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Chemoenzymatic Synthesis of Enantiomerically Pure *syn*-Configured 1-Aryl-3-methylisochroman Derivatives

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A two-step synthesis of various enantiomerically pure 1-aryl-3-methylisochroman derivatives was accomplished through asymmetric biocatalytic ketone reduction followed by an oxa-Pictet–Spengler reaction. The compounds were obtained in good to excellent yield (47–92 %) in favor of the *syn* diastereomers [*dr* (*syn*/*anti*) up to 99:1]. Enantiopure arylpropanols serving as pronucleophiles for the C–C bond-formation step were obtained by biocatalytic reduction by employing enantiocomplementary alcohol dehydrogenases, which gave access to the (*S*) and (*R*) enantiomer with up to >99 % conversion and up to >99 % *ee*.

Introduction

The structural motif of 1-functionalized isochromans (3,4-dihydro-1*H*-benzo[*c*]pyranes) can be found in various synthetic[1] and natural products[2] possessing multiple bioactive properties. Several approaches to access this scaffold have been published in the literature,[3] and the most common approach is the oxa-Pictet–Spengler reaction.[4] It represents the oxygen analogue to the classical Pictet–Spengler reaction,[5] but it has received comparatively less attention than its nitrogen counterpart. The reaction proceeds by condensation of a β-arylethanol with a carbonyl compound to form a hemiacetal intermediate that undergoes cyclization to yield the corresponding isochroman. Given that the substrates are not limited solely to arylethanols, oxygenated heterocycles other than aryl-1*H*-pyrans have been constructed as well.[6] In view of our ongoing interest in utilizing biocatalysts in the synthesis of bioactive compounds,[7] diastereomerically pure 1-aryl-3-methylisochromans attracted our attention; of particular interest was thereby the stereochemical outcome with respect to a second stereocenter. Methods to access this scaffold have already been published by employing minerals[8] and Lewis[9] and Brønsted acids[10] as catalysts, but thorough studies including a second stereocenter are scare[4a] or target orientated.[11]

Results and Discussion

For the envisaged study, biocatalytic reduction of the corresponding ketones was chosen to access enantiomerically pure 1-aryl-2-propanols, as described by others previously.[18a] Thus, various alcohol dehydrogenases (ADHs)[12] were assayed by employing ketone **1a** as the model substrate (50 mM); among several enzymes tested, ADH-A,[13] ADH-T,[14] ADH-CP,[14] ADH-LB,[14] ADH-LK,[15] and Evo-200[16] proved to be best, and they furnished alcohols **2a**–**e** under the optimized conditions with high *ee* values and good conversions (Table 1). For example, the ADH originating from *Rhodococcus ruber* (ADH-A) afforded (*S*)-configured alcohols **2a**–**e** with perfect optical purity (>99 %*ee*) at conversions ≥98 %. Notably, the optical purities as well as the conversions were, in general, independent of the substitution pattern on the aromatic ring (Table 1, entries 1, 5, 9, 13, 17). The analogous (*R*) enantiomers were obtained, for example, by ADH Evo-200, likewise with perfect *ee* values (>99 %) at excellent conversions (Table 1, entries 3, 8, 11, 16, 20). Also, other enzymes employed (i.e., ADH-LK, ADH-LB, ADH-T, and ADH-CP) were remarkably efficient; in most cases, their use led to optically pure alcohols.

Notably, some enantiomerically pure alcohols obtained serve as valuable intermediates in the synthesis of bioactive compounds; for example, trimethoxy derivative **2e** is a central building block of the natural products Virologins, which were found to possess antifungal and antileishmanial

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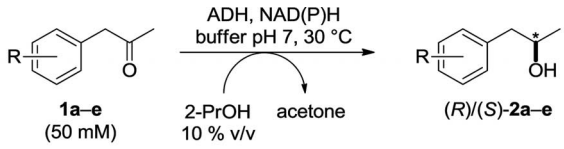
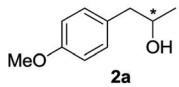
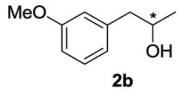
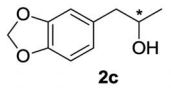
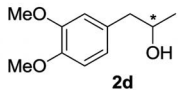
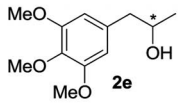
Table 1. Biocatalytic reduction of ketones **1a**–**e** to yield enantiopure arylpropanols (*R*)- and (*S*)-**2a**–**e**.[a]



Entry	Product	ADH	*c* [%][b]	*t* [h]	*ee* [%][c]
1	 **2a**	ADH-A	98	24	>99 (*S*)
2		ADH-T	96	24	>99 (*S*)
3		Evo-200	95	24	>99 (*R*)
4		ADH-LK	85	48	>99 (*R*)
5	 **2b**	ADH-A	99	24	>99 (*S*)
6		ADH-T	99	24	97 (*S*)
7		ADH-CP	87	24	97 (*S*)
8		Evo-200	99	24	>99 (*R*)
9	 **2c**	ADH-A	98	24	>99 (*S*)
10		ADH-T	96	24	>99 (*S*)
11		Evo-200	95	24	>99 (*R*)
12		ADH-LK	85	48	>99 (*R*)
13	 **2d**	ADH-A	99	24	>99 (*S*)
14		ADH-T	99	24	97 (*S*)
15		ADH-CP	87	48	97 (*S*)
16		Evo-200	99	24	>99 (*R*)
17	 **2e**	ADH-A	99	24	>99 (*S*)
18		ADH-T	59	48	>99 (*S*)
19		ADH-CP	90	48	>99 (*S*)
20		Evo-200	99	24	>99 (*R*)

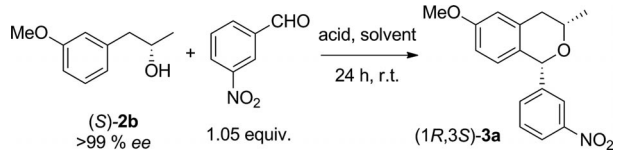
[a] Reaction conditions (analytical scale): 50 mM ketone **1a**–**e** (dissolved in 100 μL 2-PrOH) in K-phosphate buffer (0.9 mL, 100 mM, pH 7.0) containing 1 mM NAD(P)H, 2 mM $MgCl_2$, and various amounts of the ADH (see the Supporting Information); 30 °C in an Eppendorf orbital shaker. [b] Determined by GC analysis on an achiral stationary phase. [c] Determined by GC analysis on a chiral stationary phase.

activities;[17] methylene-bridged aryl propanol **2c**[18] is a starting material for the drug candidate Talampanel and related benzodiazepine derivatives.[19] Even though this drug failed in 2010 in clinical studies (phase II), it still serves as a lead compound for the determination of the mode of action of particular receptors.[20]

The biotransformations were repeated on preparative scale (75 mM; up to 680 mg), and alcohols **2a**–**e** were furnished in optically pure form (>99% *ee*) and isolated in approximately 95% yield. Next, the oxa-Pictet–Spengler reaction was investigated by using various sulfonic acids as catalysts to find suitable reaction conditions for the condensation of *meta*-methoxyaryl alcohol (*S*)-**2b** and *meta*-nitrobenzaldehyde in different solvents (Table 2).

Alcohol (*S*)-**2b** was chosen as a model pronucleophile, as its methoxy group activates the *para* position to the methoxy group, and this promotes ring closure. The first attempt, which involved the use of methanesulfonic acid (MsOH, 0.1 equiv.) in CH_2Cl_2, afforded product (1*R*,3*S*)-**3a** in 72% yield with a *dr* of 98:2 in favor of the *syn* diastereomer (Table 2, entry 1); interestingly, this result is complementary to that in the literature: the use of HCl as the catalyst provided predominately the *anti* isomer if alcohol *rac*-**2c** was condensed with 4-nitrobenzaldehyde.[21] The rel-

Table 2. Optimization of the oxa-Pictet–Spengler reaction.



Entry	Acid[a]	Solvent	Yield [%][b]	*dr* (*syn*/*anti*)[c]
1	MsOH (0.1 equiv.)	CH_2Cl_2	72	98:2
2	MsOH (0.1 equiv.)	toluene	60	95:5
3	MsOH (0.1 equiv.)	Et_2O	n.r.	–
4	MsOH (0.1 equiv.)	MeCN	5	98:2
5	MsOH (0.1 equiv.)	THF	n.r.	–
6	PTSA (0.1 equiv.)	THF	n.r.	–
7	PTSA (0.1 equiv.)	Et_2O	n.r.	–
8	PTSA (0.1 equiv.)	toluene	25	99:1
9	PTSA (0.1 equiv.)	CH_2Cl_2	78	98:2
10	PTSA (0.2 equiv.)	CH_2Cl_2	92	98:2
11	TfOH (0.1 equiv.)	toluene	87	91:9
12	TfOH (0.1 equiv.)	CH_2Cl_2	82[d]	94:6
13	TfOH (0.1 equiv.)	CH_2Cl_2	87[e]	96:4

[a] MsOH = methanesulfonic acid, TfOH = trifluoromethanesulfonic acid, PTSA = *para*-toluenesulfonic acid. [b] Yield of isolated product after chromatography; n.r. = no reaction. [c] Determined by analysis of the crude reaction mixture by ^1H NMR spectroscopy. [d] Reaction time was 4 h. [e] Reaction time at 0 °C was 8 h.

