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Chemoenzymatic Stereoselective Synthesis of *trans*-Flavan-4-ols via Lipase-Catalyzed Kinetic Resolutions

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Abstract: Flavan-4-ols are a subclass of flavonoids that are present in complex molecules with application in the industrial sector as pigments, antioxidants, or antimitotics, among many others. The most traditional way to achieve their synthesis is from naturally abundant flavanones, asymmetric transfer hydrogenation reactions or bioreduction being well known strategies, while their preparation from racemic flavan-4-ols has been less explored. In this article, we have focused on the synthesis of a series of *trans*-flavan-4-ols bearing different substitution patterns in the aromatic ring to explore later the potential of lipases as biocatalysts for stereoselective acylation reactions. Therefore, a series of flavanones have been chemically prepared, starting from the corresponding benzaldehydes by aldol condensation with 2′-hydroxyacetophenone in a strongly basic medium, and later transformed into the corresponding racemic *trans*-flavan-4-ols following a carbonyl reduction, Mitsunobu reaction, and ester deprotection sequence. A screening of lipases and optimization of the reaction conditions for the stereoselective acylation of racemic 2-phenylchroman-4-ol were performed before expanding the best reaction conditions to the kinetic resolution of other 2-arylchroman-4-ols. Interestingly, the combination of AK lipase from *Pseudomonas fluorescens* as enzyme and vinyl acetate as both acyl donor and solvent allowed the performance of highly asymmetric transformations ($E > 200$, 50–99% ee_S and >99% ee_P) under mild reaction conditions (30 °C and 250 rpm).

Keywords: asymmetric synthesis; flavanols; kinetic resolution; lipases; Mitsunobu reaction

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1. Introduction

Flavan-4-ols, also known as 2-arylchroman-4-ols or 3-deoxyflavoids, are privileged structures in flavonoid chemistry [1], since their structural cores are present in many biologically active compounds with interesting properties as anticarcinogenic, antidiabetic, antioxidant, antimitotic, and biocidal agents [2,3]. Their chemical structure, together with the ones from flavone and flavanone, is represented in Figure 1. Remarkably, the relative and absolute configurations of the C-2 and C-4 centers possess a key role in building their biological profiles [4–9]; for that reason, the development of highly (stereo)selective methods towards the production of optically active flavan-4-ols is nowadays considered an attractive synthetic field, organometallic chemistry and enzymes being useful catalysts for the development of asymmetric processes.

Traditionally, the most straightforward approaches to produce racemic flavan-4-ols consist of reductions in flavanones and flavones, selectively leading to the corresponding *cis*-isomers as major products. In this context, the use of sodium borohydride [10,11] or catalytic hydrogenation employing palladium on charcoal [12,13] have afforded a series of racemates in high yields. The preferential formation of *cis*-flavan-4-ols can be easily explained considering that the hydride or catalyst would approach the flavanone from the less hindered face, opposite the aromatic group at C-2, favoring the addition of the hydride or hydrogen to the carbonyl from that face. As mentioned before, the reduction in flavones to the corresponding racemic *cis*-flavan-4-ols is also possible but requires a

stronger reducing agent such as $NiCl_2/NaBH_4$, also occurring with total control of the selectivity [14]. Alternatively, the synthesis of the *trans*-flavan-4-ols is also feasible but requires the formation of *cis*-isomers and subsequent inversion of the C-4 center configuration. Janeczko and co-workers described the synthesis of racemic *trans*-flavan-4-ol from its *cis*-isomer through a bimolecular nucleophilic substitution by alcohol activation with tosyl chloride in pyridine and subsequent hydrolysis under basic conditions in aqueous medium [15].

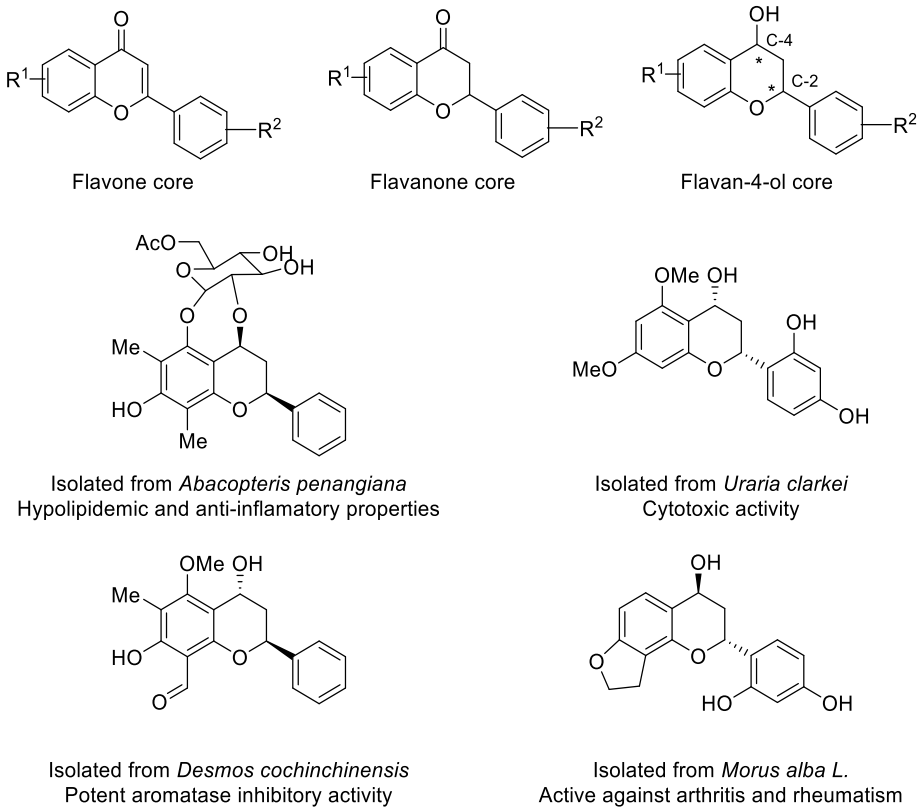
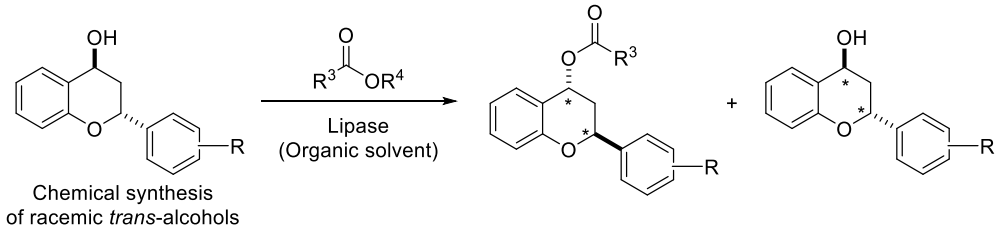


Figure 1. General structure of flavones, flavanones and flavan-4-ols. Above appear the structures of naturally occurring flavan-4-ols including examples of all four different absolute configurations at the C-2 and C-4 positions.

Similarly, the stereoselective synthesis of *cis*-flavan-4-ol enantiomers has received much more attention than the one of its *trans*-analogues, metal [16–18] and enzyme catalysis [15,19–24] facilitating the preparation of chiral flavan-4-ols with excellent stereoselectivity levels. Among the enzymatic methods, the desymmetrization of flavanones through bioreduction processes and the kinetic resolution of flavanols and their corresponding acetates using hydrolases are the most demanding strategies. The practical application of redox processes is usually hampered by the formation of complex product mixtures, low isolated yields, and working with very low substrate concentrations [13,17–19,22], while the use of lipases as biocatalysts have provided better results for practical applications [19–21]. For instance, Kasahara and co-workers reported the hydrolysis of 2-phenylchroman-4-yl acetate using the lipase from *Pseudomonas cepacia* (PSL) that allows the recovery of (2*R*,4*R*)-alcohol and (2*S*,4*S*)-acetate with high enantiomeric excess values (93% and 95% *ee*, respectively) [19]. Tanaka and co-workers found that the lipase AY is a highly selective catalyst for enantiocomplementary hydrolysis and acetylation procedures of racemic *cis*-flavan-4-ol and its acetate [20]. Finally, the lipase from *Candida cylindracea* also resulted to be an efficient biocatalyst, in this case, when applied to the stereoselective acetylation of a series of *cis*-flavan-4-ol, obtaining the corresponding (2*R*,4*R*)-4-acetoxyflavans and the

remaining (2*S*,4*S*)-flavan-4-ols with moderate to excellent optical purities, depending on the substitution patterns at the different positions of both aromatic rings [21].

Interestingly, there is only one report about the stereoselective enzymatic synthesis of *trans*-flavan-4-ols, which was covered by Janeczko and co-workers [15], describing *Rhodococcus rubra* KCh 82 as the most suitable reductive enzyme to produce (2*R*,4*S*)-*trans*-alcohol (41% yield, >99% *ee*), (*S*)-flavanone (50% yield, 59% *ee*), and (2*S*,4*S*)-*cis*-alcohol (9% yield, 40% *ee*), while for the oxidation of the racemic *trans*-alcohol, *Yarrowia lypolytica* catalyzed a highly selective oxidation, forming (*R*)-flavanone (52% yield, 85% *ee*) and (2*S*,4*R*)-*trans*-alcohol (48% yield, 93% *ee*) after 6 days at 25 °C. Unfortunately, there are no reports about the action of hydrolases towards the asymmetric production of *trans*-flavan-4-ols, so based on the biological importance of the flavanols family, herein, we aim to develop a general methodology for the selective preparation of a series of racemic *trans*-flavan-4-ols, later studying their kinetic resolutions through lipase-catalyzed acetylation reactions (Scheme 1).



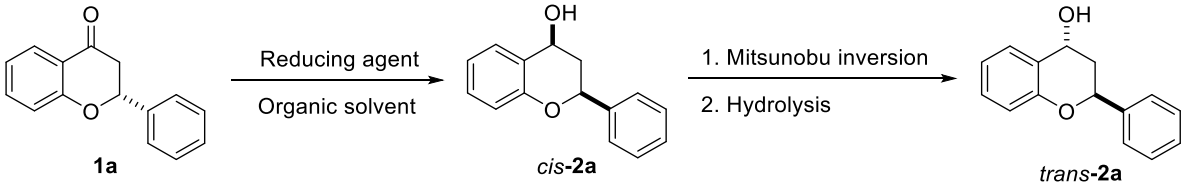
Scheme 1. Enzymatic kinetic resolution of *trans*-flavan-4-ols through stereoselective acetylation reaction for the production of the corresponding optically active esters and alcohols.

