Synthesis of Enantioenriched 2-((Hetera)cyclo)alkylchromanols and their Spirocyclic Analogs through Enzymatic Resolution

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Dedicated to the memory of Kyrylo Burmagin and Yaroslav Maiboroda

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Abstract: An efficient approach to the multigram synthesis of 2-((hetera)cyclo)alkylchromanols and their spirocyclic analogs based on enzymatic resolution is described. It is shown that enzymatic acylation could be used for the preparation of enantioenriched title compounds with primary alkyl substituents at the C-2 position. Meanwhile, enzymatic hydrolysis of the corresponding acetates was optimal for the preparation of the target alcohols when significant steric hindrance is present, e.g., due to the α-branching. The latter factor was demonstrated to be crucial for the enzymatic reaction rate in both cases. The synthetic utility of the obtained chiral alcohols was demonstrated through Mitsunobu configuration inversion, as well as by preparation of the corresponding primary amines – valuable sp^3-enriched building blocks for medicinal chemistry.

Introduction

Benzo[*b*]pyran, or chroman, is one of the most important oxygen-containing heterocyclic systems found in numerous natural products, as well as marketed and investigational drugs.[1–10] Among them, 2-substituted chromans are especially notable: their naturally occurring representatives include tocopherols (vitamin E), tetrahydrocannabinols, and various 2-arylchroman (flavan) derivatives, e.g., apiforol and luteoforol (Figure 1, *A*). Many classic studies in this area are related to 2-arylchromane derivatives, a subclass of flavonoid natural products. With an increased interest to sp^3-enriched compounds (i.e., those having higher fraction of sp^3-hybrid carbon atoms) in drug discovery observed in the last decades,[11–13] 2-((hetera)cyclo)alkylchromanes and their spirocyclic analogs become very promising chemotypes and synthetic targets. Some of them have already paved their way to medicinal

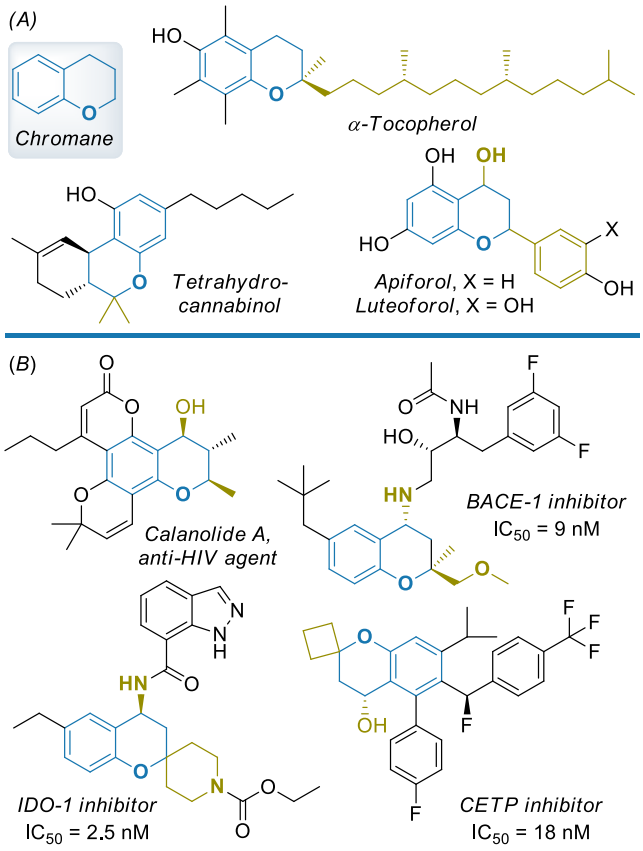
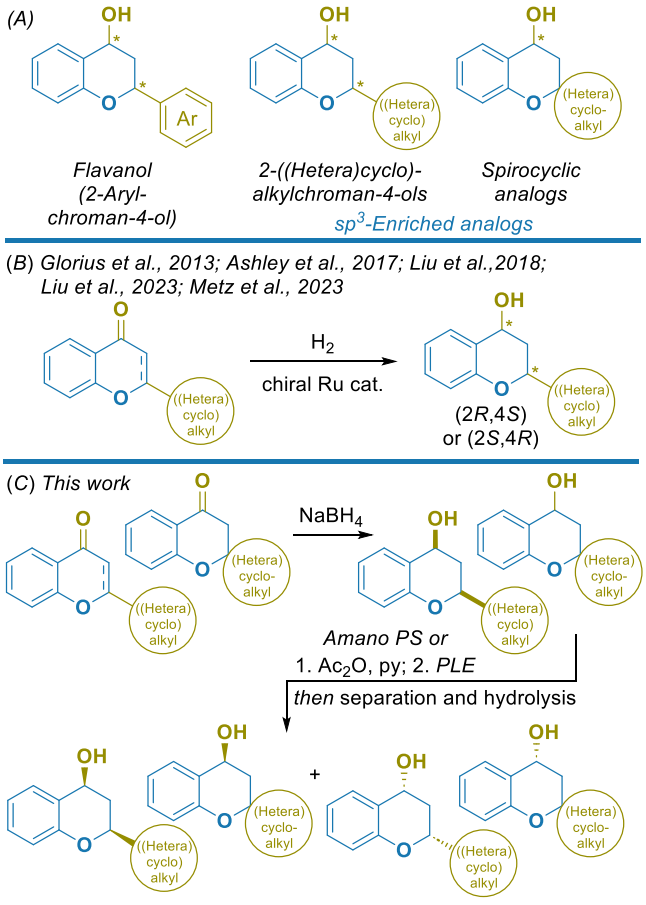