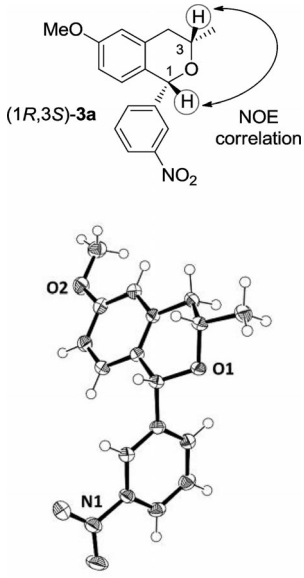
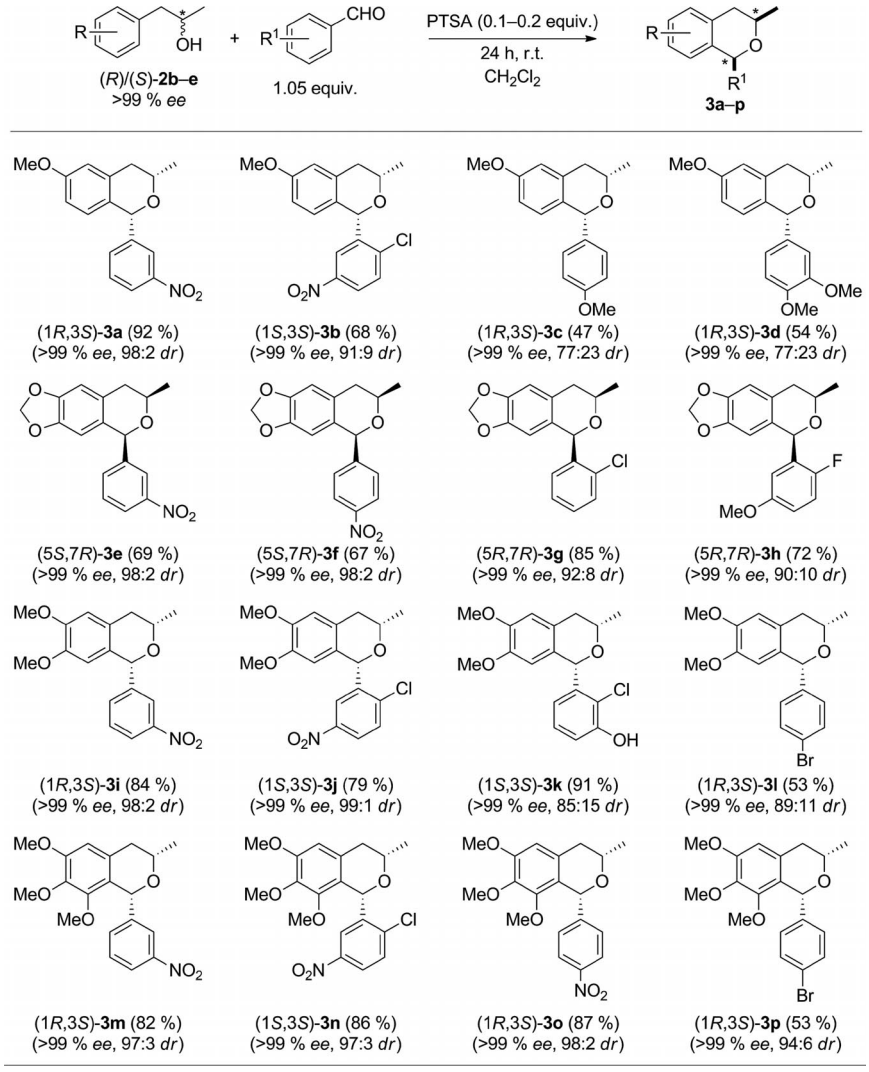


Figure 1. Observed NOE correlation for isochroman (1*R*,3*S*)-**3a** and a stereoscopic ORTEP plot thereof.

ative and absolute configuration of chroman **3a** was assigned here to be (1*R*,3*S*) on the basis of the known absolute configuration of alcohol (*S*)-**2b** and a NOE correlation between the protons at C1 and C3. Structural confirmation was additionally obtained by single-crystal X-ray analysis (Figure 1).

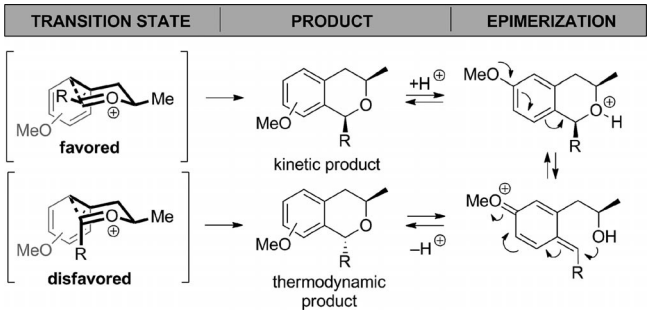
Testing various other solvents, CH_2Cl_2 proved to be best. Interestingly, the ethers THF and Et_2O failed to give any product (Table 2, entries 3, 5, 6, 7). The use of *para*-toluenesulfonic acid monohydrate (PTSA) gave almost the same results, but a slightly improved yield was obtained with the use of CH_2Cl_2 as the solvent (Table 2, entry 9). An increase in the number of equivalents of PTSA from 0.1 to 0.2 equiv. was beneficial, and the yields were further enhanced to 92% without any affect on the diastereomeric outcome (98:2; Table 2, entry 10). Trifluoromethanesulfonic acid (TfOH) resulted in significantly shorter reaction times (4 and 8 h) most likely as a result of the increased acidity of the sulfonic acid (Table 2, entries 12 and 13), albeit it went in hand with reduced diastereoselectivity.



Scheme 1. Scope of the oxa-Pictet–Spengler reaction under the optimized reaction conditions.

Having established suitable reaction conditions, the substrate scope of the reaction was investigated with respect to the alcohol and the aldehyde. Various aromatic aldehydes were treated with enantiopure alcohols **2b**–**e** to afford corresponding *syn*-configured chromans **3a**–**p** (as judged by NMR spectroscopy) in yields ranging from 47 to 92% at high diastereocontrol (Scheme 1). However, upon using alcohol (*S*)-**2a** as the pronucleophile, no product formation could be detected, probably because of the lack of activation; even an increase in the acid concentration (PTSA up to 0.5 equiv.) proved to be unsuccessful (data not shown).[22] The reaction proceeded smoothly with enantiopure alcohols **2b**–**e**: the best results were obtained with aldehydes bearing an electron-withdrawing group such as, for example, 3- and 4-nitrobenzaldehyde. In these cases, outstanding diastereomeric ratios [*dr* (*syn*/*anti*) ≥97:3] and good yields were obtained (67–92%; e.g., for **3e**, **3i**, and **3m**). Moreover, electronically poor arylaldehydes bearing a sterically demanding substituent in the *ortho* position (e.g., a chlorine atom) were readily converted with high selectivity (e.g., for **3b**, **3g**, and **3j**).[23]

Electronically rich aromatic aldehydes such as 4-methoxy- (**3c**) and 3,4-dimethoxybenzaldehyde (**3d**) gave only moderate yields of the products (47 and 52% for **3c** and **3d**, respectively) albeit at a constant *dr* (*syn*/*anti*) of 77:23. This result might be rationalized by acid-catalyzed epimerization of the product owing to activation of the benzylic position. Protonation of the O2 oxygen atom would lead to reversible ring opening, which could afford *trans*-chroman (1*S*,3*S*)-**3d** as the thermodynamic product;[24] this would also explain why predominantly the *anti* isomer was observed if related compounds were condensed with HCl as the catalyst.[21] However, on the basis of our results and the results of others, the corresponding *cis* diastereomer should be favored as the kinetic product: the predefined substituent at C3 as well as the residue of the aldehyde would occupy a pseudoequatorial position in the oxonium ion intermediate in the form of a Zimmermann–Traxler-like transition state (Scheme 2).[4a,26]



Scheme 2. Plausible transition states and possible epimerization explaining the stereochemical outcome of the oxa-Pictet–Spengler reaction.

Conclusions

The asymmetric synthesis of enantiomerically pure 1-aryl-3-methylchroman derivatives was successfully established. The two-step sequence involved a biocatalytic hydrogen-transfer reduction and an atom-efficient and diastereoselective oxa-Pictet–Spengler reaction. The corresponding (*R*)- and (*S*)-configured aryl alcohols were obtained with perfect *ee* values and yields (≥97%*ee* and ca. 95% yield) depending on the choice of alcohol dehydrogenase employed. The oxa-Pictet–Spengler reaction proceeded with high *syn* diastereoselectivity if catalyzed at 21 °C by PTSA (0.1–0.2 equiv.). The resulting 1-arylchromans were generally isolated in high yield (up to 92%) with excellent diastereoselectivities [up to *dr* (*syn*/*anti*) ≥99:1].

Experimental Section

General Methods: All starting materials were obtained from commercial suppliers and were used as received unless stated otherwise. The reactions were performed with standard Schlenk techniques under a N_2 atmosphere in oven-dried (125 °C) glassware. Solvents were dried and purified by conventional methods prior to use. Preparative chromatographic separations were performed by column chromatography on silica gel 60 (0.063–0.200 mm). Solvents for flash chromatography (petroleum ether/ethyl acetate) were distilled before use. Petroleum ether (PE) refers to a fraction with a boiling point between 63 and 69 °C. TLC was performed with precoated aluminum sheets with detection by UV (254 nm) and/or by staining with anisaldehyde solution or cerium molybdenum solution. Optical rotation was measured with a Perkin–Elmer Polarimeter 341. ^{1}H NMR and ^{13}C NMR spectra were recorded at 20 °C; chemical shifts are given in ppm relative to Me_4Si [Me_4Si: $\delta(^1H) = 0.0$ ppm] or relative to the resonance of the solvent [$CDCl_3$: $\delta(^1H) = 7.26$ ppm, $\delta(^{13}C) = 77.0$ ppm].

The alcohol dehydrogenases ADH-CP (*Candida parapsilosis*) and ADH-T (*Thermoanaerobacter* sp.) were kindly donated from Codexis, Inc., in the form of a glycerol solution.[14] Alcohol dehydrogenase Evo-200 (origin not stated) was bought from evocatal GmbH in the form of a freeze-dried powder. ADH-LB (*Lactobacillus brevis*),[14,27] ADH-LK (*Lactobacillus kefir*),[15] and ADH-A (*Rhodococcus ruber*)[13] were prepared as described previously and used in the form of a crude stock solution.

For better comparison of the enzymatic activity, the activity for the reduction of acetophenone was determined by measuring the initial rate following the absorbance at 340 nm. One unit of activity was defined as the amount of enzyme that catalyzes the oxidation of 1 μmol NAD(P)H per minute under standard conditions (25 °C, pH 7.0). The assay mixture contained the substrate solution [970 μL, potassium phosphate buffer (100 mM, pH 7.0), acetophenone (10 mM), and $MgCl_2$ (2 mM)], NAD(P)H solution (20 μL, 12.5 mM), and the enzyme solution (10 μL). Reactions were started by the addition of the enzyme solution, and the absorbance was followed over 1 min. All measurements were performed at least in triplicate. The resulting activies were determined to be as follows: ADH-CP (*Candida parapsilosis*): 22.6 U mL^{-1}, ADH-T (*Thermoanaerobacter* sp.): 265.9 U mL^{-1}; Evo-200 (1.0 mg mL^{-1} stock solution): 0.86 U mL^{-1}, ADH-LB (*Lactobacillus brevis*): 123.1 U mL^{-1}; ADH-LK (*Lactobacillus kefir*): 407.5 U mL^{-1}; ADH-A (*Rhodococcus ruber*): 4.46 U mL^{-1}.

