)-1-oxoisochromane-4-carboxylate (cis-**40**, trans-**40**).* Prepared according to general procedure B, using aldehyde **S1** (42.0 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 73:27 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, *cis*-**40** and *trans*-**40** were isolated combined as a pale yellow oil (71.6 mg, 84%). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: *cis*-**40** 42.9 min; *trans*-**40** 20.9 min (minor enantiomer) and 23.5 min (major enantiomer).TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.16, $[\alpha]_D^{20}$ = -3.4 (*c* = 0.01, $CHCl_3$);* *cis*-**40**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 7.1 Hz, 1H), 7.56 (app. t, 1H), 7.49 (app. t, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 6.96-6.88 (m, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 4.67-4.55 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.84 (d, *J* = 2.8 Hz, 1H), 3.66 (s, 3H), 2.29-2.25 (m, 2H), 1.92-1.89 (m, 2H), 1.76-1.64 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1, 165.5, 164.5, 147.8, 136.6, 133.8, 130.8, 129.1, 127.5, 125.4, 122.1, 78.3, 60.2, 52.6, 47.9, 32.2, 31.6, 23.8, 14.3; *trans*-**40**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.8 Hz, 1H), 7.54 (app. t, 1H), 7.48 (app. t, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 6.96-6.88 (m, 1H), 5.78 (d, *J* = 14.5 Hz, 1H), 4.97-4.84 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.89 (d, *J* = 6.9 Hz, 1H), 3.79 (s, 3H), 2.24-2.22 (m, 2H) 1.87-1.82 (m, 2H), 1.76-1.64 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.5, 166.5, 163.7, 147.7, 135.8, 134.2, 130.6, 128.8, 127.2, 124.5, 122.1, 78.6, 60.2, 52.8, 48.5, 33.0, 31.4, 23.4, 14.2; IR (neat): 2953, 1717, 1652, 1459, 1367, 1265, 1159, 1032, 976, 706, 625; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{19}H_{22}O_6Na$ 369.1308; Found 369.1309.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**40**: *trans*-**40** in a 73:27 ratio

Methyl-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1-oxoisochromane-4-carboxylate (*cis*-***41***, *trans*-***41***). Prepared according to general procedure B, using aldehyde **S2** (42.6 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 24 h to give a diastereomeric mixture of carboxylic acids in a 70:30 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, *cis*-**41** and *trans*-**41** were isolated combined as a pale yellow oil (64.4 mg, 75%). CSP-HPLC analysis: Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**41** 364.7 min; *trans*-**41** 220.1 min (minor enantiomer) and 190.1 min (major enantiomer). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.17; $[\alpha]_D^{20}$ = -4.4 (*c* =0.02, $CHCl_3$);* *cis*-**41**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 7.8 Hz, 1H), 7.61 (app. t, 1H), 7.51 (app. t, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 4.88-4.77 (bs, 1H), 4.76-4.68 (m, 1H), 3.95 (d, *J* = 3.5 Hz, 1H), 3.69 (s, 3H), 3.48-3.33 (m, 2H),

2.12-2.03 (m, 2H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.2, 164.5, 156.1, 136.7, 133.8, 130.7, 129.1, 127.4, 125.2, 77.2, 67.9, 52.6, 47.7, 36.9, 33.1, 28.3; *trans*-**41**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 6.2 Hz), 7.63 (app. t, 1H), 7.49 (app. t, 1H), 7.27 (d, *J* 8.0 Hz, 1H), 5.04-4.96 (m, 1H), 4.88-4.77 (bs, 1H), 3.96 (d, *J* = 5.6 Hz, 1H), 3.82 (s, 3H), 3.48-3.33 (m, 2H), 1.92-1.89 (m, 1H), 1.84-1.77 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.3, 163.5, 155.9, 135.7, 134.3, 130.5, 128.8, 127.4, 124.4, 79.5, 77.2, 52.8, 48.2, 36.7, 30.1, 28.3; IR (neat): 3383, 2976, 1705, 1609, 1516, 1458, 1366, 1241, 1161, 1086, 1031, 994, 734, 605; HRMS (ESI) m/z: $[M- H]^-$ Calcd. for $C_{18}H_{22}NO_6$ 348.1447; Found 348.1450.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**41**: *trans*-**41** in a 84:16 ratio