2. Results and Discussion

The synthesis of racemic *trans*-flavan-4-ol (*trans*-**2a**) will be described and reaction conditions optimized before extending this methodology to a representative number of *trans*-flavan-4-ols bearing different substitution patterns at the aromatic ring present in the C-2 position. Continuing with the selection of *trans*-**2a** as model substrate, its kinetic resolution will be carefully analyzed using different hydrolases, trying to find adequate conditions for the preparation of optically active products with good yields and high chemical and optical purities.

2.1. Chemical Synthesis of trans-Flavan-4-ols

Flavanone **1a** was selected as a commercial starting material for the synthesis of *trans*-flavan-4-ol (*trans*-**2a**) following the strategy depicted in Scheme 2, which involves the reduction in the carbonyl group of ketone **1a** to afford the corresponding *cis*-**2a**, followed by Mitsunobu inversion of the stereogenic center located at the C-4 position, and final chemical hydrolysis of the protected alcohol.



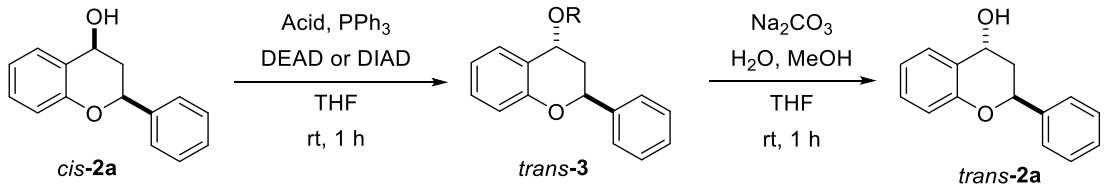
Scheme 2. Synthetic approach to convert flavanone (**1a**) into *trans*-flavan-4-ol (*trans*-**2a**) by a reduction–Mitsunobu inversion–deprotection sequence.

Firstly, the chemical reduction was performed at a very low temperature to achieve a total selectivity towards the *cis*-isomer formation, so flavanone (**1a**) was reacted with $LiAlH_4$ in anhydrous THF at −78 °C. Remarkably, the alcohol *cis*-**2a** was obtained after 12 h with complete control of the selectivity and in 95% yield after column chromatography purification. The relative *cis*-configuration was confirmed by comparison of its NMR data

with the ones already described in the literature [10–20]. The next step consists of selective inversion of the relative configuration of the hydroxyl group at the C-4 position in order to obtain the *trans*-**2a** isomer. Without any doubt, the Mitsunobu reaction is, nowadays, one of the most straightforward pathways to invert the configuration of a determined stereocenter [25–29], and it is based on the conversion of the starting alcohol into a better leaving group, usually an ester, following a S_N2 mechanism. To achieve this, triphenylphosphine (PPh_3), a carboxylic acid as nucleophile and an alkyl azodicarboxylate are employed, generally diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD).

The acidic strength is closely related to the efficiency of the Mitsunobu reaction [30], so four acids with variable pKa values (acetic acid, *p*-nitrobenzoic acid, chloroacetic acid and *p*-toluensulfonic acid) were employed in the presence of DEAD or DIAD as disclosed in Table 1. Although there was no influence about the use of one or another azodicarboxylate (even vs. odd entries), the use of the acidic source resulted to be a key factor, since no reaction was observed with acetic acid (entries 1 and 2), while *p*-nitrobenzoic acid, chloroacetic acid and *p*-toluensulfonic acid led to high conversions into the corresponding protected *trans*-alcohol **3**. The best results were found with the strongest acids, chloroacetic acid (entries 5 and 6) and *p*-toluensulfonic acid (PTSA, entries 7 and 8), next treating the reaction crudes with sodium carbonate in tetrahydrofuran and the presence of water and methanol. Thus, the *trans*-**2a** was obtained after liquid–liquid extraction and column chromatography with high isolated yields (86–88%) and similar selectivities (76-84% *dr*). The *trans*:*cis* ratios were unequivocally calculated by ^{1}H-NMR analyses of the reaction crudes by comparison of the two signals corresponding to the CHs at C-2 and C-4 positions, observing their chemical shifts at 5.10 and 5.18 ppm for the starting *cis*-**2a**, while the signals shift to 4.88 and 5.33 for the *trans*-**2a**.

Table 1. Investigation of the optimal conditions for the Mitsunobu protocol for the C-4 configuration inversion of racemic *cis*-**2a** to produce the corresponding *trans*-**2a**.

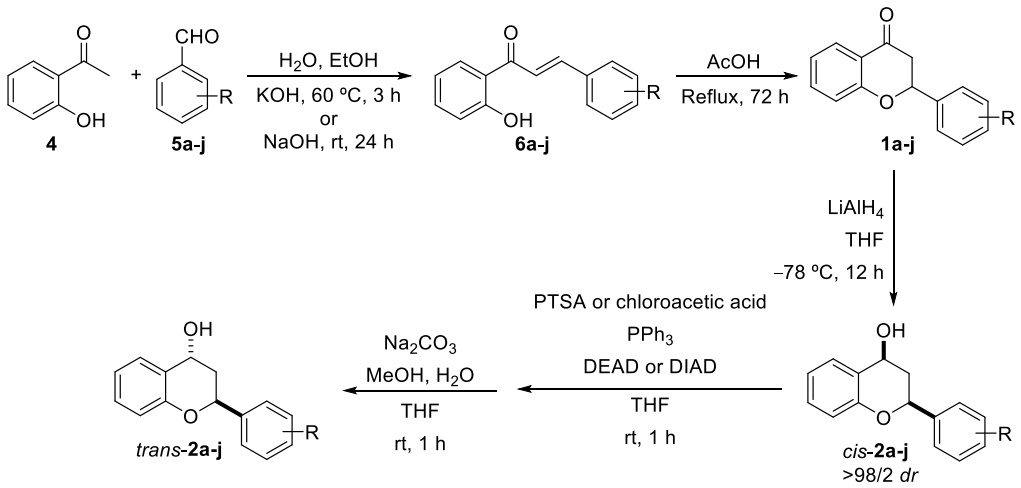


Entry	Azodicarboxylate	Acid	pKa	*dr* (*trans*/*cis*) [a]	Yield (%) [b]
1	DEAD	AcOH	4.76	-	-
2	DIAD	AcOH	3.41	-	-
3	DEAD	*p*-NO_2-C_6H_4-COOH	3.41	90/10	75
4	DIAD	*p*-NO_2-C_6H_4-COOH	3.41	91/9	74
5	DEAD	Cl-CH_2COOH	2.87	91/9	86
6	DIAD	Cl-CH_2COOH	2.87	88/12	87
7	DEAD	PTSA	−2.1	92/8	88
8	DIAD	PTSA	−2.1	91/9	86

[a] Diastereomeric ratio was determined by ^{1}H-NMR analysis of the crude Mitsunobu–hydrolysis sequence; [b] Isolated yield of *trans*-flavan-4-ol (**2a**) after flash column chromatography.

Trying to obtain the alcohol *trans*-**2a** with total selectivity, another approach was attempted by reacting racemic *cis*-**2a** with trifluoroacetic anhydride in the presence of pyridine in order to generate the corresponding triflate, and further hydrolysis led to *trans*-**2a**. However, no improvement was achieved in terms of selectivity (79% yield, 90/10 *trans*/*cis* ratio). The impossibility to increase the *trans*:*cis* ratio over 9:1 may be explained as a consequence of the occurrence of an epimerization process, which has been observed in esters derived from flavan-4-ols in acidic media [31].

Since only the flavanone **1a** was commercially available, the synthesis of flavanones **1b–j** bearing different substituents, such as electron-withdrawing and electron-donor groups, in the aromatic ring at the C-2 position was chemically carried out (Scheme 3), which will allow us to have a deeper understanding on the reactivity of lipases with the corresponding *trans*-flavan-4-ol substrates. The strategy consisted of the aldol condensation between 2′-hydroxyacetophenone (**4**) and the corresponding benzaldehydes **5b–j** in strongly basic media such as in the presence of potassium hydroxide for 3 h at 60 °C, but also similar results were found for 24 h at room temperature with sodium hydroxide, followed by an acid-promoted intramolecular Michael-type addition of the resulting 2′-hydroxychalcone **6b–j** intermediates using refluxing glacial acetic acid as both catalyst and solvent for 72 h [32,33]. Results are depicted in Table 2, the flavanones **1b–j** being isolated after column chromatography in moderate yields (36–47%). Interestingly, no significant differences were observed when considering electron-withdrawing (entries 2–6) or electron-donor groups (entries 7–10) at different positions of the C-2 aromatic ring.



Scheme 3. Synthesis of flavanones **1a–j** followed by chemical reduction and final Mitsunobu inversion–deprotection sequence to produce racemic flavanols *trans*-**2a-j**.

Table 2. Non stereoselective chemical synthesis of flavanones **1a–j**, *cis*- and *trans*-alcohols **2a–j**.

Entry	R	1a–j (%) [a]	*cis*-2a–j (%) [a,b]	*trans*-2a–j (%) [a,b]	
				Method A	Method B
1	H (**a**)	36	95	88 (92/8)	87 (88/12)
2	2-F (**b**)	41	90	77 (88/12)	88 (87/13)
3	3-F (**c**)	39	92	76 (89/11)	84 (93/7)
4	4-F (**d**)	42	96	74 (90/10)	59 (91/9)
5	4-Cl (**e**)	47	92	80 (90/10)	79 (88/12)
6	4-Br (**f**)	40	95	79 (95/5)	68 (93/7)
7	2-OMe (**g**)	45	93	78 (91/9)	51 (90/10)
8	3-OMe (**h**)	37	95	76 (89/11)	44 (84/16)
9	4-OMe (**i**)	41	95	81 (88/12)	78 (85/15)
10	4-Me (**j**)	42	91	78 (89/11)	86 (90/10)

[a] Isolated yields after column chromatography purification; [b] Diastereomeric ratio was determined by ^{1}H-NMR analysis and appear in brackets. Alcohols *cis*-**2b–j** were obtained after chemical reduction with >98/2 *dr* in all cases.