Synthesis of Reference and Starting Materials

1-(4-Methoxyphenyl)propan-2-ol: Ketone **1a** (1.00 g, 6.09 mmol) was dissolved in dry MeOH (25 mL) before $NaBH_4$ (242 mg, 6.39 mmol) was added at room temperature. Upon completion of

the reaction as indicated by TLC (ca. 10 min), the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 (4 × 20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 70:30) afforded *rac*-**2a** as a colorless oil in 99% yield (946 mg, 5.99 mmol). Analytical data are in agreement with those previously published.[18a] R_f (PE/EtOAc = 80:20) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, $^3J_{3,2}$ = 6.2 Hz, 3 H, 3-H), 1.56 (br. s, 1 H, OH), 2.62 (dd, $^3J_{1a,2}$ = 8.0 Hz, $^2J_{1a,1b}$ = 13.6 Hz, 1 H, 1-H_a), 2.74 (dd, $^3J_{1b,2}$ = 4.9 Hz, $^2J_{1b,1a}$ = 13.6 Hz, 1 H, 1-H_b), 3.79 (s, 3 H, OMe), 4.02 (ddq, $^3J_{2,1b}$ = 4.8 Hz, $^3J_{2,3}$ = 6.1 Hz, $^3J_{2,1a}$ = 7.9 Hz, 1 H, 2-H), 6.86 (d, $^3J_{2'3'}$ = 8.7 Hz, 2 H, arom.-H), 7.13 (d, $^3J_{3',2'}$ = 8.7 Hz, 2 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (C-3), 45.0 (C-1), 55.4 (OCH_3), 69.1 (C-2), 114.1, 130.5, (arom.-CH), 130.6 (arom.-C_{ipso}), 158.4 (arom.-C_{ipso}) ppm. GC–MS (EI, 70 eV): *m*/*z* (%) = 166 [M^+] (27), 122 [$C_8H_{10}O^{+\cdot}$] (100), 107 [$C_7H_7O^+$] (31), 45 [$C_2H_5O^+$] (20).

1-(3-Methoxyphenyl)propan-2-ol: Ketone **1b** (200 mg, 1.22 mmol) was dissolved in dry MeOH (5 mL) before $NaBH_4$ (53 mg, 1.25 mmol) was added at room temperature. Upon completion of the reaction (ca. 10 min), the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 (4 × 5 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 70:30) afforded *rac*-**2b** as a colorless oil in 99% yield (200 mg, 1.22 mmol). Analytical data are in agreement with those previously published.[18a] R_f (PE/EtOAc = 80:20) = 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, $^3J_{3,2}$ = 6.2 Hz, 3 H, 3-H), 1.55 (br. s, 1 H, OH), 2.66 (dd, $^3J_{1a,2}$ = 8.1 Hz, $^2J_{1a,1b}$ = 13.4 Hz, 1 H, 1-H_a), 2.78 (dd, $^3J_{1b,2}$ = 4.8 Hz, $^2J_{1b,1a}$ = 13.4 Hz, 1 H, 1-H_b), 3.81 (s, 3 H, OMe), 4.02 (ddq, $^3J_{2,1b}$ = 4.8 Hz, $^3J_{2,3}$ = 6.1 Hz, $^3J_{2,1a}$ = 8.2 Hz, 1 H, 2-H), 6.78 (m_c, 3 H, arom.-H), 7.22 (m_c, 2 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0 (C-3), 46.0 (C-1), 55.3 (OCH_3), 68.9 (C-2), 112.0, 115.2, 121.8, 129.7 (arom.-CH), 140.2 (arom.-C_{ipso}), 159.9 (arom.-C_{ipso}) ppm. GC–MS (EI, 70 eV): *m*/*z* (%) = 166 [M^+] (16), 121 [$C_8H_9O^+$] (100), 45 [$C_2H_5O^+$] (6).

1-[3,4-(Methylenedioxy)phenyl]propan-2-ol: According to a known procedure,[18a] 5-bromobenzo[*d*][1,3]dioxole (2.00 g, 9.95 mmol) was dissolved in dry Et_2O (25 mL) and cooled to –78 °C. *n*BuLi was added dropwise (2.5 M in *n*-hexane, 5 mL, 12.44 mmol) over 20 min, and the mixture was stirred for a further 30 min prior to the addition of 2-methyloxirane (871 μL, 12.44 mmol). The reaction temperature was slowly raised to room temperature (ca. 2 h), and the reaction mixture was stirred for 60 min more. The organic phase was poured onto a saturated aqueous solution of NH_4Cl (100 mL), and the aqueous phase was extracted with EtOAc (4 × 30 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 80:20) afforded *rac*-**2c** as a colorless oil in 82.3% yield (1.47 g, 8.17 mmol). Analytical data are in agreement with those previously published.[18a] R_f (PE/EtOAc = 80:20) = 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, $^3J_{3,2}$ = 6.3 Hz, 3 H, 3-H), 1.78 (br. s, 1 H, OH), 2.59 (dd, $^3J_{1a,2}$ = 7.9 Hz, $^2J_{1a,1b}$ = 13.6 Hz, 1 H, 1-H_a), 2.69 (dd, $^3J_{1b,2}$ = 5.0 Hz, $^2J_{1b,1a}$ = 13.6 Hz, 1 H, 1-H_b), 4.02 (ddq, $^3J_{2,1b}$ = 5.1 Hz, $^3J_{2,3}$ = 6.3 Hz, $^3J_{2,1a}$ = 7.9 Hz, 1 H, 2-H), 5.92 (s, 2 H, OCH_2O), 6.62–6.77 (m, 3 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (C-3), 45.5 (C-1), 69.0 (C-2), 100.9 (OCH_2O), 108.4, 109.8, 122.3 (arom.-CH), 132.3, 146.2, 147.8 (arom.-C_{ipso}) ppm. GC–MS (EI, 70 eV): *m*/*z* (%) = 180 [M^+] (30), 135 [$C_8H_7O_2^+$] (100).

1-[3,4-(Methylenedioxy)phenyl]propan-2-one: Dess–Martin periodinane (DMP; 1.53 g, 3.61 mmol) was added to a stirred solution of *rac*-**2c** (620 mg, 3.44 mmol) in wet CH_2Cl_2 (20 mL) at room temperature. After 2 h, DMP (0.1 equiv.) was added (150 mg, 0.36 mmol), and the mixture was stirred until TLC revealed completion of the reaction. The mixture was then quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (25 mL) and a half-saturated aqueous solution of $NaHCO_3$ (25 mL). After the effervescence had ceased, the water phase was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 90:10) afforded **1c** as a colorless liquid in 85.6% yield (523 mg, 2.94 mmol). Analytical data are in agreement with those previously published.[28] R_f (PE/EtOAc = 80:20) = 0.33. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, Me), 3.60 (s, 2 H, 1-H), 5.94 (s, 2 H, OCH_2O), 6.61–6.69 (m, 2 H, arom.-H), 6.77 (m_c, 1 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3 (C-3), 50.7 (C-1), 101.7 (OCH_2O), 108.6, 109.9, 122.6 (arom.-CH), 127.9, 146.8, 148.0 (arom.-C_{ipso}), 206.6 (C=O) ppm. GC–MS (EI, 70 eV): *m*/*z* (%) = 178 [M^+] (25), 135 [$C_8H_7O_2^+$] (100).

1-(3,4-Dimethoxyphenyl)propan-2-ol: Ketone **1d** (200 mg, 1.03 mmol) was dissolved in dry MeOH (5 mL) before $NaBH_4$ (41 mg, 1.08 mmol) was added at room temperature. Upon completion of the reaction (ca. 10 min, detected by TLC), the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 50:50) afforded *rac*-**2d** as a colorless oil in 96% yield (195 mg, 1.00 mmol). Analytical data are in agreement with those previously published.[18a] R_f (PE/EtOAc = 60:40) = 0.22. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, $^3J_{3,2}$ = 6.2 Hz, 3 H, 3-H), 1.68 (br. s, 1 H, OH), 2.60 (dd, $^3J_{1a,2}$ = 8.2 Hz, $^2J_{1a,1b}$ = 13.6 Hz, 1 H, 1-H_a), 2.74 (dd, $^3J_{1b,2}$ = 4.6 Hz, $^2J_{1b,1a}$ = 13.6 Hz, 1 H, 1-H_b), 3.85 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.98 (ddq, $^3J_{2,1b}$ = 4.7 Hz, $^3J_{2,3}$ = 6.3 Hz, $^3J_{2,1a}$ = 8.2 Hz, 1 H, 2-H), 6.72–6.76 (m, 2 H, arom.-H), 6.80–6.84 (m, 1 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (C-3), 45.5 (C-1), 55.9 (OCH_3), 56.0 (OCH_3), 69.0 (C-2), 111.4, 112.6, 121.4 (arom.-CH), 131.1, 147.8, 149.1 (arom.-C_{ipso}) ppm. GC–MS (EI, 70 eV): *m*/*z* (%) = 196 [M^+] (34), 151 [$C_9H_{11}O_2^+$] (100), 137 [$C_8H_9O_2^+$] (40).

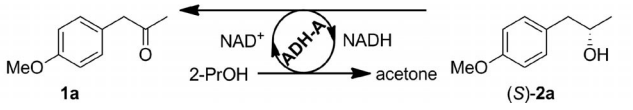
1-(3,4,5-Trimethoxyphenyl)propan-2-ol: Ketone **1e** (250 mg, 1.11 mmol) was dissolved in dry MeOH (11 mL) before $NaBH_4$ (21 mg, 0.56 mmol) was added at room temperature. Upon completion of the reaction as detected by TLC (ca. 10 min), the reaction was aborted by removing MeOH under reduced pressure. Subsequent flash chromatography (PE/EtOAc = 50:50) afforded *rac*-**2e** as a colorless oil in 98% yield (246 mg, 1.09 mmol). Analytical data are in agreement with those previously published.[17a] R_f (PE/EtOAc = 50:50) = 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, $^3J_{3,2}$ = 6.2 Hz, 3 H, 3-H), 1.69 (br. s, 1 H, OH), 2.60 (dd, $^3J_{1a,2}$ = 8.3 Hz, $^2J_{1a,1b}$ = 13.5 Hz, 1 H, 1-H_a), 2.75 (dd, $^3J_{1b,2}$ = 4.5 Hz, $^2J_{1b,1a}$ = 13.5 Hz, 1 H, 1-H_b), 3.83 (s, 3 H, OMe), 3.86 (s, 6 H, OMe), 4.01 (ddq, $^3J_{2,1b}$ = 4.5 Hz, $^3J_{2,3}$ = 6.2 Hz, $^3J_{2,1a}$ = 8.3 Hz, 1 H, 2-H), 6.44 (s, 1 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (C-3), 45.5 (C-1), 55.9 (OCH_3), 56.0 (OCH_3), 69.0 (C-2), 111.4, 112.6, 121.4 (arom.-CH), 131.1, 147.8, 149.1 (arom.-C_{ipso}) ppm. GC–MS (EI, 70 eV): *m*/*z* (%) = 226 [M^+] (43), 181 [$C_{10}H_{13}O_3^+$] (100), 167 [$C_9H_{11}O_3^+$] (100).