Methyl 1-oxo-3-phenylisochroman-4-carboxylate (*cis*-***42***). Prepared according to general procedure B, using freshly distilled benzaldehyde (25.0 μL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, the diastereomer *cis*-**42** was isolated as a white solid (37.5 mg, 54%, 92% *ee*). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), *n*-hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: 17.6 min (minor enantiomer) and 22.3 min (major enantiomer). M.p. 115-117 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.41; $[\alpha]_D^{20}$ = -4.3 (*c* = 0.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.8 Hz, 1H), 7.63 (app. t, 1H), 7.56 (app. t, 1H), 7.52-7.48 (m, 2H), 7.44 (app. t, 2H), 7.42-7.36 (m, 2H), 5.78 (d, *J* = 3.7 Hz, 1H), 4.14 (d, *J* = 3.7 Hz, 1H), 3.50 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.6, 164.4, 136.3, 136.2, 134.0, 131.0, 129.3, 128.7, 128.6, 127.3, 125.6, 125.3, 79.4, 52.3, 50.7; IR (neat): 2955, 1721, 1601, 1454, 1431, 1244, 1080, 997, 782, 701; HRMS (APCI) m/z: $[M - H]^-$ Calcd. for $C_{17}H_{13}O_4$ 281.0819; Found 281.0811.

*Methyl 1-oxo-3-phenylisochroman-4-carboxylate (trans-**42**)*[6]

Prepared according to general procedure B, using freshly distilled benzaldehyde (25 μL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, the diastereomer *trans*-**42** was isolated as a white solid (24.3 mg, 35%, 64% *ee*). CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**42** 17.0 min (minor enantiomer) and 19.5 min (major enantiomer). M.p. 118-120 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.38. (lit.,[6] m.p. 129-132 °C); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 1H), 7.60 (app. t, 1H), 7.49 (app. t, 1H), 7.44-7.30 (m, 5H), 7.20 (d, *J* = 8.0 Hz, 1H), 5.86 (d, *J* = 8.3 Hz, 1H), 4.34 (d, *J* = 8.3 Hz, 1H), 3.69 (s, 3H).

Methyl-3-(4-bromophenyl)-1-oxoisochromane-4-carboxylate (*cis*-**43**). Prepared according to general procedure B, using recrystallised *p*-bromobenzaldehyde (45.5 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 22 h to give a diastereomeric mixture of carboxylic acids in a 60:40 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *cis*-**43** was isolated as a white solid (47.9 mg, 54%, 92% *ee*). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), *n*-hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 221 nm, retention times: 87.1 min (minor enantiomer) and 91.2 min (major enantiomer). M.p. 135-137 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.35; $[\alpha]_D^{20}$ = -7.6 (*c* = 0.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 7.8 Hz, 1H), 7.65 (app. t, 1H), 7.60-7.54 (m, 3H), 7.39 (m, 3H), 5.75 (d, *J* = 3.6 Hz, 1H), 4.14 (d, *J* = 3.6 Hz, 1H), 3.49 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.4, 164.1, 136.0, 135.2, 134.1, 131.8, 131.0, 129.4, 127.4, 127.3, 125.1, 122.8, 78.7, 52.5, 50.3; IR (neat): 3061, 3018, 2952, 1725, 1601, 1490, 1258, 1009, 822, 736, 692; HRMS (ESI) m/z: $[M - H]^-$ Calcd. for $C_{17}H_{12}O_4Br$ 358.9924; Found 358.9920.

*Methyl-3-(4-bromophenyl)-1-oxoisochromane-4-carboxylate (trans-**43**)*[6]

Prepared according to general procedure B, using recrystallised *p*-bromobenzaldehyde (45.5 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 22 h to give a diastereomeric mixture of carboxylic acids in a 60:40 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**43** was isolated as a white solid (31.7 mg, 36%, 74% *ee*). CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 70.0 min (minor enantiomer) and 80.7 min (major enantiomer). M.p. 137-138 °C (lit.,[6] m.p. 138-140 °C); TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.38; ^1H NMR(400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 7.9 Hz, 1H), 7.61 (app. t, *J* = 7.9 Hz, 1H), 7.55-7.45 (m, 3H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 5.80 (d, *J* = 8.5 Hz, 1H), 4.28 (d, *J* = 8.5 Hz, 1H), 3.71 (s, 3H).