Next, flavanones **1b–j** were reduced to the racemic alcohols *cis*-**2b–j** using $LiAlH_4$ in THF at −78 °C, which were obtained in very high yields (90–96%) and with total control of the selectivity independently of the nature of their substituents and their substitution pattern (>98/2 *dr*). Finally, *cis*-flavan-4-ols **2b–j** were reacted under the best reaction conditions previously found for substrate **2a** (Method A: PPh_3, DEAD and PTSA; Method B: PPh_3, DIAD and chloroacetic acid) and after hydrolysis with aqueous Na_2CO_3 in THF/MeOH,

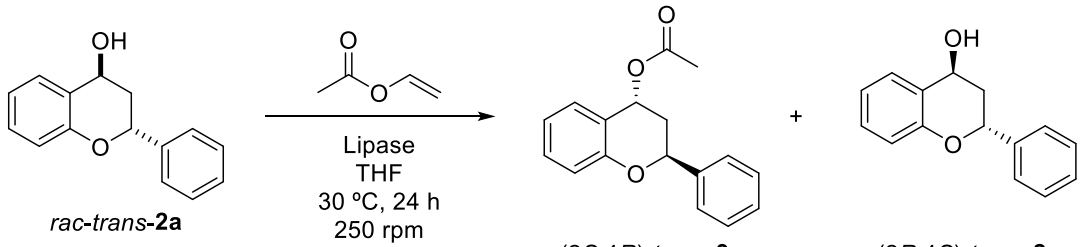
the corresponding *trans*-flavan-4-ols **2b–j** were obtained in good to high yields and good to high selectivities in all the cases. It must be mentioned that Mitsunobu reactions led to complex mixtures; therefore, the isolated yields were sometimes highly dependent on the efficiency of the purification process performed by column chromatography technique on silica gel.

2.2. Lipase-Catalyzed Kinetic Resolution of trans-Flavan-4-ols **2a–j**

Once the preparation of *trans*-flavan-4-ols **2a–j** was achieved, the potential of hydrolytic enzymes including a series of lipases and an acylase was explored, in order to produce optically active alcohols and esters via a classical kinetic resolution through the stereoselective acetylation of the racemic alcohols. Based on the previous successful studies dealing with the resolution of *cis*-alcohols using lipases [19–21], the alcohol *trans*-**2a** was selected as a model substrate to find a selective hydrolase, which preferentially would acetylate one of its enantiomers using standard conditions for this type of process such as 3 equivalents of vinyl acetate (VinOAc) as activated ester, THF as solvent, 30 °C and a 100 mM substrate concentration, using orbital shaking (250 rpm) to preserve the stability of the selected immobilized biocatalyst.

The set of hydrolases was composed by *Candida antarctica* lipase type A (CAL-A), *Candida antarctica* lipase type B (CAL-B), *Pseudomonas cepacia* lipase (PSL), *Rhizomucor miehei* lipase (RML), lipase AK from *Pseudomonas fluorescens*, and acylase from *Aspergillus melleus* (Acylase). In all cases a substrate:enzyme ratio 1:1 (weight:weight) was initially used and the reactions were performed for 24 h, searching for active and stereoselective enzymes (Table 3). In terms of selectivity, CAL-B, RML, and Acylase displayed poor results (entries 2, 4, and 6), leading to a broad conversion range (15–48%), while CAL-A, PSL, and lipase AK led to moderate to excellent enantioselectivities (entries 1, 3, and 5), highlighting the perfect stereodiscrimination displayed by AK lipase (E > 200). Therefore, the use of this lipase was selected for further reaction intensification.

Table 3. Screening of hydrolases for the kinetic resolution of *trans*-flavan-4-ol (**2a**, 100 mM) using 3 equivalents of vinyl acetate in dry THF at 30 °C and 250 rpm.



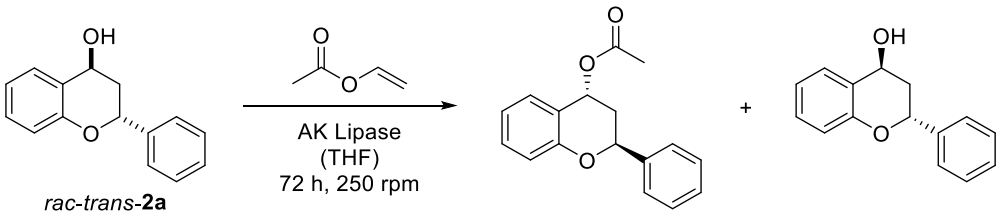
Entry	Hydrolase	c (%) [a]	ee_P (%) [b]	ee_S (%) [b]	E [c]
1	CAL-A	8	98	9	89
2	CAL-B	15	50	9	3
3	PSL	22	92	14	28
4	RML	18	30	8	2
5	AK	19	>99	23	>200
6	Acylase from *A. melleus*	48	9	8	1

[a] Conversion values were calculated as $c = ee_S/(ee_S + ee_P)$; [b] Enantiomeric excess values of product **3a** (ee_P) and substrate **2a** (ee_S) were determined by HPLC analysis; [c] Enantiomeric ratio values were calculated: $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.

After having determined that Amano lipase AK from *Pseudomonas fluorescens* could be a suitable lipase for performing the kinetic resolution of *trans*-**2a**, the influence of other parameters that affect the enzymatic catalysis was investigated. Therefore, different temperatures (30 and 45 °C), enzyme:substrate ratios (1:1 and 2:1 w/w), and loading of VinOAc

(3–109 equiv.) were studied in order to discover optimal conditions for kinetic resolution purposes, which means the achievement of around 50% conversion and the recovery of the resulting acetate and the remaining alcohol with high optical purities. Reactions were carried out taking aliquots every 24 h for 4 days, which were analyzed by chiral HPLC (see conditions in the Experimental section). To compare the biotransformations, the data obtained after 72 h have been summarized in Table 4, since no significant improvements were achieved from this point, and in some cases, the perfect selectivity attained after 3 days decreased in some extent after prolonged reaction times. Starting from the initial conditions achieved in the enzyme screening and displayed in Table 3 (entry 5), the temperature was increased to 45 °C, observing a significant improvement in the conversion value (27%, entry 1), although doubling the enzyme loading (entry 2) with respect to the reaction described in Table 3 led to a more significant improvement, reaching 41% conversion after 72 h and, again, excellent selectivity.

Table 4. Optimization of the AK lipase-catalyzed kinetic resolution of *trans*-**2a** by acetylation using vinyl acetate (VinOAc).



Entry	VinOAc (equiv)	T (°C)	AK:2a (*w*:*w*)	*c* (%) [a]	ee_P (%) [b]	ee_S (%) [b]	*E* [c]
1	3	45	1:1	27	>99	37	>200
2	3	30	2:1	41	>99	68	>200
3	6	30	1:1	44	>99	80	>200
4	109 [d]	30	1:1	50	>99	>99	>200

[a] Conversion values were calculated as $c = ee_S/(ee_S + ee_P)$; [b]. Enantiomeric excess values of product **3a** (ee_P) and substrate **2a** (ee_S) were determined by HPLC analysis; [c]. Enantiomeric ratio values were calculated: $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$; [d] This is a 100 mM solution in vinyl acetate as solvent in the absence of THF.

Continuing at 30 °C but doubling the activated ester ratio from three to six equivalents (entry 3), the conversion reached 44%, which was later much more improved, selecting VinOAc as both acyl donor and solvent (109 equivalents for a 100 mM substrate concentration, entry 4). In this case, a perfect 50% conversion into the enantiopure acetate (2*S*,4*R*)-**3a** and the remaining alcohol (2*R*,4*S*)-**2a** was possible after 48 h (entry 4). Final hydrolysis of the enantiopure acetate (2*S*,4*R*)-**3a** using an aqueous solution of Na_2CO_3 in a mixture of MeOH/THF at room temperature for 2 h led to the corresponding alcohol (2*S*,4*R*)-**2a** in 91% isolated yield without loss of the optical purity, affording, in this manner, both alcohol enantiomers through a chemoenzymatic strategy.

After comparison of the optical rotation values of the products obtained by lipase-catalyzed kinetic resolution (see experimental section), the absolute configuration of the so-obtained enantiopure *trans*-**2a** was assigned as (2*R*,4*S*) [34,35], while for the acetate *trans*-**2a**, (2*S*,4*R*)-stereochemistry was proposed. This assignment is also in agreement with the one proposed when applying Kazlauskas' rule for the resolution of secondary alcohols [36]. Finally, under optimized conditions, i.e., 100 mM *trans*-**3a** in VinOAc, 30 °C and 250 rpm, the resolutions of racemic alcohols *trans*-**2b**–**j** were developed, finding, in all cases, excellent selectivities but different activity values depending on the position of the substitution of the phenyl ring at the C-2 position (Table 5). In all cases, those reactions with substrates bearing *para*-substitutions were completely selective (entries 4, 5, 6, 9, and 10), noticing slower reactions when considering flavanols with substituents at the *ortho*-position (entries 2 and 7). Satisfyingly, the biotransformation of model substrate *trans*-**2a** was scaled

up to 250 mg of substrate, achieving very high isolated yields in both enantiopure alcohol and acetate after column chromatography purification.

Table 5. Lipase-catalyzed kinetic resolution of *trans*-**2a-j** (100 mM) by acetylation using AK lipase (1:1 w/w substrate:enzyme) and vinyl acetate (VinOAc) as both acyl donor and solvent at 30 °C and 250 rpm.

Entry	R	t (h)	c (%) [a]	ee_P (%) [b]	ee_S (%) [b]	E [c]
1	H (**a**)	48	50	>99 (48)	>99 (46)	>200
2	2-F (**b**)	72	36	>99	57	>200
3	3-F (**c**)	48	50	>99	99	>200
4	4-F (**d**)	72	49	>99	97	>200
5	4-Cl (**e**)	48	50	>99	>99	>200
6	4-Br (**f**)	48	50	>99	>99	>200
7	2-OMe (**g**)	72	33	>99	50	>200
8	3-OMe (**h**)	72	47	>99	90	>200
9	4-OMe (**i**)	48	50	>99	>99	>200
10	4-Me (**j**)	48	50	>99	99	>200

[a] Conversion values were calculated as $c = ee_S/(ee_S + ee_P)$; [b] Enantiomeric excess values were determined by HPLC analysis. Isolated yields appear in parentheses for the semi-preparative reaction carried out with 250 mg of substrate *trans*-**2a**; [c] Enantiomeric ratio values were calculated: $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.

3. Materials and Methods

Chemical reagents were purchased from Sigma-Aldrich (Steinheim, Germany), VWR International (Barcelona, Spain), and Thermo Fisher Scientific (Waltham, MA, USA) and used as received, except tetrahydrofuran, which was dried under an inert atmosphere using the sodium-benzophenone system. Regarding the enzymes employed in this contribution, *Pseudomonas cepacia* (PSL, 23,000 U/g), lyophilized lipase AK from *Pseudomonas fluorescens* (AK, 23,700 U/g), and Acylase from *Aspergillus melleus* (>0.5 U/g) were also purchased from Sigma-Aldrich (Steinheim, Germany), *Candida antarctica* type A lipase (CAL-A) was obtained from ChiralVision (3000 U/g, Den Hoorn, Netherlands), while *Candida antartica* type B lipase (CAL-B, Novozym-435, 7300 PLU/g) and *Rhizomucor miehei* lipase (RML, 150 IUN/g) were kindly donated by Novozymes company (Bagsværd, Denmark).