Representative Procedure for the Biotransformations on an Analytical Scale: Ketone **1a**–**e** (50 mM) was dissolved in 2-PrOH (100 μL) prior to the addition to the potassium phosphate buffer (900 μL, 100 mM, 2 mM $MgCl_2$, pH 7.0) containing the respective alcohol dehydrogenase and NAD^+/$NADP^+$ (1 mM; see Tables S1–S4 in the

Supporting Information). The reactions were performed in an Eppendorf thermomix (vertical position; 600 rpm) at 30 °C for 24–48 h (total volume 1.0 mL). The reactions were aborted by the addition of a saturated aqueous solution of Na_2CO_3 (100 μL) and extraction with EtOAc (2 × 500 μL). The combined organic layer was dried with $MgSO_4$ and an aliquot withdrawn for further analysis. For screening results and chiral and achiral analytics, see the Supporting Information.

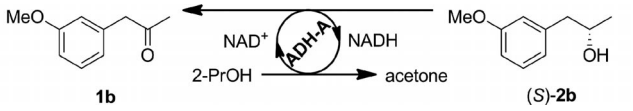
Biotransformations on a Preparative Scale

(*S*)-1-(4-Methoxyphenyl)propan-2-ol [(*S*)-2a]



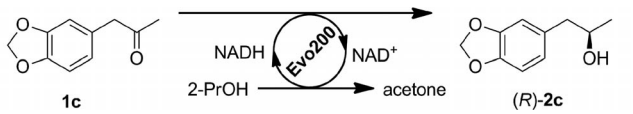
Ketone **1a** (123 mg, 0.72 mmol), dissolved in 2-PrOH (1.00 mL), was added to a KPi buffer (100 mM, 2 mM $MgCl_2$, pH 7.0, 9.0 mL) containing NAD^+ (1 mM) and the alcohol dehydrogenase ADH-A (4.46 U). Completion of the reaction was detected by TLC, and the reaction mixture was then extracted with EtOAc (4 × 8 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 60:40) afforded enantiopure (*S*)-**2a** (>99%*ee*) in 98% yield (122 mg, 0.73 mmol) as a colorless oil. Spectroscopic data are in agreement with those reported for its racemate. Optical rotation for (*S*)-**2a**: $[\alpha]_D^{20}$ = +24.5 (*c* = 1.9, $CHCl_3$; >99%*ee*); ref.[25] $[\alpha]_D^{20}$ = +27.0 (*c* = 4.4, $CHCl_3$; >99%*ee*).

(*S*)-1-(3-Methoxyphenyl)propan-2-ol [(*S*)-2b]



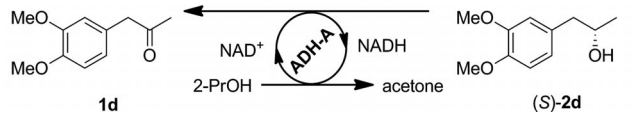
Ketone **1b** (369 mg, 2.15 mmol), dissolved in 2-PrOH (3.00 mL), was added to a KPi buffer (100 mM, 2 mM $MgCl_2$, pH 7.0, 27.0 mL) containing NAD^+ (1.00 mM) and the alcohol dehydrogenase ADH-A (13.38 U). The mixture was shaken at 30 °C for 48 h (600 rpm) until completion of the reaction was detected (TLC), and it was then extracted with EtOAc (4 × 25 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 60:40) afforded enantiopure (*S*)-**2b** (>99%*ee*) in 93% yield (349 mg, 2.10 mmol) as a colorless oil. Spectroscopic data are in agreement with those reported for its racemate. Optical rotation for (*S*)-**2b**: $[\alpha]_D^{20}$ = +30.0 (*c* = 2.0, $CHCl_3$; >99%*ee*); ref.[18a] $[\alpha]_D^{20}$ = +30.3 (*c* = 1.0, $CHCl_3$; 99%*ee*).

(*R*)-1-[3,4-(Methylenedioxy)phenyl]propan-2-ol [(*R*)-2c]



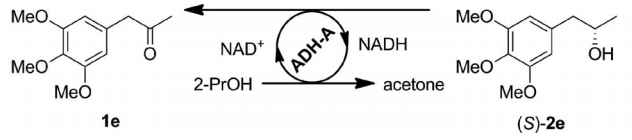
Ketone **1c** (405.6 mg, 2.25 mmol), dissolved in 2-PrOH (3.00 mL), was added to a KPi buffer (100 mM, 2 mM $MgCl_2$, pH = 7.0, 27.0 mL) containing NAD^+ (1.00 mM) and the alcohol dehydrogenase Evo-200 (25.8 U). The mixture was shaken at 30 °C for 48 h (600 rpm) until completion of the reaction was detected via TLC and was then extracted with EtOAc (4 × 25 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 80:20) afforded the enantiopure alcohol (*R*)-**2c** (*ee* >99%) in 97% yield (369 mg, 2.20 mmol) as colorless oil. Spectroscopic data are in agreement with those reported for its racemate. Optical rotation for (*R*)-**2c**: $[\alpha]_D^{20}$ = –32.9 (*c* = 1.2, $CHCl_3$, >99%*ee*); optical rotation for (*S*)-**2c**, ref.[24] $[\alpha]_D^{20}$ = +34.4 (*c* = 1.0, $CHCl_3$, 99%*ee*).

(*S*)-1-(3,4-Dimethoxyphenyl)propan-2-ol [(*S*)-2d]



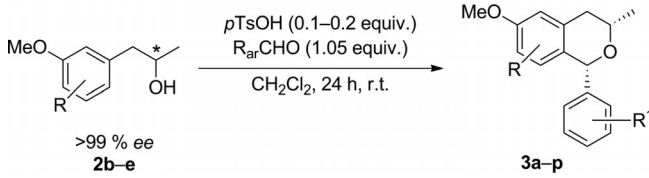
Ketone **1d** (291.3 mg, 1.50 mmol), dissolved in 2-PrOH (2.00 mL), was added to a KPi buffer (100 mM, 2 mM $MgCl_2$, pH 7.0, 18.0 mL) containing NAD^+ (1.00 mM) and the alcohol dehydrogenase ADH-A (8.92 U). The mixture was shaken at 30 °C for 48 h (600 rpm) until completion of the reaction was detected (TLC), and it was then extracted with EtOAc (4 × 15 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 70:30) afforded enantiopure (*S*)-**2d** (>99%*ee*) in 94% yield (279 mg, 1.42 mmol) as a colorless oil that slowly crystallized upon standing. Spectroscopic data are in agreement with those reported for its racemate. Optical rotation for (*S*)-**2d**: $[\alpha]_D^{20}$ = +29.3 (*c* = 0.80, $CHCl_3$; >99%*ee*); ref.[11b] $[\alpha]_D^{20}$ = +26.8 (*c* = 1.85, $CHCl_3$; 99.5%*ee*).

(*S*)-1-(3,4,5-Trimethoxyphenyl)propan-2-ol [(*S*)-2e]



Ketone **1e** (673 mg, 3.00 mmol), dissolved in 2-PrOH (4.00 mL), was added to a KPi buffer (100 mM, 1 mM $MgCl_2$, pH 7.0, 36.0 mL) containing NAD^+ (1.00 mM) and the alcohol dehydrogenase ADH-A (17.84 U). The mixture was shaken at 30 °C for 48 h (120 rpm) until completion of the reaction was detected by TLC, and it was then extracted with EtOAc (4 × 30 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash chromatography (silica, PE/EtOAc = 70:30 to 50:50) afforded enantiopure (*S*)-**2e** (>99%*ee*) in 94% yield (637 mg, 1.42 mmol) as a colorless oil. Spectroscopic data are in agreement with those reported for its racemate. Optical rotation for (*S*)-**2e**: $[\alpha]_D^{20}$ = +20.8 (*c* = 0.80, $CHCl_3$; >99%*ee*); ref.[17a] $[\alpha]_D^{20}$ = +8 (*c* = 1.85, $CHCl_3$; 92%*ee*).

Oxa-Pictet–Spengler Reaction under the Optimized Conditions



Representative Procedure: Enantiopure alcohol **2b**–**e** (50 mg) was dissolved in dry CH_2Cl_2 (4 mL) prior to the addition of the corresponding aldehyde (1.05 equiv.) and *p*TsOH (between 0.1 and 0.2 equiv.) at 21 °C. The reaction mixture was stirred for 24 h and was then quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined

organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica by using various solvents and mixtures to afford analogues isochroman **3a**–**p**.

(1*R*,3*S*)-6-Methoxy-3-methyl-1-(3-nitrophenyl)isochroman [(1*R*,3*S*)-3a]: Alcohol (*S*)-**2b** (53.5 mg, 0.322 mmol), *m*-nitrobenzaldehyde (51.1 mg, 0.338 mmol), and *p*TsOH (12.2 mg, 64 μmol) were used to provide isochroman (1*R*,3*S*)-**3a** as a slightly yellow solid (84.7 mg, 0.296 mmol) in 92% yield [*dr* (*syn*/*anti*) = 98:2] after chromatography (PE/EtOAc = 90:10). R_f (PE/EtOAc = 80:20) = 0.47, m.p. 121.4–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, $^3J_{Me,3}$ = 6.2 Hz, 1 H, Me at C-3), 2.77 (dd, $^3J_{4a,3}$ = 3.0 Hz, $^2J_{4a,4b}$ = 16.2 Hz, 1 H, 4-H_a), 2.93 (dd, $^3J_{4b,3}$ = 11.0 Hz, $^2J_{4b,4a}$ = 16.2 Hz, 1 H, 4-H_b), 3.77 (s, 3 H, OMe), 4.03 (ddq, $^3J_{3,4a}$ = 3.2 Hz, $^3J_{3,Me}$ = 6.2 Hz, $^3J_{3,4b}$ = 11.0 Hz, 1 H, 3-H), 5.80 (s, 1 H, 1-H), 6.52 (m_c, 1 H, arom.-H), 6.62 (m_c, 1 H, arom.-H), 6.68 (s, 1 H, 5-H), 7.51 (t, *J* = 7.9 Hz, 1 H, 5′-H), 7.68 (d, *J* = 7.8 Hz, 1 H, 6′-H), 8.17 (d, *J* = 8.4 Hz, 1 H, 4′-H), 8.22 (s, 1 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (Me at C-3), 36.7 (C-4), 55.3 (OMe), 71.6 (C-3), 79.9 (C-1), 112.6, 113.4, 123.2, 123.8, 127.5 (arom.-CH), 128.9 (C-8a), 129.6, 135.0 (arom.-CH), 135.6 (C-4a), 144.9 (C-1′), 148.5 (C-3′), 158.6 (C-6) ppm. IR (ATR film): $\tilde{\nu}$ = 3094, 2889, 1607, 1526, 1498, 1345, 1163, 859, 735 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 299 [M^+] (23), 177 [$C_{11}H_{13}O_2^+$] (100). $[\alpha]_D^{20}$ = –42.8 [*c* = 1.03, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 98:2]. HRMS (TOF-MS, EI+): calcd. for $C_{17}H_{17}NO_4$ 299.1158; found 299.1167.