Methyl 3-(4-chlorophenyl)-1-oxoisochroman-4-carboxylate (*cis*-**44**). Prepared according to general procedure B, using recrystallised 4-chlorobenzaldehyde (34.6 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 36 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, the diastereomer *cis*-**44** was isolated as white solid (42.1 mg, 54%, 85% *ee*) CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), *n*-hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: 21.3 min (minor enantiomer) and 22.8 min (major enantiomer). M.p. 65-68 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.70; $[\alpha]^{20}_D$ = -11.6 (*c* = 0.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 7.8 Hz, 1H), 7.60 (app. t, 1H), 7.56 (app. t, 1H), 7.45-7.36 (m, 5H), 5.74 (d, *J* = 3.4 Hz, 1H), 4.12 (d, *J* = 3.4 Hz, 1H), 3.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.4, 164.1, 136.0, 134.7, 134.6, 134.2, 131.0, 129.4, 128.9, 127.4, 127.0, 125.1, 78.6, 52.5, 50.4; IR (neat): 2953, 2926, 2862, 1736, 1709, 1602, 1459, 1261, 1001, 826, 740; HRMS (ESI) m/z: $[M + H]^+$ Calcd. for $C_{17}H_{14}O_4Cl$ 317.0580; Found: 317.0568.

*Methyl 3-(4-chlorophenyl)-1-oxoisochroman-4-carboxylate (trans-**44**)*[6]

Prepared according to general procedure B, using recrystallised 4-chlorobenzaldehyde (34.6 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 36 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 80:20 hexanes:EtOAc,

the diastereomer *trans*-**44** was isolated as a white solid (29.6 mg, 38%, 78% *ee*). CSP-HPLC analysis Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 20.2 min (minor enantiomer) and 23.0 min (major enantiomer). M.p. 71-73 °C (lit.,[6] m.p. 70-72 °C); TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.7 Hz, 1H), 7.61 (app. t, *J* = 7.7 Hz, 1H), 7.50 (app. t, *J* = 7.7 Hz, 1H), 7.39-7.29 (m, 4H), 7.19 (d, *J* = 7.7 Hz, 1H), 5.82 (d, *J* = 8.7 Hz, 1H), 4.30 (d, *J* = 8.7 Hz, 1H), 3.71 (s, 3H).

Methyl 3-(3-bromophenyl)-1-oxoisochromane-4-carboxylate (*cis-**45**)*. Prepared according to general procedure B, using freshly distilled 3-bromobenzaldehyde (28.7 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 40 h to give a diastereomeric mixture of carboxylic acids in a 55:45 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *cis*-**45** was isolated as a white solid (39.1 mg, 44%, 88% *ee*). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), *n*-hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: 58.7 min (minor enantiomer) and 78.6 min (major enantiomer). M.p. 92-94 °C; TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.50; $[\alpha]_D^{20}$ = -5.9 (*c* = 0.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 7.9 Hz, 1H), 7.67-7.59 (m, 2H), 7.56-7.49 (m, 2H), 7.42-7.32 (m, 2H) 7.30-7.26 (m, 1H), 5.73 (d, *J* = 3.7 Hz, 1H), 4.12 (d, *J* = 3.7 Hz, 1H), 3.47 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 168.4, 164.0, 138.4, 135.9, 134.2, 131.9, 131.1, 130.2, 129.4, 128.8, 127.4, 125.1, 124.3, 122.8, 78.4, 52.5, 50.4; IR (neat): 2947, 1722, 1601, 1458, 1358, 1286, 1261, 1225, 1112, 1085, 1056, 996, 971, 989, 787, 717, 689, 638, 584; HRMS (APCI) m/z: [M + Na]$^+$ Calcd. for $C_{17}H_{13}BrO_4Na$ 382.9888; Found: 382.9889.

*Methyl 3-(3-bromophenyl)-1-oxoisochromane-4-carboxylate (trans-**45**)*

Prepared according to general procedure B, using freshly distilled 3- bromobenzaldehyde (28.7 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 40 h to give a diastereomeric mixture of carboxylic acids in a 55:45 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**45** was isolated as a white solid (35.3 mg, 39%, 72% *ee*). CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 16.7 min (minor enantiomer) and 18.8 min (major enantiomer). M.p. 100-105°C; TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.46; $[\alpha]_D^{20}$ = +8.8 (*c* = 0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 7.9 Hz, 1 H), 7.64 (app. t, *J* = 7.9 Hz, 1H), 7.59 (s, 1H), 7.55-7.52 (m, 1H), 7.51-7.49 (m, 1H), 7.36-7.31 (m, 1H), 7.28-7.20 (m, 2H), 5.83 (d, *J* = 8.7 Hz, 1H), 4.32 (d, *J* = 8.7 Hz, 1H), 3.74 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 169.8, 163.7, 138.8, 135.8, 134.6, 132.3, 130.7, 130.3, 129.9, 129.0, 126.7, 125.4, 124.3, 122.8, 79.7, 52.8, 50.7. IR (neat)/cm^{-1}: 2940, 1720, 1601, 1455, 1348, 1285, 1260, 1235, 1112, 1075, 1054, 995, 971, 989, 783, 713, 687, 584; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd. for $C_{17}H_{14}BrO_4$ 360.9888; Found: 360.9887.