Figure 1. Some biologically active 2-substituted chromanes: natural products (*A*) and synthetic compounds (*B*).

chemistry, e.g. calanolide A, an experimental HIV-1 reverse transcriptase inhibitor,[14] potent beta-secretase 1 (BACE-1),[15] indoleamine 2,3-dioxygenase-1 (IDO1),[16] or cholesteryl ester transfer protein (CETP)[17] inhibitors (Figure 1, *B*).

To ensure the presence of a synthetic handle suitable for further synthetic modifications in the target molecules, we have turned our attention to sp^3-enriched 2-substituted chroman-4-ols as promising building blocks for drug discovery (Scheme 1, *A*). Since these compounds have one or two chiral centers, a method for their synthesis should consider their preparation in enantioenriched form. A major part of the known approaches is based on asymmetric catalytic hydrogenation (Scheme 1, *B*).[18–23] A major drawback of these methods is the use of expensive catalysts, sometimes with limited accessibility. On the contrary, approaches based on the enzymatic resolution of racemates are in general relatively cheap, easy to scale-up, and can provide both enantiomers of the compound, which is beneficial at the early stages of drug discovery projects. While enzymatic kinetic resolution was reported for (aryl-substituted) flavanols,[24–27] to the best of our knowledge, it was not used for their sp^3-enriched counterparts.

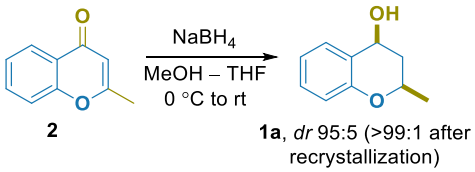


Scheme 1. (*A*) Flavanols, sp^3-enriched 2-substituted chroman-4-ols, and their spirocyclic analogs. (*B*) Synthesis of chiral sp^3-enriched chroman-4-ols through asymmetric catalytic hydrogenation (*known methods*). (*C*) Synthesis of the title compounds through enzymatic kinetic resolution (*this work*).

In this work, we report a convenient multigram preparation of enantioenriched 2-((hetera)cyclo)alkyl)chroman-4-ols and their spirocyclic analogs through enzymatic resolution (Scheme 1, *C*). We demonstrate that depending on the size of the substituent(s) at the C-2 position, enzymatic acetylation (promoted by *Burkholderia Cepacia* lipase, *Amano PS*) or enzymatic hydrolysis (promoted by porcine liver esterase, *PLE*) is optimal to obtain *cis*-isomeric chromanols with over 99% *ee*. Finally, we illustrate the synthetic utility of the synthesized chiral alcohols by performing model Mitsunobu reactions and further transformations, eventually leading to enantioenriched *trans*-isomeric chromanols and the corresponding primary amines – valuable building blocks for medicinal chemistry.

Results and Discussion

We started our study with enzymatic resolution of racemic methyl-substituted *cis*-chromanol **1a**. Compound **1a** was obtained in 81% yield by reduction of 2-methylchromon (**2**) with $NaBH_4$ in THF – MeOH (1:1, v/v) (Scheme 2). Initial diastereomeric ratio (95:5) could be improved to >99:1 after recrystallization from hexane – *i*-PrOH (19:1).



Scheme 2. Synthesis of racemic chromanol **1a**.

Enzymatic acetylation of **1a** with isopropenyl acetate in the presence of *Amano PS* lipase in *t*-BuOMe at 30 °C reached nearly 50% conversion after 15 h (monitored by ^{1}H NMR spectroscopy) (Table 1, Entry 1). After the chromatographic separation and alkaline hydrolysis of acetate (2*S*,4*R*)-**3a**, both enantiomers (2*R*,4*S*)-**1a** and (2*S*,4*R*)-**1a** were obtained in 84% and 71% yield, respectively, with over 99% *ee* following recrystallization. Notably, the target products could be obtained on up to 79 g scale in a single run.