(1*S*,3*S*)-1-(2-Chloro-5-nitrophenyl)-6-methoxy-3-methylisochroman [(1*S*,3*S*)-3b]: Alcohol (*S*)-**2b** (53.5 mg, 0.322 mmol), 2-chloro-5-nitrobenzaldehyde (62.7 mg, 0.338 mmol), and *p*TsOH (10.7 mg, 66.4 μmol) were used to provide isochroman (1*S*,3*S*)-**3b** as a colorless solid (73.5 mg, 0.220 mmol) in 68.4% yield [*dr* (*syn*/*anti*) = 91:9] after chromatography (PE/EtOAc = 95:5). The pure *syn* diastereomer was obtained by recrystallization from $CHCl_3$. R_f (PE/EtOAc = 80:20) = 0.58, m.p. 108.5–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, $^3J_{Me,3}$ = 6.2 Hz, 1 H, Me at C-3), 2.80 (dd, $^3J_{4a,3}$ = 3.1 Hz, $^2J_{4a,4b}$ = 16.3 Hz, 1 H, 4-H_a), 2.96 (dd, $^3J_{4b,3}$ = 11.0 Hz, $^2J_{4b,4a}$ = 16.3 Hz, 1 H, 4-H_b), 3.77 (s, 3 H, OMe at C-6), 4.08 (ddq, $^3J_{3,4a}$ = 3.3 Hz, $^3J_{3,Me}$ = 6.2 Hz, $^3J_{3,4b}$ = 10.9 Hz, 1 H, 3-H), 6.27 (s, 1 H, 1-H), 6.55–6.71 (m, 3 H, arom.-H), 6.58 (d, $^3J_{3',4'}$ = 8.9 Hz, 1 H, 3′-H), 8.1 (dd, $^4J_{4'6'}$ = 2.8 Hz, $^3J_{4',3'}$ = 8.8 Hz, 1 H, 4′-H), 8.22 (d, $^4J_{6',4'}$ = 2.8 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (Me at C-3), 36.5 (C-4), 55.4 (OMe), 71.7 (C-3), 75.9 (C-1), 112.7, 113.6 (arom.-CH), 123.8 (C-4′), 125.9 (C-6′), 126.8 (arom.-CH), 128.0 (C-8a), 130.5 (C-3′), 135.6 (C-2′), 140.2 (C-4a), 142.8 (C-1′), 147.2 (C-5′), 158.7 (C-6) ppm. IR (ATR film): $\tilde{\nu}$ = 3090, 2986, 2866, 1609, 1523, 1341, 1055, 738, 524 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 333 [M^+] (40), 302 [$C_{16}H_{13}ClNO_3^+$] (26), 177 [$C_{11}H_{13}O_2^+$] (100). $[\alpha]_D^{20}$ = –76.0 [*c* = 1.10, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{17}H_{16}ClNO_4$ 333.0768; found 333.0767.

(1*R*,3*S*)-6-Methoxy-1-(4-methoxyphenyl)-3-methylisochroman [(1*R*,3*S*)-3c]: Alcohol (*S*)-**2b** (53.5 mg, 0.322 mmol), *p*-methoxybenzaldehyde (46 mg, 0.338 mmol), and *p*TsOH (10.7 mg, 66.4 μmol) were used to provide isochroman (1*R*,3*S*)-**3c** as a colorless solid (43.2 mg, 0.152 mmol) in 47.2% yield [*dr* (*syn*/*anti*) = 77:23] after chromatography (PE/EtOAc = 90:10). The pure *syn* diastereomer was obtained by recrystallization from $CHCl_3$. R_f (PE/EtOAc = 80:20) = 0.50, m.p. 72.8–73.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{Me,3}$ = 6.2 Hz, 1 H, Me at C-3), 2.73 (dd, $^3J_{4a,3}$ = 3.1 Hz, $^2J_{4a,4b}$ = 16.1 Hz, 1 H, 4-H_a), 2.93 (dd, $^3J_{4b,3}$ = 10.9 Hz, $^2J_{4b,4a}$ = 16.2 Hz, 1 H, 4-H_b), 3.77 (s, 3 H, OMe at C-6), 3.79 (s, 3 H, OMe at C-4′), 4.00 (ddq, $^3J_{3,4a}$ = 3.2 Hz, $^3J_{3,Me}$ = 6.2 Hz, $^3J_{3,4b}$ = 10.8 Hz, 1 H, 3-H), 5.62 (s, 1 H, 1-H), 6.55–6.67 (m, 3 H, arom.-H), 6.87 (d, $^3J_{2',3'}$ = 8.7 Hz, 2 H, 2′-H), 7.25 (d, $^3J_{3',2'}$ = 8.7 Hz, 2 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (Me at C-3), 37.0 (C-4), 55.3 (OMe), 55.4 (OMe), 71.4 (C-3), 80.5 (C-1), 112.2, 113.0, 114.0, 127.9 (arom.-CH), 130.1 (C-8a), 135.1 (C-4a), 135.6 (C-1′), 158.2, 159.5 (C_{ipso}) ppm. IR (ATR film): $\tilde{\nu}$ = 2963, 2837, 1603, 1500, 843, 791, 533 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 284 [M^+] (96), 177 [$C_{11}H_{13}O_2^+$] (54), 135 [$C_9H_{11}O^+$] (100). $[\alpha]_D^{20}$ = –10.2 [*c* = 0.72, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{18}H_{20}O_3$ 284.1412; found 284.1396.

(1*R*,3*S*)-1-(3,4-Dimethoxyphenyl)-6-methoxy-3-methylisochroman [(1*R*,3*S*)-3d]: Alcohol (*S*)-**2b** (53.5 mg, 0.322 mmol), 3,4-dimethoxybenzaldehyde (56.2 mg, 0.338 mmol), and *p*TsOH (10.7 mg, 66.4 μmol) were used to provide isochroman (1*R*,3*S*)-**3d** as a viscous oil (54.7 mg, 0.174 mmol) in 54.1% yield [*dr* (*syn*/*anti*) = 77:23] after chromatography (PE/EtOAc = 80:20). The pure *syn* diastereomer was obtained by preparative TLC. R_f (PE/EtOAc = 70:30) = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, $^3J_{Me,3}$ = 6.1 Hz, 1 H, Me at C-3), 2.73 (dd, $^3J_{4a,3}$ = 3.0 Hz, $^2J_{4a,4b}$ = 16.3 Hz, 1 H, 4-H_a), 2.89 (dd, $^3J_{4b,3}$ = 10.9 Hz, $^2J_{4b,4a}$ = 16.2 Hz, 1 H, 4-H_b), 3.77 (s, 3 H, OMe at C-6), 3.83 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 4.01 (ddq, $^3J_{3,4a}$ = 3.0 Hz, $^3J_{3,Me}$ = 6.1 Hz, $^3J_{3,4b}$ = 10.9 Hz, 1 H, 3-H), 5.62 (s, 1 H, 1-H), 6.59–6.67 (m, 3 H, arom.-H), 6.81 (m_c, 1 H, arom.-H), 6.82–6.86 (m, 1 H, arom.-H), 6.92 (m_c, 1 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0 (Me at C-3), 36.8 (C-4), 55.2 (OMe), 55.8 (OMe), 55.9 (OMe), 71.4 (C-3), 80.8 (C-1), 110.8, 111.5, 112.1, 112.9, 121.4, 127.7 (arom.-CH), 130.5 (C-8a), 135.2 (C-1′), 135.4 (C-4a), 148.9 (C-4′), 149.1 (C-3′), 158.1 (C-6) ppm. IR (ATR film): $\tilde{\nu}$ = 2958, 2920, 2852, 1607, 1501, 1233, 1135, 1025, 822, 757, 567 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 314 [M^+] (100), 283 [$C_{18}H_{19}O_3^+$] (54), 177 [$C_{11}H_{13}O^+$] (49). $[\alpha]_D^{20}$ = –4.5 [*c* = 0.20, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{19}H_{22}O_4$ 314.1518; found 314.1513.

(5*S*,7*R*)-7-Methyl-5-(3-nitrophenyl)-7,8-dihydro-5*H*-[1,3]dioxolo-[4,5-*g*]isochromene [(5*S*,7*R*)-3e]: Alcohol (*R*)-**2c** (37.1 mg, 0.206 mmol), 3-nitrobenzaldehyde (32.6 mg, 0.216 mmol), and *p*TsOH (7.8 mg, 41.1 μmol) were used to provide isochroman (5*S*,7*R*)-**3e** as a colorless solid (44.6 mg, 0.142 mmol) in 69.1% yield [*dr* (*syn*/*anti*) = 98:2] after flash chromatography (silica, PE/EtOAc = 90:10). R_f (PE/EtOAc = 80:20) = 0.54, m.p. 154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, $^3J_{Me,3}$ = 6.2 Hz, 1 H, Me at C-7), 2.68 (dd, $^3J_{8a,7}$ = 2.5 Hz, $^2J_{8a,8b}$ = 16.0 Hz, 1 H, 8-H_a), 2.85 (dd, $^3J_{8b,3}$ = 11.0 Hz, $^2J_{8b,8a}$ = 15.9 Hz, 1 H, 8-H_b), 3.99 (ddq, $^3J_{7,8a}$ = 3.0 Hz, $^3J_{7,Me}$ = 6.2 Hz, $^3J_{7,8b}$ = 10.8 Hz, 1 H, 7-H), 5.74 (s, 1 H, 5-H), 5.85 (d, $^2J_{2a,2b}$ = 6.7 Hz, 1 H, 2-H_a), 5.86 (d, $^2J_{2b,2a}$ = 6.7 Hz, 1 H, 2-H_b), 6.05 (s, 1 H, 9-H), 6.60 (s, 1 H, 4-H), 7.53 (dd ap. as t, $^3J_{5',4'}$ = 7.8 Hz, $^3J_{5',6'}$ = 7.9 Hz, 1 H, 5′-H), 7.68 (dt, $^4J_{6',2'}$ = 2.7 Hz, $^3J_{6',5'}$ = 7.9 Hz, 1 H, 6′-H), 8.18 (m_c, 1 H, 4′ and 6′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (Me at C-7), 36.4 (C-8), 71.6 (C-7), 80.1 (C-5), 101.1 (C-2), 106.3 (C-9), 108.5 (C-4), 123.3, 123.8 (arom.-CH), 127.5 (C-4a), 129.4 (C-8a), 129.6, 135.0 (arom.-CH), 144.7 (C-1′), 146.2 (arom.-C_{ipso}), 146.7 (arom.-C_{ipso}), 148.5 (C-3′) ppm. IR (ATR film): $\tilde{\nu}$ = 2976, 2905, 1523, 1504, 1482, 1347, 1239, 1039, 737, 687 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 313 [M^+] (100), 191 [$C_{11}H_{11}O_3^+$] (96). $[\alpha]_D^{20}$ = –20.9 [*c* = 1.0, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 98:2]. HRMS (TOF-MS, EI+): calcd. for $C_{17}H_{15}NO_5$ 313.0950; found 313.0958.