*Methyl 3-(4-(methoxycarbonyl)phenyl)-1-oxoisochromane-4-carboxylate (cis-**46**).* Prepared according to general procedure B, using recrystallised methyl 4-formylbenzoate (40.4 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *cis*-**46** was isolated as a white solid (46.0 mg, 55%, 94% *ee*). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 33.8 min (major enantiomer) 55.7 min (minor enantiomer). M.p. 144-146 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.31; $[\alpha]^{20}_D$ = -10.4 (*c* = 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 7.67 (app. t, 1H), 7.66- 7.53 (m, 3H), 7.38 (d, *J* = 7.0 Hz, 1H), 5.82 (d, *J* = 3.5 Hz, 1H), 4.17 (d, *J* = 3.5 Hz, 1H), 3.93 (s, 3H), 3.43 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 168.3, 166.6, 164.1, 141.2, 136.0, 134.4, 131.1, 130.5, 129.9, 129.5, 127.4, 125.7, 125.1, 78.8, 52.5, 52.3, 50.3; IR (neat): 3016, 2162, 2030, 1748, 1611, 1428, 1280, 1250, 1193, 1072, 921, 870, 742, 642; HRMS (APCI) m/z: [M + Na]$^+$ Calcd. for $C_{19}H_{16}O_6Na$ 363.0839; Found: 363.0839.

*Methyl 3-(4-(methoxycarbonyl)phenyl)-1-oxoisochromane-4-carboxylate (trans-**46**)*

Prepared according to general procedure B, using recrystallised methyl 4-formylbenzoate (40.4 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *trans*-**46** was isolated as a white solid (31.8 mg, 38%, 83% *ee*). CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 32.2 min (minor enantiomer) and 37.9 min (major enantiomer). M.p. 156-158°C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.32, $[\alpha]^{20}_D$= + 6.3 (*c* = 0.04 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 2H), 7.64 (app. t, *J* = 7.9 Hz, 1H), 7.57-7.45 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 1H), 5.95 (d, *J* = 8.2 Hz, 1H), 4.35 (d, *J* = 8.2 Hz, 1H), 3.94 (s, 3H), 3.73 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 169.8, 166.5, 163.7, 141.4, 135.7, 134.7, 130.8, 130.7, 130.0, 129.0, 126.8, 126.7, 124.4, 80.0, 52.8, 52.3, 50.6; IR (neat): 3010, 2158, 2029, 1735, 1020, 1609, 1425, 1280, 1250, 1184, 1279, 1107, 1056, 1018, 921, 869, 736, 641; HRMS (APCI): m/z: [M + Na]$^+$ Calcd. for $C_{19}H_{16}O_6Na$ 363.0839; Found: 363.0835.

Methyl 3-(4-cyanophenyl)-1-oxoisochromane-4-carboxylate (*cis-**47***). Prepared according to general procedure B, using recrystallised 4-cyanobenzaldehyde (32.3 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48h to give a diastereomeric mixture of carboxylic acids in a 58:42 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 75:25 hexanes:EtOAc, the diastereomer *cis*-**47** was isolated as a white solid (78.4 mg, 51%, 89% *ee*). CSP-HPLC analysis: ACQUITY UPC^2, Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/IPA 1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 3.5 min (major enantiomer) and 3.6 min (minor enantiomer). M.p. 126-128 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.25; $[\alpha]^{20}_D$ = -1.7 (*c* = 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.68-7.61 (m, 3H), 7.56 (app. t, 1H), 7.39 (d, *J* = 7.6, 1H), 5.82 (d, *J* = 3.6 Hz, 1H), 4.16 (d, *J* = 3.6 Hz, 1H), 3.45 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 168.1, 163.6, 141.3, 135.7, 134.3, 132.5, 131.1, 129.6, 127.5, 126.5, 124.9,

118.3, 112.7, 78.2, 52.5, 49.9; IR (neat): 2922, 2231, 1742, 1609, 1458, 1356, 1275, 1164, 1080, 1064, 971, 816, 704, 557; HRMS (ESI) m/z: [M - H]$^-$ Calcd. for $C_{18}H_{12}NO_4$ 306.0771; Found: 306.0784.