NMR spectra were recorded on a Bruker AV300 MHz spectrometer (Bruker Co., Faellanden, Switzerland) including ^{1}H, ^{13}C, and ^{19}F NMR monodimensional experiments. All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. High performance liquid chromatography (HPLC) analyses were performed on an HP 1100 chromatograph (Agilent Technologies, Inc., Wilmington, DE, USA) equipped with a VIS–UV detector using different chiral columns (25 cm × 4.6 mm, 5 µm particle size, Chiral Technologies, Mainz, Germany) for the measurement of the corresponding alcohol and ester enantiomeric excess values. HPLC injections were made using a 0.8 mL/min flow, mixtures of hexane and 2-propanol as eluent, 30 °C column temperature, and 210 and 214 nm as wavelengths (see chromatograms in the Supplementary Material section). Measurement of the op-tical rotation values was carried out at 590 nm on an Autopol IV Automatic polarime-ter (Rudolph Research Analytical, Hackettstown, NJ, USA).

Melting points were measured in a Gallenkamp apparatus, introducing the samples in open capillary tubes and the measurements are uncorrected. IR spectra were recorded on a Jasco FT/IR-4700 spectrophotometer (Jasco-Spain, Madrid, Spain), and νmax values are given in cm^{-1} for the main absorption bands. High resolution mass spectra (HRMS) experiments were carried out by electrospray ionization in positive mode (ESI+) using a VG AutoSpecQ high-resolution mass spectrometer (Fision Instrument, Mildford, MA, USA). Thin-layer chromatography (TLC) was conducted with Merck Silica Gel 60 F254 precoated plates (Merck KGaA, Darmstadt, Germany) and visualized with a UV lamp, plus either potassium permanganate or vanillin stains. Column chromatographies were performed using silica gel 60 (230–240 mesh) (Merck KGaA, Darmstadt, Germany).

3.1. Synthesis of Flavanones **1a–j**

An aqueous solution of KOH (4.9 g, 122.4 mmol in 12 mL of water) was carefully added to a solution of 2′-hydroxyacetophenone (**4**, 2.0 g, 14.7 mmol) in ethanol (30 mL), a yellow precipitate usually being formed. The mixture was stirred for 5–10 min. After this time, the corresponding benzaldehyde **5a**–**j** (14.7 mmol) dissolved in ethanol (7 mL) was added, observing that the color of the solution turned from yellow to intense red. The reaction was stirred for 3 h at 60 °C, and at this point, the reaction was quenched by pouring it onto ice. The reaction mixture was acidified to pH = 2 with an aqueous concentrated HCl solution, and the desired 2′-hydroxychalcone was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. A solution of the recovered crude 2′-hydroxychalcone 6a–j was dissolved in glacial acetic acid (7 mL for each mmol of crude chalcone) was refluxed for 72 h. After this time, the reaction was quenched by pouring it on water (10 mL for each mmol of crude chalcone), observing a brown precipitate of the corresponding flavanone **1a**–**j**, which was extracted with dichloromethane (3 × 30 mL). The organic phases were combined, washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Since some acetic acid remained in the round-bottom flask, toluene (3 × 10 mL) was added to co-evaporate the remaining AcOH. The final product was purified by column chromatography on silica gel using hexane:EtOAc 5:1 as eluent (36–47% isolated yield, Table 2).

2-Phenylchroman-4-one (**1a**). White solid. Mp: 77–78 °C. R_f (hexane:EtOAc 5:1): 0.45. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.94 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.58–7.33 (m, 6H), 7.12–7.01 (m, 2H), 5.49 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.10 (dd, *J* = 16.9, 13.2 Hz, 1H), 2.90 (dd, *J* = 16.9, 3.0 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 192.09, 161.69, 138.87, 136.33, 128.98 (2C), 128.91, 127.18, 126.28 (2C), 121.75, 121.07, 118.26, 79.73, 44.80 ppm. Data are in agreement with those from the commercial source.

2-(2-Fluorophenyl)chroman-4-one (**1b**). Yellow liquid. R_f (hexane:EtOAc 5:1): 0.49. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.78 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.69–7.63 (m, 1H), 7.53 (ddd, *J* = 10.0, 4.9, 1.9 Hz, 1H), 7.42–7.37 (m, 1H), 7.30–7.18 (m, 3H), 5.93 (dd, *J* = 13.1, 3.2 Hz, 1H), 3.21 (dd, *J* = 16.9, 13.1 Hz, 1H), 3.07 (dd, *J* = 16.9, 3.2 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 191.68, 161.63, 159.73 (d, *J* = 247.7 Hz), 136.31, 130.37 (d, *J* = 8.6 Hz), 127.58 (d, *J* = 3.5 Hz), 127.26, 126.30 (d, *J* = 12.8 Hz), 124.73 (d, *J* = 3.5 Hz), 121.92, 121.05, 118.20, 115.87 (d, *J* = 21.3 Hz), 73.98 (d, *J* = 3.1 Hz), 43.83 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –118.33 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{15}H_{12}FO_2$: 243.0821; found 243.0813.

2-(3-Fluorophenyl)chroman-4-one (**1c**). Colourless oil. R_f (hexane:EtOAc 5:1): 0.45. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.94 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.53 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.47–7.34 (m, 1H), 7.30–7.19 (m, 2H), 7.15–7.02 (m, 3H), 5.49 (dd, *J* = 12.9, 3.3 Hz, 1H), 3.05 (dd, *J* = 16.9, 12.9 Hz, 1H), 2.91 (dd, *J* = 16.9, 3.3 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 191.55, 163.12 (d, *J* = 246.9 Hz), 161.37, 141.42 (d, *J* = 7.3 Hz), 136.45, 130.61 (d, *J* = 8.2 Hz), 127.22, 121.98, 121.73 (d, *J* = 3.0 Hz), 121.04, 118.23, 115.75 (d, *J* = 21.2 Hz), 113.34 (d, *J* = 22.7 Hz), 78.88, 44.77 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –111.80 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{15}H_{12}FO_2$: 243.0821; found, 243.0817.

2-(4-Fluorophenyl)chroman-4-one (**1d**). Yellow solid. Mp: 97–99 °C. R_f (hexane:EtOAc 5:1): 0.41. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.93 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.59–7.41 (m, 3H), 7.19–6.99 (m, 4H), 5.47 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.06 (dd, *J* = 16.9, 13.1 Hz, 1H), 2.87 (dd, *J* = 16.8, 3.0 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 191.80, 162.94 (d, *J* = 247.6 Hz), 161.50, 136.39, 134.73 (d, *J* = 3.2 Hz), 128.16 (d, *J* = 8.3 Hz, 2C), 127.20, 121.88, 121.01, 118.20, 115.92 (d, *J* = 21.7 Hz, 2C), 79.04, 44.78 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –112.79 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{15}H_{12}FO_2$: 243.0821; found, 243.0816.

2-(4-Chlorophenyl)chroman-4-one (**1e**). Pale yellow solid. Mp: 87–89 °C. R_f (hexane:EtOAc 5:1): 0.46. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.93 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.52 (ddd, *J* = 9.0, 7.6, 1.8 Hz, 1H), 7.48–7.34 (m, 4H), 7.12–7.01 (m, 2H), 5.47 (dd, *J* = 13.0, 3.1 Hz, 1H), 3.04 (dd, *J* = 16.9, 13.0 Hz, 1H), 2.88 (dd, *J* = 16.9, 3.2 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 191.64, 161.41, 137.38, 136.42, 134.70, 129.17 (2C), 127.63 (2C), 127.21, 121.94, 121.01,

118.21, 78.94, 44.72 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{15}H_{12}ClO_2$: 259.0526; found, 259.0511.

2-(4-Bromophenyl)chroman-4-one (**1f**). Pale yellow solid. Mp: 114–117 °C. R_f (hexane:EtOAc 5:1): 0.53. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.93 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.65–7.46 (m, 3H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.13–7.01 (m, 2H), 5.45 (dd, *J* = 12.9, 3.1 Hz, 1H), 3.04 (dd, *J* = 16.9, 13.0 Hz, 1H), 2.88 (dd, *J* = 16.9, 3.2 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 191.59, 161.40, 137.92, 136.43, 132.14 (2C), 127.93 (2C), 127.22, 122.84, 121.96, 121.02, 118.22, 78.98, 44.70 ppm. ESI-TOF-HRMS: $[M + Na]^+$ calcd. for $C_{15}H_{11}BrO_2Na$: 324.9835; found, 324.9833.

2-(2-Methoxyphenyl)chroman-4-one (**1g**). Viscous yellow solid. R_f (hexane:EtOAc 5:1): 0.39. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.95 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.50 (ddd, *J* = 8.6, 5.5, 1.8 Hz, 1H), 7.46–7.29 (m, 1H), 7.12–7.04 (m, 3H), 6.92 (dd, *J* = 8.4, 1.1 Hz, 1H), 5.86 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.83 (s, 3H), 3.05–2.83 (m, 2H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 192.75, 162.10, 155.83, 136.05, 129.47, 127.55, 127.12, 126.47, 121.46, 121.09, 120.95, 118.20, 110.57, 74.73, 55.41, 43.78 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{16}H_{15}O_3$: 255.1021; found, 255.1016.

2-(3-Methoxyphenyl)chroman-4-one (**1h**). Yellow solid. Mp: 80–83 °C. R_f (hexane:EtOAc 5:1): 0.41. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.93 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.10–7.01 (m, 4H), 6.92 (ddd, *J* = 8.3, 2.5, 1.0 Hz, 1H), 5.45 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.84 (s, 3H), 3.08 (dd, *J* = 16.9, 13.2 Hz, 1H), 2.89 (dd, *J* = 16.9, 3.1 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 192.01, 161.59, 160.03, 140.40, 136.30, 130.05, 127.14, 121.74, 121.02, 118.41, 118.24, 114.17, 111.97, 79.57, 55.41, 44.81 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{16}H_{15}O_3$: 255.1021; found, 255.1010.