(5*S*,7*R*)-7-Methyl-5-(4-nitrophenyl)-7,8-dihydro-5*H*-[1,3]dioxolo-[4,5-*g*]isochromene [(5*S*,7*R*)-3f]: Alcohol (*R*)-**2c** (57.6 mg, 0.32 mmol), 4-nitrobenzaldehyde (50.7 mg, 0.336 mmol), and

*p*TsOH (12.2 mg, 63.9 μmol) were used to provide isochroman (5*S*,7*R*)-**3f** as a slightly yellow solid (67.2 mg, 0.215 mmol) in 67.1% yield [*dr* (*syn*/*anti*) = 98:2] after chromatography (PE/EtOAc = 80:20). R_f (PE/EtOAc = 80:20) = 0.54, m.p. 171.3–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{Me,7}$ = 6.1 Hz, 1 H, Me at C-7), 2.69 (dd, $^3J_{8a,7}$ = 2.8 Hz, $^2J_{8a,8b}$ = 15.9 Hz, 1 H, 8-H_a), 2.82 (dd, $^3J_{8b,3}$ = 10.9 Hz, $^2J_{8b,8a}$ = 16.1 Hz, 1 H, 8-H_b), 3.99 (ddq, $^3J_{7,8a}$ = 2.7 Hz, $^3J_{7,Me}$ = 6.0 Hz, $^3J_{7,8b}$ = 10.8 Hz, 1 H, 7-H), 5.73 (s, 1 H, 5-H), 5.85 (d, $^2J_{2a,2b}$ = 7.6 Hz, 1 H, 2-H_a), 5.87 (d, $^2J_{2b,2a}$ = 7.6 Hz, 1 H, 2-H_b), 6.04 (s, 1 H, 9-H), 6.60 (s, 1 H, 4-H), 7.52 (d, $^3J_{2',3'}$ = 8.7 Hz, 2 H, 2′-H), 8.21 (d, $^3J_{3',2'}$ = 8.7 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (Me at C-7), 36.5 (C-8), 71.6 (C-7), 80.0 (C-5), 101.0 (C-2), 106.2 (C-9), 108.5 (C-4), 124.0 (C-3′), 127.4 (C-4a), 129.4 (C-8a), 129.6 (C-2′), 146.2 (C-4′), 146.7 (arom.-C_{ipso}), 147.8 (arom.-C_{ipso}), 149.7 (C-1′) ppm. IR (ATR film): $\tilde{\nu}$ = 2966, 2916, 2855, 1520, 1500, 1476, 1346, 1347, 1182, 748, 699 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 313 [M^+] (100), 191 [$C_{11}H_{11}O_3^+$] (78). $[\alpha]_D^{20}$ = –17.4 [*c* = 1.25, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 98:2]. HRMS (TOF-MS, EI+): calcd. for $C_{17}H_{15}NO_5$ 313.0950; found 313.0955.

(5*R*,7*R*)-5-(2-Chlorphenyl)-7-methyl-7,8-dihydro-5*H*-[1,3]dioxolo-[4,5-*g*]isochromene [(5*R*,7*R*)-3g]: Alcohol (*R*)-**2c** (51.0 mg, 0.283 mmol), 2-chlorobenzaldehyde (41.8 mg, 0.297 mmol), and *p*TsOH (10.8 mg, 56.6 μmol) were used to provide isochroman (5*R*,7*R*)-**3g** as a colorless solid (72.8 mg, 0.240 mmol) in 85.0% yield [*dr* (*syn*/*anti*) = 92:8] after flash chromatography (silica, PE/EtOAc = 98:2). The pure *syn* diastereomer was obtained by an additional chromatographic separation (elutes first). R_f (PE/EtOAc = 80:20) = 0.66, m.p. 92.3–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{Me,7}$ = 6.2 Hz, 1 H, Me at C-7), 2.67 (dd, $^3J_{8a,7}$ = 2.8 Hz, $^2J_{8a,8b}$ = 15.9 Hz, 1 H, 8-H_a), 2.82 (dd, $^3J_{8b,3}$ = 11.0 Hz, $^2J_{8b,8a}$ = 15.9 Hz, 1 H, 8-H_b), 4.01 (ddq, $^3J_{7,8a}$ = 3.0 Hz, $^3J_{7,Me}$ = 6.1 Hz, $^3J_{7,8b}$ = 10.8 Hz, 1 H, 7-H), 5.83 (d, $^2J_{2a,2b}$ = 5.8 Hz, 1 H, 2-H_a), 5.84 (d, $^2J_{2b,2a}$ = 5.8 Hz, 1 H, 2-H_b), 6.17 (s, 1 H, 5-H), 6.18 (s, 1 H, 9-H), 6.57 (s, 1 H, 4-H), 7.16–7.26 (m, 2 H, arom.-H), 7.32 (m_c, 1 H, arom.-H), 7.39 (m_c, 1 H, arom-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (Me at C-7), 36.5 (C-8), 71.6 (C-7), 76.7 (C-5), 100.9 (C-2), 106.3 (C-9), 108.3 (C-4), 127.4 (C-4a), 127.5, 129.2, 129.6 (arom.-CH), 130.3 (C-8a), 130.6 (arom.-CH), 133.6 (C-2′), 140.4 (C-1′), 146.1 (arom.-C_{ipso}), 146.4 (arom.-C_{ipso}) ppm. IR (ATR film): $\tilde{\nu}$ = 2969, 2923, 1482, 1238, 1028, 800 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 302 [M^+] (63), 223 [$C_{16}H_{15}O^+$] (100), 191 [$C_{11}H_{11}O_3^+$] (88). $[\alpha]_D^{20}$ = +50.7 [*c* = 1.15, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{17}H_{15}ClO_3$ 302.0710; found 302.0709.

(5*R*,7*R*)-5-(2-Fluoro-5-methoxyphenyl)-7-methyl-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isochromene [(5*R*,7*R*)-3h]: Alcohol (*R*)-**2c** (47.9 mg, 0.266 mmol), 2-fluoro-5-methoxybenzaldehyde (43.0 mg, 0.279 mmol), and *p*TsOH (10.1 mg, 53.2 μmol) were used to provide isochroman (5*R*,7*R*)-**3h** as a colorless solid (60.7 mg, 0.192 mmol) in 72.2%yield [*dr* (*syn*/*anti*) = 90:10] after flash chromatography (silica, PE/EtOAc = 95:5). The pure *syn* diastereomer was obtained by an additional chromatographic separation (elutes first). R_f (PE/EtOAc = 80:20) = 0.37, m.p. 125.8–126.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, $^3J_{Me,7}$ = 6.2 Hz, 1 H, Me at C-7), 2.66 (dd, $^3J_{8a,7}$ = 3.1 Hz, $^2J_{8a,8b}$ = 15.9 Hz, 1 H, 8-H_a), 2.82 (dd, $^3J_{8b,3}$ = 11.0 Hz, $^2J_{8b,8a}$ = 16.0 Hz, 1 H, 8-H_b), 3.73 (s, 3 H, OMe), 3.99 (ddq, $^3J_{7,8a}$ = 3.1 Hz, $^3J_{7,Me}$ = 6.1 Hz, $^3J_{7,8b}$ = 10.8 Hz, 1 H, 7-H), 5.86 (d, $^2J_{2a,2b}$ = 5.7 Hz, 1 H, 2-H_a), 5.87 (d, $^2J_{2b,2a}$ = 5.7 Hz, 1 H, 2-H_b), 6.00 (s, 1 H, 5-H), 6.22 (s, 1 H, 9-H), 6.57 (s, 1 H, 4-H), 6.76–6.83 (m, 2 H, arom.-H), 7.01 (m_c, 1 H, arom.-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (Me at C-7), 36.5 (C-8), 55.9 (d, $J_{Me,F}$ = 2.5 Hz, OMe), 71.6 (C-7), 73.7 (C-5), 100.9 (C-2), 106.2 (C-9), 108.3 (C-4), 114.5 (d, $J_{4',F}$ = 3.9 Hz, 4′-H), 115.0 (d, $J_{6',F}$ = 8.3 Hz, 6′-H), 116.2 (d, $J_{3',F}$ = 24.2 Hz, 3′-F), 127.4 (C-8a), 130.2 (C-4a), 130.3 (d, $J_{1',F}$ = 14.7 Hz, 1′-H), 146.2 (arom.-C_{ipso}), 146.4 (arom.-C_{ipso}), 155.2 (d, $J_{2',F}$ = 239.4 Hz, 2′-F), 156.0 (d, $J_{5',F}$ = 1.9 Hz, 5′-H) ppm. IR (ATR film): $\tilde{\nu}$ = 2968, 2928, 1497, 1477, 1206, 1029, 940, 812, 731 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 316 [M^+] (100), 191 [$C_{11}H_{11}O_3^+$] (47). $[\alpha]_D^{20}$ = –75.8 [*c* = 0.78, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{18}H_{17}FO_4$ 316.1111; found 316.1103.