*Methyl 3-(4-cyanophenyl)-1-oxoisochromane-4-carboxylate (trans-**47**)*

Prepared according to general procedure B, using recrystallised 4-cyanobenzaldehyde (32.3 mg, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48h to give a diastereomeric mixture of carboxylic acids in a 58:42 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, the diastereomer *trans*-**47** was isolated as yellow oil (67.6 mg, 42%, 60% *ee*). CSP-HPLC analysis. ACQUITY UPC^2, Trefoil CEL2, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN 1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 3.1 min (minor enantiomer) and 3.4 min (major enantiomer). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.23, $[\alpha]^{20}_D$ = +19.1 (*c* = 0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.65 (app. t, *J* = 7.9 Hz, 1H), 7.58.7.51 (m, 3H), 7.22 (d, *J* = 7.7 Hz, 1H), 5.94 (d, *J* = 8.5 Hz, 1H), 4.32 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H);^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 169.6, 163.4, 141.7, 135.4, 134.7, 132.6, 130.8, 129.2, 127.6, 126.7, 124.2, 118.2, 113.2, 78.6, 52.9, 50.5; IR (neat): 2921, 2215, 1730, 1609, 1454, 1356, 1272, 1167, 1078, 1061, 956, 811, 701, 557; HRMS (ESI): m/z: [M - H]$^-$ Calcd. for $C_{18}H_{12}NO_4$ 306.0771; Found: 306.0767.

Methyl 3-(4-methoxyphenyl)-1-oxoisochroman-4-carboxylate (*cis-**48***). Prepared according to general procedure B, using freshly distilled 4-methoxybenzaldehyde (30 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 48 h to give a diastereomeric mixture of carboxylic acids in a 58:42 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 85:15 hexanes:EtOAc, the diastereomer *cis*-**48** was isolated as a white solid (26.9 mg, 35%, 94% *ee*). CSP-HPLC analysis: Chiralpak IA (4.6 mm x 25 cm), *n*-hexane/IPA: 97/3, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 110.8 min (minor enantiomer) and 124.4 min (major enantiomer). M.p. 75-77 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.52; $[\alpha]^{20}_D$= -7.1 (*c* = 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 7.8 Hz, 1H), 7.61 (app. t, 1H), 7.53 (app. t, 1H), 7.40-7.34 (m, 3H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.72 (d, *J* = 3.6, 1H), 4.01 (d, *J* = 3.6 Hz, 1H), 3.83 (s, 3H), 3.48 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 168.8, 164.6, 159.7, 136.4, 133.9, 130.9, 129.2, 128.2, 127.3, 126.9, 125.3, 113.9, 79.2, 55.3, 52.4, 50.8; IR (neat): 3012, 2959, 2930, 2834, 1710, 1604, 1518, 1248, 990, 734; HRMS (ESI) m/z: [M + Na]$^+$ Calcd. for $C_{18}H_{16}O_5Na$ 335.0895; Found 335.0888.

*Methyl 3-(4-methoxyphenyl)-1-oxoisochroman-4-carboxylate (trans-**48**)*[6]

Prepared according to general procedure B, using freshly distilled 4-methoxybenzaldehyde (30.0 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 48 h to give a diastereomeric mixture of carboxylic acids in a 58:42 (*cis:trans*) ratio. After esterification and purification by flash column chromatography eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**48** was isolated and purified as a white solid (23.1 mg, 30%, 40% *ee*). CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 97/3, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 26.5 min (minor enantiomer) and 29.3 min (major enantiomer). M.p. 80-82 °C, (lit.,[6] m.p. 82-84 °C); TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.57; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.8 Hz, 1H), 7.60 (app. t, 1H), 7.49 (app. t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.77 (d, *J* = 9.0 Hz, 1H), 4.34 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H).

*Methyl 1-oxo-3-(o-tolyl) isochromane-4-carboxylate (cis-**49**)*. Prepared according to general procedure B, using freshly distilled 2-methylbenzaldehyde (28.4 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 67:33 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 85:15 hexanes: EtOAc, the diastereomer *cis*-**49** was isolated as a white solid (42.3 mg, 58%, 95% *ee*). CSP-HPLC analysis: ACQUITY UPC^2, Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 99%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 1%, 1.2 mL min^{-1}, 30 °C, UV detection at 212 nm, retention times: 3.2 min (minor enantiomer) and 3.4 min (major enantiomer). M.p. 108-110 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.38; $[\alpha]^{20}_D$ = -15.0 (*c* = 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 7.7 Hz, 1H), 7.64-7.60 (m, 2H), 7.55 (app. t, 1H), 7.35 (d, *J* = 7.3 Hz, 1H) 7.28-7.26 (m, 2H), 7.23-7.20 (m, 1H), 5.93 (d, *J* = 3.5 Hz, 1H), 4.01 (d, *J* = 3.5 Hz, 1H), 3.44 (s, 3H), 2.36 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 168.7, 164.7, 136.4, 134.2, 133.9, 133.5, 131.0, 130.6, 129.3, 128.6, 127.3, 126.4, 125.9, 125.4, 76.9, 52.3, 48.6, 19.1; IR (neat): 3071, 3024, 2952, 2929, 2844, 1718, 1602, 1457, 1250, 1003, 915, 736; HRMS (ESI) m/z: [M$^+$+ Na] Calcd. for $C_{18}H_{16}O_4Na$ 319.0940; Found 319.0932.