2-(4-Methoxyphenyl)chroman-4-one (**1i**). Yellow solid. Mp: 92–95 °C. R_f (hexane:EtOAc 5:1): 0.30. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.93 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.54–7.45 (m, 1H), 7.43 (s, 1H), 7.40 (s, 1H), 7.11–7.00 (m, 2H), 7.00–6.88 (m, 2H), 5.43 (dd, *J* = 13.3, 2.9 Hz, 1H), 3.83 (s, 3H), 3.11 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.86 (dd, *J* = 16.9, 2.9 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 192.36, 161.77, 160.10, 136.28, 130.89, 127.86 (2C), 127.16, 121.65, 121.04, 118.26, 114.33 (2C), 79.48, 55.49, 44.59 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{16}H_{15}O_3$: 255.1021; found, 255.1010.

2-(4-Methylphenyl)chroman-4-one (**1j**). Yellow solid. Mp: 80–82 °C. R_f (hexane:EtOAc 5:1): 0.36. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.94 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.50 (ddd, *J* = 8.8, 7.3, 1.8 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.09–6.99 (m, 2H), 5.44 (dd, *J* = 13.3, 2.9 Hz, 1H), 3.09 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.87 (dd, *J* = 16.9, 3.0 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 192.19, 161.69, 138.75, 136.21, 135.83, 129.56 (2C), 127.09, 126.27 (2C), 121.59, 120.99, 118.21, 79.58, 44.61, 21.28 ppm. ESI-TOF-HRMS: $[M + H]^+$ calcd. for $C_{16}H_{15}O_2$: 237.0916; found, 237.0903.

3.2. Synthesis of Racemic cis-Flavanols **2a–j**

A solution of the corresponding flavanone **1a–j** (4.5 mmol) in dry THF (15 mL) was cooled to −78 °C under a nitrogen atmosphere. Next, a 1.0 M solution of $LiAlH_4$ in THF was added dropwise (1.25 mL, 1.25 mmol), and the mixture was stirred at –78 °C. Monitorization of the reaction was undertaken by TLC analyses (hexane:EtOAc 3:1), observing the complete consumption of the starting material after 12 h. After this time, the reaction was quenched by pouring it onto icy water and, when warmed, the product was extracted with dichloromethane (3 × 20 mL). The organic phases were combined, washed with brine (3 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The reaction crudes were purified by column chromatography on silica gel, using a gradient 5:1 to 3:1 hexane:EtOAc as eluent, obtaining the corresponding *cis*-flavan-4-ols **2a–j** with total control of the selectivity (90–96% isolated yield, Table 2).

(2*S**,4*S**)-2-Phenylchroman-4-ol (*cis*-**2a**)**.** White solid. R_f (hexane:EtOAc 3:1): 0.26. Mp: 98–100 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.53 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.50–7.30 (m, 5H), 7.29–7.16 (m, 1H), 7.00 (td, *J* = 7.5, 1.3 Hz, 1H), 6.91 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.18 (dd, *J* = 11.7, 2.0 Hz, 1H), 5.10 (dd, *J* = 10.5, 6.2 Hz, 1H), 2.52 (ddd, *J* = 13.1, 6.3, 2.0 Hz, 1H), 2.14

(ddd, *J* = 13.2, 11.6, 10.4 Hz, 1H), 1.83 (s, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 154.61, 140.62, 129.32, 128.81 (2C), 128.37, 127.11, 126.22 (2C), 125.86, 121.12, 116.88, 76.98, 65.95, 40.18 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{13}O$: 209.0966; found 209.0959.

(2*S**,4*S**)-2-(2-Fluorophenyl)chroman-4-ol (*cis*-**2b**). Pale brown solid. Mp: 100–102 °C. R_f (hexane:EtOAc 3:1): 0.30. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.66–7.47 (m, 2H), 7.41–6.77 (m, 6H), 5.59–5.46 (m, 1H), 5.13 (dd, *J* = 10.5, 6.2 Hz, 1H), 2.56 (ddd, *J* = 13.1, 6.2, 1.8 Hz, 1H), 2.12 (dt, *J* = 12.9, 11.1 Hz, 1H), 1.83 (s, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 159.71 (d, *J* = 246.7 Hz), 154.43, 129.67 (d, *J* = 8.3 Hz), 129.31, 128.00 (d, *J* = 12.8 Hz), 127.45 (d, *J* = 3.7 Hz), 127.15, 125.82, 124.60 (d, *J* = 3.3 Hz), 121.26, 116.82, 115.59 (d, *J* = 21.4 Hz), 70.92 (d, *J* = 3.2 Hz), 65.71, 39.03 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –119.38 ppm. ESI-TOF-HRMS: [M-OH]+ calcd. for $C_{15}H_{12}FO$: 227.0872; found 227.0860.

(2*S**,4*S**)-2-(3-Fluorophenyl)chroman-4-ol (*cis*-**2c**). White solid. Mp: 107–113 °C. R_f (hexane:EtOAc 3:1): 0.31. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.56 (d, *J* = 7.7 Hz, 1H), 7.42 (td, *J* = 8.0, 5.8 Hz, 1H), 7.34–7.19 (m, 3H), 7.15–7.00 (m, 2H), 6.96 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.22 (dd, *J* = 11.6, 1.7 Hz, 1H), 5.14 (dd, *J* = 10.5, 6.2 Hz, 1H), 2.56 (ddd, *J* = 13.1, 6.2, 2.0 Hz, 1H), 2.13 (ddd, *J* = 13.1, 11.6, 10.5 Hz, 1H), 1.93 (s, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 163.10 (d, *J* = 246.2 Hz), 154.26, 143.23 (d, *J* = 7.3 Hz), 130.34 (d, *J* = 8.2 Hz), 129.41, 127.10, 125.74, 121.69 (d, *J* = 2.8 Hz), 121.32, 116.85, 115.16 (d, *J* = 21.2 Hz), 113.21 (d, *J* = 22.4 Hz), 76.19, 65.76, 40.18 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –112.41 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{12}FO$: 227.0872; found 227.0868.

(2*S**,4*S**)-2-(4-Fluorophenyl)chroman-4-ol (*cis*-**2d**). White solid. Mp: 129–131 °C. R_f (hexane:EtOAc 3:1): 0.27. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.57 (d, *J* = 7.7 Hz, 1H), 7.52–7.39 (m, 2H), 7.33–7.21 (m, 1H), 7.20–7.09 (m, 2H), 7.04 (td, *J* = 7.5, 1.1 Hz, 1H), 6.93 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.20 (dd, *J* = 11.7, 1.6 Hz, 1H), 5.12 (d, *J* = 6.5 Hz, 1H), 2.54 (ddd, *J* = 13.1, 6.3, 1.9 Hz, 1H), 2.15 (ddd, *J* = 13.1, 11.7, 10.6 Hz, 1H), 1.92 (d, *J* = 7.2 Hz, 1H) ppm, 1.66 (s, OH). ^{13}C NMR δ (75 MHz, $CDCl_3$): 162.68 (d, *J* = 246.6 Hz), 154.46, 136.45, 129.38, 128.00 (d, *J* = 8.2 Hz, 2C), 127.08, 125.77, 121.26, 116.84, 115.69 (d, *J* = 21.5 Hz, 2C), 76.36, 65.90, 40.26 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –113.86 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{12}FO$: 227.0872; found 227.0862.

(2*S**,4*S**)-2-(4-Chlorophenyl)chroman-4-ol (*cis*-**4e**). White solid. Mp: 158–160 °C. R_f (hexane:EtOAc 3:1): 0.26. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.39 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.26 (s, 3H), 7.18–6.99 (m, 2H), 6.88 (td, *J* = 7.5, 1.3 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.08–4.90 (m, 2H), 2.36 (ddd, *J* = 13.1, 6.3, 2.0 Hz, 1H), 1.96 (ddd, *J* = 13.1, 11.7, 10.5 Hz, 1H), 1.79 (d, *J* = 8.5 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 154.36, 139.17, 134.07, 129.40, 128.96 (2C), 127.59 (2C), 127.10, 125.74, 121.31, 116.84, 76.26, 65.80, 40.17 ppm. ESI-TOF-HRMS: $[M + Na]^+$ calcd. for $C_{15}H_{13}ClO_2Na$: 283.0496; found 283.0496.

(2*S**,4*S**)-2-(4-Bromophenyl)chroman-4-ol (*cis*-**2f**). White solid. Mp: 160–162 °C. R_f (hexane:EtOAc 3:1): 0.34. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.50–7.38 (m, 3H), 7.24 (d, *J* = 6.4 Hz, 1H), 7.19–7.09 (m, 1H), 6.92 (td, *J* = 7.5, 1.3 Hz, 1H), 6.81 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.11–4.95 (m, 2H), 2.41 (ddd, *J* = 13.1, 6.3, 2.0 Hz, 1H), 2.00 (ddd, *J* = 13.2, 11.6, 10.5 Hz, 1H), 1.74 (d, *J* = 8.3 Hz, 1H) ppm.^{13}C NMR δ (75 MHz, $CDCl_3$): 154.33, 139.70, 131.92 (2C), 129.42, 127.90 (2C), 127.09, 125.73, 122.18, 121.32, 116.85, 76.29, 65.80, 40.17 ppm. ESI-TOF-HRMS: $[M + Na]^+$ calcd. for $C_{15}H_{13}BrO_2Na$: 326.9991; found 326.9988.

(2*S**,4*S**)-2-(2-Methoxyphenyl)chroman-4-ol (*cis*-**2g**). White solid. Mp: 132–137 °C. R_f (hexane:EtOAc 3:1): 0.24. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.66–7.59 (m, 1H), 7.58–7.44 (m, 1H), 7.43–7.30 (m, 1H), 7.29–7.20 (m, 1H), 7.12–6.86 (m, 4H), 5.63 (dd, *J* = 11.3, 1.9 Hz, 1H), 5.15 (t, *J* = 6.0 Hz, 1H), 3.90 (d, *J* = 4.8 Hz, 3H), 2.63 (ddd, *J* = 13.0, 6.2, 2.0 Hz, 1H), 2.09 (s, OH), 2.08–2.00 (m, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 155.96, 154.91, 129.21, 129.11, 128.96, 127.15, 126.43, 126.11, 120.96, 120.84, 116.81, 110.55, 71.52, 66.00, 55.50, 38.76 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O_2$: 239.1072; found 239.1069.

(2*S**,4*S**)-2-(3-Methoxyphenyl)chroman-4-ol (*cis*-**2h**). Pale brown solid. Mp: 146–150 °C. R_f (hexane:EtOAc 3:1): 0.24. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.54 (d, *J* = 7.7 Hz, 1H), 7.40–7.19 (m, 2H), 7.08–6.97 (m, 3H), 6.96–6.85 (m, 2H), 5.18 (dd, *J* = 11.5, 1.7 Hz, 1H), 5.15–5.06 (m, 1H), 3.85 (s, 3H), 2.55 (ddd, *J* = 13.1, 6.2, 2.0 Hz, 1H), 2.16 (ddd, *J* = 13.1, 11.5, 10.5 Hz, 1H),

1.80 (d, *J* = 8.6 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 160.00, 154.47, 142.24, 129.88, 129.35, 127.12, 125.85, 121.15, 118.49, 116.90, 113.78, 111.86, 76.85, 65.95, 55.43, 40.22 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O_2$: 239.1072; found 239.1066.