(1*R*,3*S*)-6,7-Dimethoxy-3-methyl-1-(3-nitrophenyl)isochroman [(1*R*,3*S*)-3i]: Alcohol (*S*)-**2d** (55.1 mg, 0.281 mmol), *m*-nitrobenzaldehyde (44.6 mg, 0.295 mmol), and *p*TsOH (5.3 mg, 28 μmol) were used to provide isochroman (1*R*,3*S*)-**3i** as a slightly yellowish solid (77.8 mg, 0.236 mmol) in 84.0% yield [*dr* (*syn*/*anti*) = 98:2] after chromatography (PE/EtOAc = 80:20). R_f (PE/EtOAc = 80:20) = 0.25, m.p. 122.3–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{Me,3}$ = 6.2 Hz, 1 H, Me at C-3), 2.69 (dd, $^3J_{4a,3}$ = 2.7 Hz, $^2J_{4a,4b}$ = 15.9 Hz, 1 H, 4-H_a), 2.86 (dd, $^3J_{4b,3}$ = 11.0 Hz, $^2J_{4b,4a}$ = 15.9 Hz, 1 H, 4-H_b), 3.60 (s, 3 H, OMe at C-7), 3.85 (s, 3 H, OMe at C-6), 4.00 (ddq, $^3J_{3,4a}$ = 2.6 Hz, $^3J_{3,Me}$ = 6.1 Hz, $^3J_{3,4b}$ = 10.9 Hz, 1 H, 3-H), 5.78 (s, 1 H, 1-H), 6.06 (s, 1 H, 5-H), 6.63 (s, 1 H, 8-H), 7.52 (t, ^3J = 7.9 Hz, 1 H, 5′-H), 7.68 (dt, ^4J = 1.5 Hz, ^3J = 7.8 Hz, 1 H, 6′-H), 6.16 (dq, ^4J = 1.2 Hz, ^3J = 8.1 Hz, 1 H, 4′-H), 8.22 (t, ^4J = 2.0 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (Me at C-3), 35.9 (C-4), 55.9 (OMe), 56.0 (OMe), 71.6 (C-3), 79.7 (C-1), 109.1 (C-5), 111.3 (C-8), 123.2 (C-4′), 123.8 (C-2′), 126.5 (C-4a), 128.1 (C-8a), 129.5 (C-5′), 135.0 (C-6′), 144.7 (C-1′), 147.5 (arom.-C_{ipso}), 148.2 (arom.-C_{ipso}), 148.4 (C-3′) ppm. IR (ATR film): $\tilde{\nu}$ = 2911, 2857, 1515, 1340, 1065, 810, 736 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 329 [M^+] (100), 207 [$C_{12}H_{15}O_3^+$] (100). $[\alpha]_D^{20}$ = –42.8 [*c* = 1.03, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 98:2]. HRMS (TOF-MS, EI+): calcd. for $C_{18}H_{19}NO_5$ 329.1263; found 329.1262.

(1*S*,3*S*)-1-(2-Chloro-5-nitrophenyl)-6,7-dimethoxy-3-methylisochroman [(1*S*,3*S*)-3j]: Alcohol (*S*)-**2d** (55.1 mg, 0.281 mmol), 2-chloro-5-nitrobenzaldehyde (54.8 mg, 0.295 mmol), and *p*TsOH (5.3 mg, 28 μmol) were used to provide isochroman (1*S*,3*S*)-**3j** as a slightly orange solid (80.8 mg, 0.222 mmol) in 79.1% yield [*dr* (*syn*/*anti*) = 99:1] after chromatography (PE/EtOAc = 90:10). R_f (PE/EtOAc = 80:20) = 0.31, m.p. 139–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, $^3J_{Me,3}$ = 6.1 Hz, 1 H, Me at C-3), 2.72 (dd, $^3J_{4a,3}$ = 2.7 Hz, $^2J_{4a,4b}$ = 16.0 Hz, 1 H, 4-H_a), 2.91 (dd, $^3J_{4b,3}$ = 10.9 Hz, $^2J_{4b,4a}$ = 15.9 Hz, 1 H, 4-H_b), 3.65 (s, 3 H, OMe at C-7), 3.87 (s, 3 H, OMe at C-6), 4.05 (ddq, $^3J_{3,4a}$ = 3.0 Hz, $^3J_{3,Me}$ = 6.1 Hz, $^3J_{3,4b}$ = 10.9 Hz, 1 H, 3-H), 6.17 (s, 1 H, 5-H), 6.26 (s, 1 H, 1-H), 6.64 (s, 1 H, 8-H), 7.60 (d, $^3J_{3',4'}$ = 8.8 Hz, 1 H, 3′-H), 8.10 (dd, $^4J_{4'6'}$ = 2.8 Hz, $^3J_{4',3'}$ = 8.8 Hz, 1 H, 4′-H), 8.22 (d, $^4J_{6',4'}$ = 2.8 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (Me at C-3), 35.9 (C-4), 56.0 (OMe), 56.1 (OMe), 71.9 (C-3), 75.8 (C-1), 108.6 (C-5), 111.6 (C-8), 123.9 (C-6′), 126.0 (C-4′), 126.5 (C-4a), 127.5 (C-8a), 130.5 (C-3′), 140.1 (C-2′), 142.8 (C-1′), 147.3 (C-5′), 147.8 (arom.-C_{ipso}), 148.4 (arom.-C_{ipso}) ppm. IR (ATR film): $\tilde{\nu}$ = 3083, 2962, 2923, 1525, 1345, 1216, 1077, 741 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 363 [M^+] (100), 207 [$C_{12}H_{15}O_3^+$] (97). $[\alpha]_D^{20}$ = –58.1 [*c* = 1.22, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{18}H_{18}ClNO_5$ 363.0873; found 363.0899.

2-Chloro-3-[(1*S*,3*S*)-6,7-dimethoxy-3-methylisochroman-1-yl]-phenol [(1*S*,3*S*)-3k]: Alcohol (*S*)-**2d** (50.0 mg, 0.255 mmol), 2-chloro-3-hydroxybenzaldehyde (41.9 mg, 0.267 mmol), and *p*TsOH (9.7 mg, 56 μmol) were used to provide isochroman (1*S*,3*S*)-**3k** as a colorless solid (77.4 mg, 0.231 mmol) in 90.6% yield [*dr* (*syn*/*anti*)

= 85:15] after chromatography (PE/EtOAc = 70:30). The pure *syn* diastereomer was obtained by column chromatography with pure CH_2Cl_2. R_f (PE/EtOAc = 70:30) = 0.35, m.p. 181.7–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, $^3J_{Me,3}$ = 6.2 Hz, 1 H, Me at C-3), 2.68 (dd, $^3J_{4a,3}$ = 2.8 Hz, $^2J_{4a,4b}$ = 15.8 Hz, 1 H, 4-H$_a$), 2.85 (dd, $^3J_{4b,3}$ = 10.9 Hz, $^2J_{4b,4a}$ = 15.8 Hz, 1 H, 4-H$_b$), 3.64 (s, 3 H, OMe at C-7), 3.86 (s, 3 H, OMe at C-6), 4.05 (ddq, $^3J_{3,4a}$ = 3.1 Hz, $^3J_{3,Me}$ = 6.2 Hz, $^3J_{3,4b}$ = 10.9 Hz, 1 H, 3-H), 5.82 (s, 1 H, OH), 6.12 (s, 1 H, 1-H), 6.19 (s, 1 H, 5-H), 6.61 (s, 1 H, 8-H), 6.90 (dd, $^4J_{4',6'}$ = 1.6 Hz, $^3J_{4',5'}$ = 7.7 Hz, 1 H, 4′-H), 6.97 (dd, $^4J_{6',4'}$ = 1.6 Hz, $^3J_{6',5'}$ = 8.1 Hz, 1 H, 6′-H), 7.14 (dd appears as t, $^3J_{5',6'}$ = 7.9 Hz, $^3J_{5',4'}$ = 7.9 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (Me at C-3), 36.0 (C-4), 56.0 (OMe), 56.1 (OMe), 71.7 (C-3), 76.7 (C-1), 108.9 (C-5), 111.2 (C-8), 115.7 (C-6′), 120.1 (C-2′), 122.4 (C-4′), 126.5 (C-4a), 128.2 (C-5′), 128.6 (C-4a), 140.7 (C-1′), 147.5 (arom.-C$_{ipso}$), 148.0 (arom.-C$_{ipso}$), 151.5 (C-3′) ppm. IR (ATR film): $\tilde{\nu}$ = 3424, 2988, 2882, 1512, 1297, 1249, 1209, 1071, 773 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 334 [M$^+$] (100), 207 [$C_{12}H_{15}O_3^+$] (82). $[\alpha]_D^{20}$ = –64.4 [*c* = 1.05, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 98:2]. HRMS (TOF-MS, EI+): calcd. for $C_{18}H_{19}ClO_4$ 334.0972; found 334.0986.

(1*R*,3*S*)-1-(4-Bromophenyl)-6,7-dimethoxy-3-methylisochroman [(1*R*,3*S*)-3l]: Alcohol (*S*)-**2d** (50.0 mg, 0.255 mmol), 4-bromobenzaldehyde (49.5 mg, 0.268 mmol), and *p*TsOH (8.8 mg, 51 μmol) were used to provide isochroman (1*R*,3*S*)-**3l** as a colorless viscous oil (58.3 mg, 0.161 mmol) in 53.0% yield [*dr* (*syn*/*anti*) = 89:11] after chromatography (PE/EtOAc = 85:15). The pure *syn* diastereomer was obtained by column chromatography with pure CH_2Cl_2. R_f (PE/EtOAc = 80:20) = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{Me,3}$ = 6.1 Hz, 1 H, Me at C-3), 2.68 (dd, $^3J_{4a,3}$ = 2.9 Hz, $^2J_{4a,4b}$ = 15.8 Hz, 1 H, 4-H$_a$), 2.83 (dd, $^3J_{4b,3}$ = 10.9 Hz, $^2J_{4b,4a}$ = 15.8 Hz, 1 H, 4-H$_b$), 3.62 (s, 3 H, OMe at C-7), 3.86 (s, 3 H, OMe at C-6), 3.98 (ddq, $^3J_{3,4a}$ = 3.1 Hz, $^3J_{3,Me}$ = 6.1 Hz, $^3J_{3,4b}$ = 10.8 Hz, 1 H, 3-H), 5.63 (s, 1 H, 1-H), 6.10 (s, 1 H, 5-H), 6.61 (s, 1 H, 8-H), 7.21 (d, $^3J_{2',3'}$ = 8.4 Hz, 2 H, 2′-H), 7.47 (d, $^3J_{3',2'}$ = 8.4 Hz, 2 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (Me at C-3), 36.0 (C-4), 55.9 (OMe), 56.0 (OMe), 71.5 (C-3), 80.1 (C-1), 109.3 (C-5), 111.0 (C-8), 122.1 (C-6′), 126.3 (C-8a), 129.1 (C-4a), 130.5 (C-2′), 131.7 (C-3′), 140.5 (C-1′), 147.3 (arom.-C$_{ipso}$), 147.9 (arom.-C$_{ipso}$) ppm. IR (ATR film): $\tilde{\nu}$ = 2961, 2923, 1514, 1214, 1059, 1011, 872, 845, 823 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 362 [M$^+$] (72), 239 [$C_{16}H_{15}O_2^+$] (100), 207 [$C_{12}H_{15}O_3^+$] (79). $[\alpha]_D^{20}$ = +14.1 [*c* = 1.22, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{18}H_{19}BrO_3$ 362.0518. found 362.0519.