Methyl 1-oxo-3-(o-tolyl) isochromane-4-carboxylate (*trans-**49***)[6]

Prepared according to general procedure B, using freshly distilled 2-methylbenzaldehyde (28.4 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 67:33 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**49** was isolated as a white solid (20.4 mg, 28%, 82% *ee*). CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 83/17, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 22.3 min (minor enantiomer) and 35.6 min (major enantiomer). M.p. 109-110 °C, (lit.,[6] 114-116 °C); TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.7 Hz, 1H), 7.62 (app. t, 1H), 7.51 (app. t, 1 H), 7.31 (d, *J* = 7.7 Hz, 1H) 7.28-7.13 (m, 4H), 6.08 (d, *J* = 8.7 Hz, 1H), 4.48 (d, *J* = 8.7 Hz, 1H), 3.68 (s, 3H), 2.45 (s, 3H).

Methyl 1-oxo-3-(thiophen-2-yl)isochroman-4-carboxylate (*cis-**50***). Prepared according to general procedure B, using freshly distilled 2-thiophenecarboxaldehyde (23 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 6 days to give a diastereomeric mixture of carboxylic acids in a 56:44 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, the diastereomer *cis*-**50** was isolated as a brown solid (35.5 mg, 50%, 86% *ee*). CSP-HPLC analysis: Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 97/3, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: 21.8 min (minor enantiomer) and 25.8 min (major enantiomer). M.p. 110-112 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.35, $[\alpha]^{20}_D$ = -3.2 (*c* = 0.01,

$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 7.9 Hz, 1H), 7.62 (app. t, 1H), 7.54 (app. t, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.16 (d, *J* = 1.2, 3.7 Hz, 1H), 7.03 (dd, *J* = 3.7, 5.1 Hz, 1H), 6.00 (d, *J* = 3.6 Hz, 1H), 4.20 (d, *J* = 3.6 Hz, 1H), 3.57 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.6, 163.9, 138.4, 135.9, 134.1, 131.1, 129.4, 127.4, 126.8, 126.1, 125.6, 125.0, 52.7, 50.7, 30.9; IR (neat): 3104, 3011, 2951, 2925, 1727, 1703, 1605, 1459, 1431, 1359, 1332, 1226, 1081, 943, 714; HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{15}H_{13}O_4S$ 289.0529; Found: 289.0518.

*Methyl 1-oxo-3-(thiophen-2-yl)isochroman-4-carboxylate (trans-**50**)*[6]

Prepared according to general procedure B, freshly distilled 2-thiophenecarboxaldehyde (23 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol).The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acids in a 56:44 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, the diastereomer *trans*-**50** was isolated as a white solid (26.2 mg, 37%, 57% *ee*). CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 30.3 min (minor enantiomer) and 32.9 min (major enantiomer). M.p. 110-112 °C (lit.,[6] 126-128 °C); TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.36. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.9 Hz, 1H), 7.63 (app. t, 1H), 7.51 (app. t, 1H), 7.33-7.21 (m, 2H), 7.09-7.01 (m, 1H), 6.96-6.89 (m, 1H), 6.19 (d, *J* = 6.1 Hz, 1H), 4.35 (d, *J* = 6.1 Hz, 1H), 3.75 (s, 3H).

Methyl 1-oxo-3-(pyridin-2-yl)isochromane-4-carboxylate (*cis*-***51***). Prepared according to general procedure B, using freshly distilled pyridin-2 carboxaldehyde (23.5 µL, 0.246 mmol) and homophthalic anhydride (**1**, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *cis*-**51** was isolated as a thick yellow oil (40.4 mg, 58%, 80% *ee*). CSP-HPLC analysis: Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: 52.0 min (major enantiomer) and 78.3 min (minor enantiomer). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.20; $[\alpha]^{20}_D$= -1.14 (c = 0.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 7.7 Hz, 1H), 7.86-7.78 (m, 2H), 7.65 (app. t, 1H), 7.55 (app. t, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.30 (m, 1H), 5.84 (d, *J* = 3.6 Hz, 1H), 4.63 (d, *J* = 3.6 Hz, 1H), 3.44 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.8, 164.0, 156.0, 149.0, 137.0, 136.4, 134.2, 130.9, 129.2, 127.9, 125.1, 123.2, 120.7, 79.6, 52.3, 47.9; IR (neat): 2968, 1715, 1601, 1453, 1420, 1287,1253, 1119, 1002, 862, 824, 731, 720; HRMS (ESI) m/z: $[M - H]^-$ Calcd. for $C_{16}H_{12}NO_4$ 282.0766; Found 282.0769.