(2*S**,4*S**)-2-(4-Methoxyphenyl)chroman-4-ol (*cis*-**2i**). White solid. Mp: 99–100 °C. R_f (hexane:EtOAc 3:1): 0.27. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.52 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.43–7.32 (m, 2H), 7.29–7.11 (m, 1H), 7.04–6.82 (m, 4H), 5.18–5.02 (m, 2H), 3.83 (s, 3H), 2.49 (ddd, *J* = 13.1, 6.3, 1.9 Hz, 1H), 2.15 (ddd, *J* = 13.1, 11.7, 10.5 Hz, 1H), 1.89 (d, *J* = 8.0 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 159.69, 154.71, 132.69, 129.28, 127.68 (2C), 127.09, 125.85, 121.04, 116.86, 114.18 (2C), 76.69, 66.04, 55.47, 39.98 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O_2$: 239.1072; found 239.1065.

(2*S**,4*S**)-2-(4-Methylphenyl)chroman-4-ol (*cis*-**2j**). White solid. Mp: 106–108 °C. R_f (hexane:EtOAc 3:1): 0.42. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.45 (d, *J* = 7.7 Hz, 1H), 7.29 (s, 1H), 7.22–7.08 (m, 4H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.05–4.96 (m, 1H), 5.02 (d, *J* = 6.6 Hz, 1H), 2.43 (ddd, *J* = 13.1, 6.3, 1.9 Hz, 1H), 2.31 (s, 3H), 2.08 (ddd, *J* = 13.1, 11.6, 10.6 Hz, 1H), 1.77 (d, *J* = 8.6 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 154.69, 138.18, 137.61, 129.47 (2C), 129.28, 127.10, 126.23 (2C), 125.86, 121.03, 116.89, 76.87, 66.01, 40.08, 21.33 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O$: 223.1123; found 223.1114.

3.3. Synthesis of Racemic trans-Flavanols **2a–j**

The corresponding *cis*-flavan-4-ol **2a–j** (200–500 mg, 0.88–2.05 mmol) was dissolved in dry THF (15 mL per mmol of *cis*-flavan-4-ol) under nitrogen atmosphere, successively adding triphenylphosphine (two equivalents) and PTSA (two equivalents, Method A) or chloroacetic acid (two equivalents, 2.0 mmol, Method B). Next, DEAD (two equivalents, Method A) or DIAD (two equivalents, 2.0 mmol, Method B) was introduced in the Schlenk tube, and the mixture was stirred at room temperature. Monitorization of the reaction was undertaken by TLC analyses (hexane:EtOAc 3:1), observing the complete consumption of the starting material after 1 h. After this time, the reaction was stopped by removal of the solvent under reduced pressure. The residue was then hydrolyzed by treatment with a mixture of an aqueous saturated Na_2CO_3 solution (10 mL per mmol of starting *cis*-flavan-4-ol), methanol (10 mL per mmol of starting *cis*-flavan-4-ol), and THF (15 mL per mmol of starting *cis*-flavan-4-ol) for 1 h at room temperature. The desired *trans*-flavan-4-ol *trans*-**2a–j** was extracted from the mixture with dichloromethane (3 × 30 mL). The organic phases were combined, washed with brine (3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The reaction crudes were purified by column chromatography on silica gel using an eluent gradient of hexane:EtOAc 5:1 to 3:1 (74–88% isolated yield, Table 2), obtaining the racemic *trans*-**2a–j** as major diastereoisomer.

(2*S**,4*R**)-2-Phenylchroman-4-ol (*trans*-**2a**)**.** White solid. Mp: 116–118 °C. R_f (hexane:EtOAc 3:1): 0.34. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.56–7.30 (m, 7H), 7.05–6.98 (m, 2H), 5.33 (dd, *J* = 11.9, 2.2 Hz, 1H), 4.88 (t, *J* = 3.2 Hz, 1H), 2.32 (dt, *J* = 14.4, 2.4 Hz, 1H), 2.23–2.13 (m, 2H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 154.99, 141.05, 130.13, 128.79, 128.71 (2C), 128.17, 126.38 (2C), 123.57, 120.95, 117.61, 73.18, 63.96, 38.36 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{13}O$: 209.0966; found 209.0958.

(2*S**,4*R**)-2-(2-Fluorophenyl)chroman-4-ol (*trans*-**2b**). White solid. Mp: 86–88 °C. Rf R_f (hexane:EtOAc 3:1): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.60 (m, 1H), 7.38–7.32 (m, 2H), 7.29–7.22 (m, 2H), 7.17–7.10 (m, 1H), 7.03–6.98 (m, 2H), 5.64 (dd, *J* = 11.8 Hz, *J* = 2.1 Hz, 1H), 4.82 (t, *J* = 2.9 Hz, 1H), 2.73 (brs, 1H), 2.32 (dt, *J* = 14.3 Hz, *J* = 2.3 Hz, 1H), 2.22–2.10 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9 (d, *J* = 274.4 Hz), 154.71, 130.11 (d, *J* = 20.4Hz), 129.51 (d, *J* = 8.2 Hz), 128.19 (d, *J* = 12.6 Hz), 127.84 (d, *J* = 3.9 Hz), 124.42, 124.38, 123.44, 120.97, 117.38, 115.56 (d, *J* = 21.4 Hz), 67.47 (d, *J* = 3.0 Hz, 63.6, 37.1), 37.05. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{12}FO$: 227.0872; found 227.0866.

(2*S**,4*R**)-2-(3-Fluorophenyl)chroman-4-ol (*trans*-**2c**). Pale yellow solid. Mp: 111–113 °C. R_f (hexane:EtOAc 3:1): 0.32. ^{1}H NMR δ (300 MHz, $CDCl_3$): δ 7.48–7.17 (m, 5H), 7.12–6.91 (m, 3H), 5.39 (dd, *J* = 12.1 Hz, *J* = 2.2 Hz, 1H), 4.85 (t, *J* = 2.8 Hz, 1H), 2.42 (bs,

1H), 2.29 (dt, *J* = 14.2 Hz, *J* = 2.3 Hz, 1H), 2.11 (dd, *J* = 12.0 Hz, *J* = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.99 (d, *J* = 245.7 Hz), 154.55, 143.61 (d, *J* = 7.4 Hz), 130.13, 130.07, 123.38 (d, *J* = 3.0 Hz), 121.04, 117.47, 114.84 (d, *J* = 21.1 Hz), 72.36, 63.69, 38.24. ^{19}F NMR δ (282 MHz, $CDCl_3$): –112.66 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{12}FO$: 227.0872; found 227.0868.

(2*S**,4*R**)-2-(4- Fluorophenyl)chroman-4-ol (*trans*-**2d**). White solid. Mp: 105–107 °C. R_f (hexane:EtOAc 3:1): 0.30. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.51–7.38 (m, 2H), 7.34 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.30–7.23 (m, 1H), 7.14–7.05 (m, 2H), 7.02–6.92 (m, 2H), 5.27 (dd, *J* = 12.0, 2.3 Hz, 1H), 4.85 (c, *J* = 3.0 Hz, 1H), 2.26 (dt, *J* = 14.4, 2.4 Hz, 1H), 2.13–2.01 (m, 2H) ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –114.27 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{12}FO$: 227.0872; found 227.0863.

(2*S**,4*R**)-2-(4-Chlorophenyl)chroman-4-ol (*trans*-**2e**). Pale yellow solid. Mp: 106–108 °C. R_f (hexane:EtOAc 3:1): 0.29. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.50–7.40 (m, 4H), 7.39–7.28 (m, 2H), 7.10–6.89 (m, 2H), 5.30 (dd, *J* = 12.0, 2.1 Hz, 1H), 4.87 (t, *J* = 2.8 Hz, 1H), 2.29 (dt, *J* = 14.3, 2.4 Hz, 1H), 2.17–2.02 (m, 2H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 154.74, 139.62, 133.85, 130.20, 130.11, 128.86 (2C), 127.73 (2C), 123.48, 121.11, 117.55, 72.48, 63.80, 38.33 ppm. ESI-TOF-HRMS: $[M + Na]^+$ calcd. for $C_{15}H_{13}ClO_2Na$: 283.0496; found 283.0495.

(2*S**,4*R**)-2-(4-Bromophenyl)chroman-4-ol (*trans*-**2f**). White solid. Mp: 117–119 °C. R_f (hexane:EtOAc 3:1): 0.30. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.51–7.42 (m, 2H), 7.33–7.02 (m, 4H), 6.95–6.85 (m, 2H), 5.16 (dd, *J* = 12.0, 2.2 Hz, 1H), 4.75 (dt, *J* = 4.1, 2.3 Hz, 1H), 2.16 (dt, *J* = 14.3, 2.4 Hz, 1H), 2.11–2.01 (m, 1H), 2.03–1.86 (m, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 154.72, 140.15, 131.82 (2C), 130.23, 130.10, 128.06 (2C), 123.48, 121.98, 121.14, 117.56, 72.52, 63.80, 38.30 ppm. ESI-TOF-HRMS: $[M + Na]^+$ calcd. for $C_{15}H_{13}BrO_2Na$: 326.9991; found 326.991.

(2*S**,4*R**)-2-(2-Methoxyphenyl)chroman-4-ol (*trans*-**2g**). White solid. Mp: 96–100 °C. R_f (hexane:EtOAc 3:1): 0.16. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.72–7.43 (m, 2H), 7.36–7.16 (m, 2H), 7.10–6.84 (m, 4H), 5.58 (d, *J* = 10.9 Hz, 1H), 5.10 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.86 (s, 3H), 2.64–2.52 (m, 1H), 2.04–1.91 (m, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 156.23, 155.30, 130.19, 129.95, 129.48, 128.91, 126.90, 123.89, 120.90, 120.75, 117.58, 110.63, 67.93, 64.24, 55.60, 37.05 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O_2$: 239.1072; found 239.1069.