(1*R*,3*S*)-6,7,8-Trimethoxy-3-methyl-1-(3-nitrophenyl)isochroman [(1*R*,3*S*)-3m]: Alcohol (*S*)-**2e** (68.0 mg, 0.30 mmol), 3-nitrobenzaldehyde (48.0 mg, 0.32 mmol), and *p*TsOH (5.6 mg, 0.03 mmol) were used to provide isochroman (1*R*,3*S*)-**3m** as a colorless viscos oil [*dr* (*syn*/*anti*) = 97:3]. The pure *syn* diastereomer (89 mg, 0.25 mmol) was obtained in 82% yield by column chromatography with pure CH_2Cl_2. R_f (CH_2Cl_2) = 0.40. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, $^3J_{Me,3}$ = 6.2 Hz, 3 H, Me at C-3), 2.64 (dd, $^3J_{4a,3}$ = 2.1 Hz, $^2J_{4a,4b}$ = 15.8 Hz, 1 H, 4-H$_a$), 2.82 (dd, $^3J_{4b,3}$ = 10.7 Hz, $^2J_{4a,4b}$ = 15.8 Hz, 1 H, 4-H$_b$), 3.19 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.82–3.92 (m, 1 H), 3.87 (s, 3 H, OMe), 5.86 (s, 1 H, 1-H), 6.48 (s, 1 H, 5-H), 7.48 (dd appears as t, $^3J_{5',4'}$ = 7.9 Hz, $^3J_{5',6'}$ = 7.9 Hz, 1 H, 5′-H), 7.66 (dt, $^3J_{6',5'}$ = 7.9 Hz, $^4J_{6',1'}$ = 1.3 Hz, $^4J_{6',4'}$ = 1.3 Hz, 6′-H), 8.12 (ddd, $^3J_{4',5'}$ = 8.3 Hz, $^4J_{4',2'}$ = 2.2 Hz, $^4J_{4',6'}$ = 1.2 Hz, 1 H, 4′-H), 8.17 (dd appears as t, $^4J_{2',6'}$ = 1.9 Hz, 1 H, $^4J_{2',4'}$ = 1.9 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (Me at C-3), 36.7 (C-4), 55.9 (OMe), 59.3 (OMe), 60.6 (OMe), 70.7 (C-3), 77.0 (C-1), 106.9 (C-5), 121.9 (C-8a), 122.5 (C-4′), 123.4 (C-2′), 129.0 (C-5′), 130.6 (C-5′), 134.8 (C-4a), 140.5 (arom.-C$_{ipso}$), 146.3 (C-1′), 148.1 (C-3′), 150.0 (arom.-C$_{ipso}$), 153.0 (arom.-C$_{ipso}$) ppm. IR (ATR film): $\tilde{\nu}$ = 2971, 2936, 1527, 1348, 1111, 1078, 1022, 737 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 362 [M$^+$] (52), 237 [$C_{13}H_{17}O_4^+$] (100), 207 [$C_{12}H_{15}O_3^+$] (50). $[\alpha]_D^{20}$ = –4.3 [*c* = 1.0, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) >99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{19}H_{21}NO_6$ 359.1369; found 359.1374.

(1*S*,3*S*)-6,7,8-Trimethoxy-3-methyl-1-(2-chloro-5-nitrophenyl)isochroman [(1*S*,3*S*)-3n]: Alcohol (*S*)-**2e** (68.0 mg, 0.30 mmol), 3-nitrobenzaldehyde (59.0 mg, 0.32 mmol), and *p*TsOH (5.6 mg, 0.03 mmol) were used to provide isochroman (1*S*,3*S*)-**3n** as a colorless oil [*dr* (*syn*/*anti*) = 97:3]. The pure *syn* diastereomer (101 mg, 0.25 mmol) was obtained in 86% yield by column chromatography with pure CH_2Cl_2. R_f (CH_2Cl_2) = 0.35. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{Me,3}$ = 6.3 Hz, 3 H, Me at C-3), 2.67 (dd, $^3J_{4a,3}$ = 1.7 Hz, $^2J_{4a,4b}$ = 16.1 Hz, 1 H, 4-H$_a$), 2.88 (dd, $^3J_{4b,3}$ = 10.7 Hz, $^2J_{4a,4b}$ = 15.9 Hz, 1 H, 4-H$_b$), 3.30 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.89 (ddq, $^3J_{3,4a}$ = 2.2 Hz, $^3J_{3,Me}$ = 6.3 Hz, $^3J_{3,4b}$ = 10.6 Hz, 1 H, 3-H), 6.29 (s, 1 H, 1-H), 6.47 (s, 1 H, 5-H), 7.56 (d, $^3J_{3',4'}$ = 8.7 Hz, 1 H, 3′-H), 7.56 (d, $^4J_{6',4'}$ = 3.0 Hz, 1 H, 6′-H), 8.03 (dd, $^3J_{4',3'}$ = 8.7 Hz, $^4J_{4',6'}$ = 3.0 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (Me at C-3), 36.4 (C-4), 56.0 (OMe), 59.6 (OMe), 60.7 (OMe), 70.9 (C-3), 73.4 (C-1), 107.1 (C-5), 121.5 (C-8a), 123.1 (C-4′), 125.0 (C-6′), 130.2 (C-3′), 130.8 (C-4a), 140.4 (C-2′), 140.9 (C-1′), 143.4 (arom.-C$_{ipso}$), 146.7 (C-3′), 149.6 (arom.-C$_{ipso}$), 153.1 (arom.-C$_{ipso}$) ppm. IR (ATR film): $\tilde{\nu}$ = 2973, 2903, 1520, 1342, 1110, 1076, 1043, 1020, 843, 829 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 393 [M$^+$] (42), 237 [$C_{13}H_{17}O_4^+$] (100), 207 [$C_{12}H_{15}O_3^+$] (33). $[\alpha]_D^{20}$ = –18.0 [*c* = 1.0, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) >99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{19}H_{20}ClNO_6$ 393.0979; found 393.1000.

(1*R*,3*S*)-6,7,8-Trimethoxy-3-methyl-1-(4-nitrophenyl)isochroman [(1*R*,3*S*)-3o]: Alcohol (*S*)-**2e** (68.0 mg, 0.30 mmol), 3-nitrobenzaldehyde (48.0 mg, 0.32 mmol), and *p*TsOH (5.6 mg, 0.03 mmol) were used to provide a reaction crude containing isochroman (1*R*,3*S*)-**3o** [*dr* (*syn*/*anti*) = 98:2]. The pure *syn* diastereomer (94 mg, 0.26 mmol) was obtained in 87% yield by column chromatography with pure CH_2Cl_2. R_f (CH_2Cl_2) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{Me,3}$ = 6.2 Hz, 3 H, Me at C-3), 2.64 (dd, $^3J_{4a,3}$ = 2.2 Hz, $^2J_{4a,4b}$ = 15.8 Hz, 1 H, 4-H$_a$), 2.79 (dd, $^3J_{4b,3}$ = 10.7 Hz, $^2J_{4a,4b}$ = 15.8 Hz, 1 H, 4-H$_b$), 3.17 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.86 (ddq, $^3J_{3,4a}$ = 2.4 Hz, $^3J_{3,Me}$ = 6.2 Hz, $^3J_{3,4b}$ = 10.4 Hz, 1 H, 2-H), 3.87 (s, 3 H, OMe), 5.85 (s, 1 H, 1-H), 6.47 (s, 1 H, 5-H), 7.47 (d, $^3J_{2',3'}$ = 8.5 Hz, 2 H, 2′-H), 8.17 (d, $^3J_{3',2'}$ = 8.6 Hz, 1 H, 2 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (Me at C-3), 36.7 (C-4), 55.9 (OMe), 59.2 (OMe), 60.6 (OMe), 70.7 (C-3), 77.0 (C-1), 106.8 (C-5), 122.0 (C-8a), 123.4 (C-2′), 129.3 (C-3′), 130.6 (C-4a), 140.4 (arom.-C$_{ipso}$), 147.2 (C-4′), 149.9 (arom.-C$_{ipso}$), 151.5 (arom.-C$_{ipso}$), 153.0 (C-3′) ppm. IR (ATR film): $\tilde{\nu}$ = 2971, 2936, 1602, 1517, 1342, 1110, 1055, 1022, 824, 749 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 362 [M$^+$] (65), 237 [$C_{13}H_{17}O_4^+$] (100), 207 [$C_{12}H_{15}O_3^+$] (18). $[\alpha]_D^{20}$ = +2.6 [*c* = 1.0, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) >99:1]. HRMS (TOF-MS, EI+): calcd. for $C_{19}H_{21}NO_6$ 359.1369; found 359.1378.

(1*R*,3*S*)-6,7,8-Trimethoxy-3-methyl-1-(4-bromophenyl)isochroman [(1*R*,3*S*)-3p]: Alcohol (*S*)-**2e** (68.0 mg, 0.30 mmol), 4-bromobenzaldehyde (59 mg, 0.32 mmol), and *p*TsOH (5.6 mg, 0.03 mmol) were used to provide isochroman (1*R*,3*S*)-**3p** as a colorless oil (62 mg, 0.16 mmol) in 53% yield [*dr* (*syn*/*anti*) = 94:6] after chromatography (CH_2Cl_2). R_f (PE/EtOAc = 90:10) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, $^3J_{Me,3}$ = 6.2 Hz, 3 H, Me at C-3), 2.61 (dd, $^3J_{4a,3}$ = 2.3 Hz, $^2J_{4a,4b}$ = 16.0 Hz, 1 H, 4-H$_a$), 2.80 (dd,

$^3J_{4b,3}$ = 10.8 Hz, $^2J_{4a,4b}$ = 15.7 Hz, 1 H, 4-H_b), 3.13 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 3.75–3.86 (m, 1 H, 2-H), 3.87 (s, 3 H, OMe), 5.73 (s, 1 H, 1-H), 6.44 (s, 1 H, 5-H), 7.18 (d, $^3J_{2',3'}$ = 8.3 Hz, 2 H, 2′-H), 7.42 (d, $^3J_{3',2'}$ = 8.5 Hz, 1 H, 2 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (Me at C-3), 36.8 (C-4), 55.9 (OMe), 59.3 (OMe), 60.5 (OMe), 70.5 (C-3), 77.3 (C-1), 106.7 (C-5), 121.3 (C-4′), 123.0 (C-8a), 130.1 (C-2′), 130.6 (C-4a), 131.3 (C-3′), 140.6 (arom.-C_{ipso}), 143.3 (C-1′), 150.2 (arom.-C_{ipso}), 152.7 (arom.-C_{ipso}) ppm. IR (ATR film): $\tilde{\nu}$ = 2969, 2935, 1490, 1455, 1431, 1407, 1069, 1022, 1010, 990, 794 cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) 394 [$M(Br^{81})^+$] (21), 392 [$M(Br^{79})^+$] (22), 237 [$C_{13}H_{17}O_4^+$] (100). $[a]_D^{20}$ = +16.8 [*c* = 1.0, $CHCl_3$; >99%*ee*, *dr* (*syn*/*anti*) = 94:6]. HRMS (TOF-MS, EI+): calcd. for $C_{19}H_{21}BrO_4$ 392.0623; found 392.0637.

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra (^{1}H, ^{13}C, HSQC, COSY) and X-ray diffraction data as well as GC and HPLC traces for chiral separation.

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