*Methyl 1-oxo-3-(pyridin-2-yl)isochromane-4-carboxylate (trans-**51**)*. Prepared according to general procedure B, freshly distilled pyridin-2 carboxaldehyde (385, 23.5 µL, 0.246 mmol) and homophthalic anhydride (147, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *trans*-**51** was isolated as a thick yellow oil (22.3 mg, 32%, 25% *ee*). CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 26.3 min (major enantiomer) and 32.8 min (minor enantiomer). TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.30; $[\alpha]^{20}_D$ = +0.3 (c = 0.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.4 Hz, 1H), 8.13 (d, 1H, *J* = 7.8 Hz), 7.69 (app. t, 1H), 7.57 (app. t, 1H), 7.53 (d, 1H, *J* = 7.9 Hz), 7.43 (app. t, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.23-7.17 (m, 1H), 6.13 (d, *J* = 4.5 Hz, 1H), 4.89 (d, *J* = 4.5 Hz, 1H), 3.80 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 170.6, 163.6, 156.3, 149.0, 137.1, 135.2, 134.2, 130.2, 128.6, 128.3, 124.6, 123.2, 121.3, 79.9, 52.8, 47.0; IR (neat): 2969, 1715, 1601, 1455, 1425, 1289,1253, 1119, 1004, 862, 824, 733, 723; HRMS (ESI): m/z: $[M - H]^-$ Calcd. for $C_{16}H_{12}NO_4$ 282.0766; Found 282.0760.

Methyl 7-bromo-1-oxo-3-(pentan-3-yl)isochromane-4-carboxylate (*cis*-***54***). Prepared according to general procedure B, using freshly distilled 2-ethylbutaraldehyde (**53**, 30.4 µL, 0.246 mmol) and anhydride **52** (59.3 mg, 0.246 mmol). The reaction was stirred for 9 days to give a diastereomeric mixture of carboxylic acids in a 84:16 ratio (*cis:trans*). After esterification, the diastereomer *cis*-**54** was isolated and purified by flash column chromatography, eluting with 90:10 hexanes:EtOAc to give *cis*-**54** as a white solid (62.0 mg, 71%, 99% *ee*). CSP-HPLC analysis: Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 14.5 min (major enantiomer). M.p. 72-75 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.67; $[\alpha]^{20}_D$ = -1.9 (c = 0.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 2.1 Hz, 1H), 7.70 (dd, *J* = 2.1, 8.1 Hz, 1 H), 7.23 (d, *J* = 8.1 Hz, 1H), 4.42 (dd, *J* = 2.9, 9.8 Hz, 1H), 3.97 (d, *J* = 2.9, 1H), 3.69 (s, 3H), 1.89-1.79 (m, 2H), 1.67-1.57 (m, 1H), 1.55-1.41 (m, 2H), 0.98-0.86 (m, 6H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.9, 163.7, 136.6, 135.9, 133.5, 128.8, 127.3, 122.9, 80.7, 52.7, 45.6, 41.6, 21.8, 20.8, 9.8, 9.6; IR (neat): 2959, 2888, 1716, 1601, 1468, 1414, 1255, 1227, 1166, 1130, 987, 907, 767, 638; HRMS (APCI) m/z: $[M + Na]^+$ Calcd. for $C_{16}H_{19}BrO_4Na$ 377.0358; Found 377.0361.