(2*S**,4*R**)-2-(3-Methoxyphenyl)chroman-4-ol (*trans*-**2h**). White solid. Mp: 105–109 °C. R_f (hexane:EtOAc 3:1): 0.30. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.47–7.20 (m, 3H), 7.16–6.98 (m, 4H), 6.94 (dd, *J* = 7.2, 2.2 Hz, 1H), 5.38–5.26 (m, 1H), 4.89 (t, J = 3.0 Hz, 1H), 3.89 (s, 3H), 2.56 (dd, J = 10.9, 6.1 Hz, 1H), 2.33 (dt, J = 14.3, 2.1 Hz, 1H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 159.87, 154.88, 130.15, 130.02, 129.72, 129.16, 127.10, 123.61, 120.88, 118.61, 117.53, 111.89, 70.15, 63.82, 55.36, 38.42 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O_2$: 239.1072; found 239.1061.

(2*S**,4*R**)-2-(4-Methoxyphenyl)chroman-4-ol (*trans*-**2i**). White solid. Mp: 128–130 °C. R_f (hexane:EtOAc 3:1): 0.21. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.49–7.41 (m, 2H), 7.36 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.35–7.26 (m, 1H), 7.07–6.94 (m, 4H), 5.26 (dd, *J* = 11.7, 2.6 Hz, 1H), 4.91–4.82 (m, 1H), 3.86 (s, 3H), 2.27 (dt, *J* = 14.3, 2.6 Hz, 1H), 2.22–2.14 (m, 2H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 159.58, 155.12, 133.12, 130.15, 130.08, 127.82 (2C), 123.57, 120.86, 117.60, 114.12 (2C), 72.86, 64.07, 55.45, 38.09 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O_2$: 239.1072; found 239.1062.

(2*S**,4*R**)-2-(4-Methylphenyl)chroman-4-ol (*trans*-**2j**). White solid. Mp: 103–106 °C. R_f (hexane:EtOAc 3:1): 0.27. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.50–7.40 (m, 3H), 7.32 (t, *J* = 6.8 Hz, 3H), 7.08–7.02 (m, 2H), 5.33 (dd, *J* = 11.8, 2.3 Hz, 1H), 4.92 (t, *J* = 3.2 Hz, 1H), 2.46 (s, 3H), 2.34 (dt, *J* = 14.4, 2.5 Hz, 1H), 2.26–2.14 (m, 2H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 155.10, 138.05, 137.95, 130.10, 129.39 (2C), 126.40 (2C), 126.23, 123.59, 120.87, 117.62, 73.07, 64.03, 38.23, 21.31 ppm. ESI-TOF-HRMS: $[M\text{-}OH]^+$ calcd. for $C_{15}H_{15}O$: 223.1123; found 223.1114.

3.4. Synthesis of trans-Flavanol Acetate **3a**

Acetic anhydride (80 μL, 0.72 mmol), triethylamine (100 μL, 0.71 mmol), and catalytic DMAP (10 mg, 0.08 mmol) were added to a solution of racemic *trans*-flavan-4-ol **2a** (50 mg, 0.24 mmol) in dichloromethane (6 mL). After stirring for 2 h at room temperature, the reaction mixture was quenched by pouring it on ice-cooled water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting reaction crude was purified via column chromatography on silica gel using hexane:EtOAc 5:1 as eluent, obtaining racemic *trans*-flavan-4-ol acetate **3a** (51.6 mg, 87%). Chemical acetylations of racemic *trans*-flavan-4-ols **2b–j** were performed in a similar manner using fractions of the Mitsunobu–deprotection column chromatographies and used only for the development of chiral HPLC methods of the so-obtained *trans*-flavanol acetates **3b–j**.

(2*S**,4*R**)-2-Phenylchroman-4-ol acetate (*trans*-**3a**)**.** White solid. Mp: 84–87 °C. R_f (hexane:EtOAc 5:1): 0.50. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.55–7.35 (m, 7H), 7.04–6.93 (m, 2H), 6.07 (t, *J* = 2.9 Hz, 1H), 5.27 (dd, *J* = 10.5, 3.9 Hz, 1H), 2.34–2.24 (m, 2H), 2.17 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.48, 155.60, 140.48, 131.11, 130.56, 128.75 (2C), 128.38, 126.39 (2C), 120.92, 119.77, 117.47, 73.66, 65.89, 35.98, 21.61 ppm. ESI-TOF-HRMS: $[M\text{-}AcO]^+$ calcd. for $C_{15}H_{13}O$: 209.0966; found 209.0956.

(2*S**,4*R**)-2-(2-Fluorophenyl)chroman-4-ol acetate (*trans*-**3b**). White solid. R_f (hexane:EtOAc 5:1): 0.61. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.51–7.35 (m, 3H), 7.35–7.21 (m, 1H), 7.17–7.03 (m, 2H), 7.03–6.88 (m, 2H), 6.05 (t, *J* = 2.9 Hz, 1H), 5.23 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.35–2.21 (m, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.50, 162.73 (d, *J* = 246.5 Hz), 155.47, 136.33 (d, *J* = 3.0 Hz), 131.15, 130.64, 128.20 (d, *J* = 8.2 Hz. 2C), 121.08, 119.71, 117.43, 115.66 (d, *J* = 21.5 Hz, 2C), 73.06, 65.80, 36.03, 21.60 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –113.81 ppm.

(2*S**,4*R**)-2-(3-Fluorophenyl)chroman-4-ol acetate (*trans*-**3c**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.54. ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.35 (dt, *J* = 8.0, 2.3 Hz, 2H), 7.34–7.21 (m, 1H), 7.19 (td, *J* = 9.0, 2.1 Hz, 3H), 7.00–6.90 (m, 2H), 6.01 (t, *J* = 2.9 Hz, 1H), 5.21 (dd, *J* = 11.7, 2.5 Hz, 1H), 2.34–2.15 (m, 2H), 2.10 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.49, 163.12 (d, *J* = 246.1 Hz), 155.29, 143.16 (d, *J* = 7.2 Hz), 131.13, 130.67, 130.33 (d, *J* = 8.2 Hz), 121.86 (d, *J* = 2.8 Hz), 121.16, 119.72, 117.44, 115.20 (d, *J* = 21.2 Hz), 113.41 (d, *J* = 22.3 Hz), 72.97, 65.67, 36.10, 21.59 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –112.47 ppm.

(2*S**,4*R**)-2-(4-Fluorophenyl)chroman-4-ol acetate (*trans*-**3d**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.61. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.51–7.35 (m, 3H), 7.35–7.21 (m, 1H), 7.17–7.03 (m, 2H), 7.03–6.88 (m, 2H), 6.05 (t, *J* = 2.9 Hz, 1H), 5.23 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.35–2.21 (m, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.50, 162.73 (d, *J* = 246.5 Hz), 155.47, 136.33 (d, *J* = 3.0 Hz), 131.15, 130.64, 128.20 (d, *J* = 8.2 Hz. 2C), 121.08, 119.71, 117.43, 115.66 (d, *J* = 21.5 Hz, 2C), 73.06, 65.80, 36.03, 21.60 ppm. ^{19}F NMR δ (282 MHz, $CDCl_3$): –113.81 ppm.

(2*S**,4*R**)-2-(4-Chlorophenyl)chroman-4-ol acetate (*trans*-**3e**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.51. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.41 (dd, *J* = 8.9, 1.8 Hz, 5H), 7.34–7.21 (m, 1H), 7.04–6.90 (m, 2H), 6.05 (t, *J* = 2.9 Hz, 1H), 5.23 (dt, *J* = 11.4, 3.3 Hz, 1H), 2.36–2.20 (m, 2H), 2.19 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.49, 155.38, 139.09, 134.15, 131.15, 130.67, 128.95 (2C), 127.77 (2C), 121.14, 119.72, 117.44, 73.00, 65.72, 36.06, 21.62 ppm.

(2*S**,4*R**)-2-(4-Bromophenyl)chroman-4-ol acetate (*trans*-**3f**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.51. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.49–7.37 (m, 2H), 7.32–7.08 (m, 4H), 6.93–6.77 (m, 2H), 5.93 (t, *J* = 3.0 Hz, 1H), 5.10 (dd, *J* = 11.4, 3.0 Hz, 1H), 2.23–2.12 (m, 1H), 2.14–2.07 (m, 1H), 2.02 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.49, 155.35, 139.63, 131.91 (2C), 131.15, 130.67, 128.08 (2C), 122.27, 121.15, 119.71, 117.44, 73.03, 65.69, 36.04, 21.62 ppm.

(2*S**,4*R**)-2-(3-Methoxyphenyl)chroman-4-ol acetate (*trans*-**3g**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.52. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.63–7.52 (m, 1H), 7.45–7.17 (m, 3H),

7.14–6.88 (m, 4H), 6.02 (t, *J* = 2.6 Hz, 1H), 5.72–5.63 (m, 1H), 3.87 (s, 3H), 2.43 (dt, *J* = 14.7, 2.0 Hz, 1H), 2.14 (d, *J* = 13.3 Hz, 4H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.62, 156.19, 156.08, 131.07, 130.45, 129.04, 126.66, 120.98, 120.72, 119.99, 117.55, 110.64, 68.58, 66.53, 55.63, 34.56, 21.60 ppm.

(2*S**,4*R**)-2-(3-Methoxyphenyl)chroman-4-ol acetate (*trans*-**3h**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.43. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.03 (s, 4H), 7.01–6.85 (m, 4H), 6.03 (s, 1H), 5.26–5.17 (m, 1H), 2.26 (d, *J* = 9.6 Hz, 1H), 2.17 (s, 1H), 2.12 (s, 3H) ppm.

(2*S**,4*R**)-2-(4-Methoxyphenyl)chroman-4-ol acetate (*trans*-**3i**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.60. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.49–7.38 (m, 3H), 7.36–7.25 (m, 1H), 7.04–6.92 (m, 4H), 6.08 (t, *J* = 3.0 Hz, 1H), 5.31–5.15 (m, 1H), 3.87 (s, 3H), 2.32 (dd, *J* = 3.0, 1.8 Hz, 1H), 2.30 (d, *J* = 3.0 Hz, 1H), 2.17 (d, *J* = 5.1 Hz, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.54, 159.78, 155.77, 132.56, 131.12, 130.54, 127.87, 120.87 (2C), 119.76, 117.49, 114.18 (2C), 72.44, 66.07, 55.48, 35.73, 21.78 ppm.

(2*S**,4*R**)-2-(4-Methylphenyl)chroman-4-ol acetate (*trans*-**3j**)**.** White solid. R_f (hexane:EtOAc 5:1): 0.55. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.45–7.17 (m, 6H), 7.01–6.89 (m, 2H), 6.05 (t, *J* = 2.8 Hz, 1H), 5.22 (dd, *J* = 8.4, 5.9 Hz, 1H), 2.38 (d, *J* = 3.6 Hz, 3H), 2.32–2.22 (m, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR δ (75 MHz, $CDCl_3$): 170.54, 155.73, 138.22, 137.51, 131.11, 130.55, 129.44 (2C), 126.42 (2C), 120.86, 119.78, 117.50, 73.56, 66.00, 35.86, 21.63, 21.31 ppm.

3.5. Screening of Biocatalysts for the Kinetic Resolution of trans-Flavanol **2a** *through an Acetylation Reaction*

Vinyl acetate (VinOAc, 24 μL, 0.26 mmol) was added to a mixture of the corresponding *trans*-flavan-4-ol *trans*-**2a–j** (20.0 mg, 0.0867 mmol), hydrolase (20 mg, 1:1 *w*/*w* enzyme:**2a**), and THF (884 μL) under a nitrogen atmosphere. The mixture was stirred under orbital shaking at 250 rpm at 30 °C for 24 h. After this time, the enzyme was filtered and washed with dichloromethane (3 × 2 mL). The filtrate was concentrated under reduced pressure, and the reaction was crude analyzed by a ^{1}H NMR experiment to corroborate the conversion obtained by chiral HPLC analyses (Table 3). After column chromatography purification using an eluent gradient 5:1 to 3:1 hexane:EtOAc, the pure products were injected on the HPLC to measure the enantiomeric excess of both *trans*-flavanol **2a** and the *trans*-flavanol acetate **3a**. For experiments detailed in Table 4, a similar procedure was developed, selecting lipase AK from *Pseudomonas fluorescens* as the best enzyme and modifying the temperature, acyl donor excess, and loading of catalyst. See HPLC conditions and retention times in Table 6.

3.6. Lipase-Catalyzed Kinetic Resolution of trans-Flavanols **2a–j** *through an Acetylation Reaction*

To a mixture of the corresponding *trans*-flavan-4-ol *trans*-**2a–j** (20.0–30.0 mg, 0.0867–0.121 mmol) and lipase AK from *Pseudomonas fluorescens* (1:1 w/w enzyme:**2a–j**), VinOAc (1 mL per 0.1 mmol of **2a–j**, 109 equivalents) was added. The mixture was stirred under orbital shaking at 250 rpm at 30 °C for three days, taking aliquots after 6, 24, 48, and 72 h. After this time, the enzyme was filtered and washed with dichloromethane (3 × 1 mL). The filtrate was concentrated under reduced pressure, and the reaction crude was analyzed by ^{1}H NMR experiment to corroborate the conversion obtained by chiral HPLC analyses (Table 5). After column chromatography purification using an eluent gradient 5:1 to 3:1 hexane:EtOAc, the pure products were injected on the HPLC to measure the enantiomeric excess of both *trans*-flavanols **2a–j** and *trans*-flavanol acetates **3a–j**. See HPLC conditions and retention times in Table 6.

Table 6. HPLC conditions and specific optical rotation values of optically active compounds [a].

Entry	(±)-Compound	Column	Hexane-2-PrOH (*v*/*v*)	Retention Times (min) [b]	$[\alpha]_D^{20}$ [c]
1	*trans*-**2a** (H)	IA	92:8	10.3 (2*S*,4*R*) and **10.9** (**2*R*,4*S***)	−77.0 (*c* 0.40, EtOH) [d,e]
2	*trans*-**3a** (H)	OJ-H	92:8	**16.6** (**2*S*,4*R***) and 28.1 (2*R*,4*S*)	+6.0 (*c* 0.37, EtOH)
3	*trans*-**2b** (2-F)	OJ-H	92:8	15.3 (2*S*,4*R*) and **19.0** (**2*R*,4*S***)	−88.6 (*c* 0.59, EtOH)
4	*trans*-**3b** (2-F)	AS	92:8	5.3 (2*R*,4*S*) and **5.6** (**2*S*,4*R***)	+3.2 (*c* 0.87, EtOH)
5	*trans*-**2c** (3-F)	IA	92:8	9.9 (2*S*,4*R*) and **10.8** (**2*R*,4*S***)	−89.5 (*c* 0.61, EtOH)
6	*trans*-**2c** (3-F)	OJ-H	92:8	**9.9** (**2*S*,4*R***) and 12.7 (2*R*,4*S*)	−2.5 (*c* 0.41, EtOH)
7	*trans*-**2d** (4-F)	IA	92:8	10.5 (2*S*,4*R*) and **12.3** (**2*R*,4*S***)	−130.0 (*c* 0.32, EtOH)
8	*trans*-**3d** (4-F)	OJ-H	92:8	**13.5** (**2*S*,4*R***) and 16.0 (2*R*,4*S*)	+8.5 (*c* 0.35, EtOH)
9	*trans*-**2e** (4-Cl)	IA	92:8	11.1 (2*S*,4*R*) and **13.1** (**2*R*,4*S***)	−79.6 (*c* 0.42, EtOH)
10	*trans*-**3e** (4-Cl)	AS	92:8	5.7 (2*R*,4*S*) and **6.2** (**2*S*,4*R***)	+5.5 (*c* 0.44, EtOH)
11	*trans*-**2f** (4-Br)	IA	92:8	11.6 (2*S*,4*R*) and **13.8** (**2*R*,4*S***)	−111.0 (*c* 0.35, EtOH)
12	*trans*-**3f** (4-Br)	OD	98:2	8.8 (2*R*,4*S*) and **9.6** (**2*S*,4*R***)	−1.0 (*c* 0.36, EtOH)
13	*trans*-**2g** (2-OMe)	OJ-H	92:8	17.7 (2*S*,4*R*) and **20.0** (**2*R*,4*S***)	−12.8 (*c* 0.18, EtOH)
14	*trans*-**3g** (2-OMe)	OJ-H	92:8	13.4 (2*R*,4*S*) and **14.6** (**2*S*,4*R***)	−3.0 (*c* 0.54, EtOH)
15	*trans*-**2h** (3-OMe)	OJ-H	92:8	26.0 (2*S*,4*R*) and **28.8** (**2*R*,4*S***)	−71.3 (*c* 0.47, EtOH)
16	*trans*-**3h** (3-OMe)	OJ-H	92:8	**16.6** (**2*S*,4*R***) and 23.2 (2*R*,4*S*)	+2.13 (*c* 0.38, EtOH)
17	*trans*-**2i** (4-OMe)	IA	92:8	15.0 (2*S*,4*R*) and **16.6** (**2*R*,4*S***)	−132.0 (*c* 0.38, EtOH)
18	*trans*-**3i** (4-OMe)	IB	92:8	**6.5** (**2*S*,4*R***) and 6.8 (2*R*,4*S*)	+18.7 (*c* 0.52, EtOH)
19	*trans*-**2j** (4-Me)	IA	92:8	10.4 (2*S*,4*R*) and **11.4** (**2*R*,4*S***)	−232.0 (*c* 0.46, EtOH)
20	*trans*-**3j** (4-Me)	OD	98:2	**7.1** (**2*S*,4*R***) and 7.9 (2*R*,4*S*)	+8.9 (*c* 0.64, EtOH)

[a] The temperature column was 30 °C and the flow 0.8 mL/min. Analyses were performed at 210 and 214 nm wavelengths; [b] Major enantiomer of the enzymatic reactions appear in bold font; [c] The specific optical rotation value of the major enantiomer in the lipase-catalyzed kinetic resolution is given; [d] Specific optical rotation values were calculated: $[\alpha]_D^{20} = \alpha/(l \times c)$. Concentration values, *c*, are expressed in g/100mL; [e] The assignment of the absolute configuration for (2*R*,4*S*)-**2a**–**j** and (2*S*,4*R*)-**3a**–**j** has been performed by comparison of the specific rotation signs of compounds (2*S*,4*R*)-**2a** [34,35] and (2*S*,4*R*)-**3a** [35], as already described in the literature.

3.7. Semi-Preparative Lipase-Catalyzed Kinetic Resolution of trans-Flavanols **2a**

VinOAc (11.05 mL) was added to a mixture of the *trans*-flavan-4-ol *trans*-**2a** (250 mg, 1.10 mmol) and lipase AK from *Pseudomonas fluorescens* (250 mg). The mixture was stirred for 48 h at 250 rpm at 30 °C, and after this time, the enzyme was filtered and washed with dichloromethane (3 × 10 mL). The filtrate was concentrated under reduced pressure, and the reaction crude purified by column chromatography purification using an eluent gradient 5:1 to 3:1 hexane:EtOAc, isolating acetate (2*S*,4*R*)-**3a** (142 mg, 48% isolated yield) and alcohol (2*R*,4*S*)-**2a** (115 mg, 46% isolated yield), both in enantiopure form.

4. Conclusions

A general methodology has been proposed for the synthesis of racemic trans-flavan-4-ols bearing different substitution patterns in the aromatic ring at the C-2 position. The five-step chemical route involved three main steps or reaction sequences: (i) the aldol condensation between 2′-hydroxyacetophenone and different benzaldehydes bearing either electron-withdrawing or electron-donor atoms or groups, followed by an intramolecular Michael-type addition in an acid medium; (ii) the chemical reduction in the flavanones, which led to the corresponding racemic *cis*-flavan-4-ols with complete selectivity and very high yields; and finally, (iii) the configuration inversion of the C-4 position by a Mitsunobu inversion reaction and subsequent chemical hydrolysis in basic conditions allows the preferential formation of the alcohol *trans*-isomers after optimization of the reaction conditions of the Mitsunobu reaction in terms of employed nucleophile and alkyl diazocarboxylate.

With a series of ten racemic *trans*-flavan-4-ols on hand, their classical kinetic resolutions were performed, selecting *trans*-flavan-4-ol as a benchmark substrate for enzyme screening and reaction conditions optimization, finding lipase AK from *Pseudomonas fluorescens* as the more selective biocatalyst, and vinyl acetate acting as both an adequate acyl donor and solvent. The (2*R*,4*S*)-alcohols and (2*S*,4*R*)-acetates were obtained, in all cases, with excellent selectivities ($E > 200$), finding different conversion values depending on the type and location of the substitution at the phenyl ring located at the C-2 position, the *para*-substituted derivatives being transformed rapidly by AK lipase from *Pseudomonas*

fluorescens (49–50% conversion) in comparison with the *meta*- (47–50%) and, especially, the *ortho*-substituted ones (33–36%).

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11111296/s1. Table S1. HPLC conditions for the chiral analyses of *trans*-flavan-4-ols **2a-j** and their corresponding acetates **3a-j**. Next, the chromatograms of *trans*-flavan-4-ols **2a-j** and *trans*-flavan-4-ol acetates **3a-j** in racemic and optically active form can be found.

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Data Availability Statement: The data presented in this study are openly available in the Repository of the University of Oviedo (https://digibuo.uniovi.es/dspace/).

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