*Methyl 3-(4-nitrophenyl)-5-oxo-2-(pentan-3-yl)tetrahydrofuran-3-carboxylate (cis-**56**)*. Prepared according to general procedure B, using freshly distilled 2-ethylbutyraldehyde (**53**, 30.3 µL, 0.246 mmol) and anhydride **56** (54.4 mg, 0.246 mmol). The reaction was stirred for 13 days to give a diastereomeric mixture of carboxylic acids in a 87:13 ratio (*cis:trans*). After esterification, the diastereomer *cis*-**56** was isolated and purified by flash column chromatography, eluting with 75:25 hexanes:EtOAc, to give *cis*-**56** as a yellow oil (43.7 mg, 53%, 95% *ee*). CSP-HPLC analysis: ACQUITY UPC[2], Trefoil CEL2, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN 1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 3.3 min (minor enantiomer) and 3.8 min (major enantiomer); TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.69; $[\alpha]^{20}_D$ = +5.0 (c = 0.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 5.06 (d, *J* = 3.4 Hz, 1H), 3.81 (s, 3H), 3.59 (d, *J* = 17.1 Hz, 1H), 2.72 (d, *J* = 17.1 Hz, 1H), 1.84-1.76 (m, 1H), 1.55-1.46 (m, 2H), 1.47-1.41 (m, 2H), 1.02-0.93 (m, 6H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 172.8, 171.0, 147.4, 127.2, 124.3, 85.9, 57.9, 53,3, 42.8, 41.6, 23.1, 20.6, 11.2, 11.0; IR (neat): 2962, 2922, 1786, 1722, 1600, 1512, 1409, 1512, 1347, 1233, 1206, 1185, 1012, 949, 853, 798, 703; HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{17}H_{22}NO_6$ 336.1441; Found: 336.1438.

Methyl 6-oxo-2-(pentan-3-yl)-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*cis*-***58***). Prepared according to general procedure D, using freshly distilled 2-ethylbutyraldehyde (**53**, 30.3 µL, 0.246

mmol). The reaction was stirred for 72 hours to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**58** was isolated as a white solid (41.6 mg, 56%, 89% *ee*). CSP-HPLC analysis: Chiralcel OD (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.3 mL min^{-1}, RT, UV detection at 254 nm, retention times: 52.7 min (enantiomer) and 55.8 (major enantiomer). M.p. 132-134 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.5; $[\alpha]_D^{20}$ = -3.6 (*c* = 0.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63-7.54 (m, 2H), 7.48-7.44 (m, 3H), 6.55 (s, 1H), 4.44 (dd, *J* = 3.1, 9.1 Hz, 1H), 3.93 (d, *J* = 3.1 Hz, 1H), 3.73 (s, 3H), 1.84-1.69 (m, 3H), 1.70-1.62 (m, 1H), 1.53-1.44 (m, 1H), 0.98-0.94 (m, 6H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.7, 165.0, 152.1, 134.9, 130.9, 129.2, 126.1, 116.8, 79.9, 52.9, 45.2, 41.7, 20.2, 19.7, 9.9, 9.6; IR (neat): 3086, 2965, 2877, 1721, 1696, 1624, 1446, 1353, 1269, 1245, 1086, 1012, 990, 893, 777, 689, 602, 576; HRMS (APCI) m/z: $[M + H]^+$ Calcd. for $C_{18}H_{23}O_4$: 303.1590; Found: 303.1598.

Methyl 2-benzhydryl-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*cis*-***60***) Prepared according to general procedure D, using freshly distilled diphenylacetaldehyde (**59**, 43.6 µL, 0.246 mmol). The reaction was stirred for 2 days furnishing only the diastereomer *cis*-**60**. Upon esterification, the reaction gave a diastereomeric mixture of esters in a 90:10 ratio (*cis*:*trans*). The major diastereomer *cis*-**60** was then isolated by flash column chromatography, eluting with 95:5 hexanes:EtOAc, as a white solid (83.3 mg, 85%, 99% *ee*). CSP-HPLC analysis: ACQUITY UPC², Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/CAN/IPA 1:1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 2.9 min. M.p. 142-144 °C; TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.67; $[\alpha]_D^{20}$ = -2.8 (*c* = 0.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.45 (m, 2H), 7.44-7.39 (m, 5H), 7.38-7.35 (m, 4H), 7.35-7.29 (m, 3H), 7.21- 7.19 (m, 1H), 6.52 (s, 1H), 5.34 (dd, *J* = 1.4, 10.6 Hz, 1H), 4.39 (d, *J* = 10.6 Hz, 1H), 3.79 (d, *J* = 1.4 Hz, 1H), 3.64 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.1, 164.4, 152.3, 140.2, 139.9, 134.6, 130.9, 129.2, 129.1, 128.6, 128.3, 128.2, 127.5, 126.9, 126.3, 116.7, 79.7, 53.7, 52.8, 44.9; IR (neat): 3088, 2971, 2923, 1660, 1592, 1506, 1472, 1311, 1217, 1072, 998, 768, 642; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{26}H_{22}O_4Na$ 421.1410; Found: 421.1407.

ASSOCIATED CONTENT

^1H and ^{13}C NMR spectra, analytical and crystallographic data. Computational study.

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