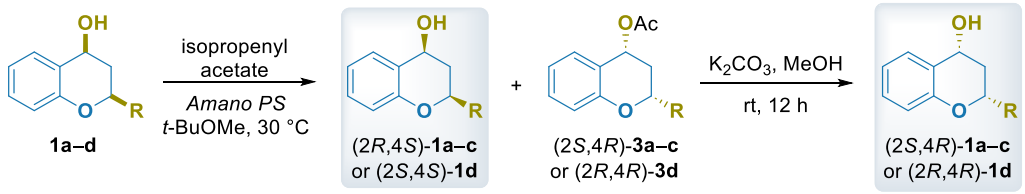
Being inspired by these results, we have attempted extending the above protocol to other 2-substituted chromanols **1b–q**. Compounds **1b–q** were obtained by the Kabbe condensation of 2-hydroxyacetophenone (**4**) and corresponding carbonyl compounds **5a–q** (41–99% yield) followed by reduction of chromanones **6a–q** with $NaBH_4$ (45–99% yield) (Scheme 3). Products **1b–q** were obtained as single *cis* diastereomers, with **1b–d** purified by recrystallization, while the others required no additional purification.

Enzymatic acetylation of **1b** and **1c** at the conditions described above for **1a** proceeded slowly, so that 50% conversion was achieved in 144 and 168 h, respectively (Table 1, Entries 2 and 3). Corresponding enantiopure alcohols were obtained with >99% *ee* following recrystallization. Apparently, the relative size of the

substituent at the C-2 position was crucial for the method efficiency. Indeed, with α-branched isopropyl derivative **1d**, 62% conversion was achieved in 36 h; furthermore, the enantiomeric excess of product (2*S*,4*S*)-**1d** was only 27% (Table 1, Entry 4). Replacing *Amano PS* with *Novozym 435* lipase as the catalyst only slightly improved the outcome (36% *ee*). Obviously, the kinetic resolution method based on the enzymatic acetylation was not suitable for chromanol **1d** and (likely) all remaining substrates **1e–q**.

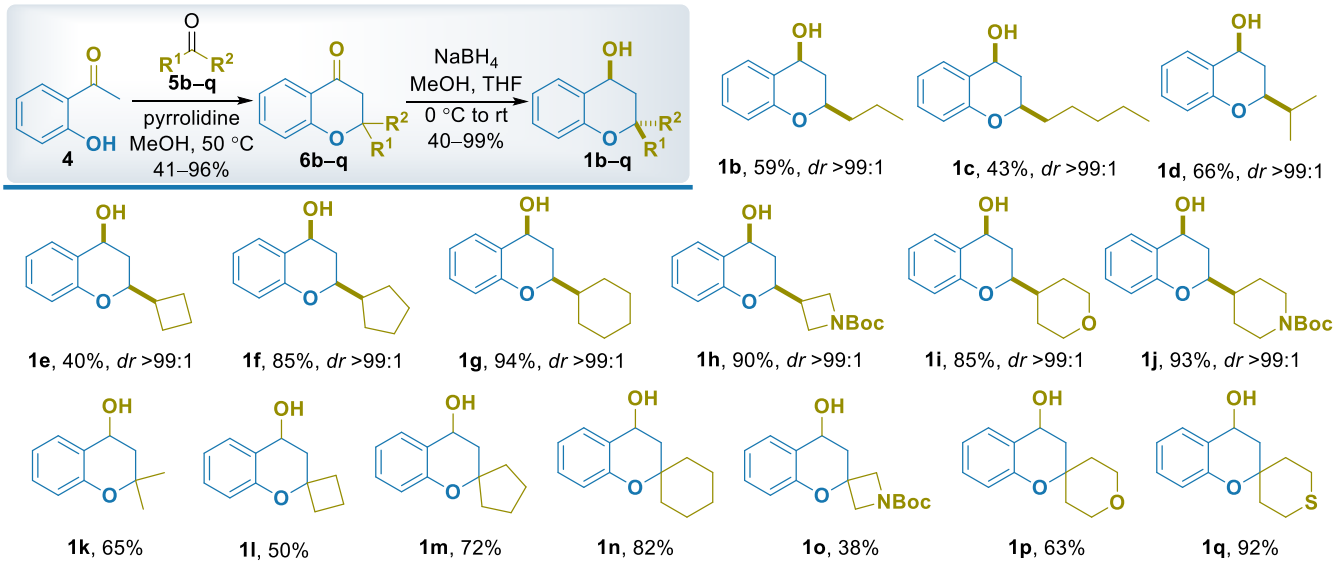
Therefore, we have turned our attention to an alternative approach to the kinetic resolution of chromanols **1d–q**, namely, enzymatic hydrolysis of racemic acetates **3d–q**. These derivatives were obtained *via* standard acetylation of alcohols **1d–q** using Ac_2O – py and were purified by column chromatography before further enzymatic reactions, with yields of 81–98% (Scheme 4). Preliminary experiments with acetate **3d** showed that porcine liver esterase (*PLE*) allowed achieving 50% conversion faster than all other enzymes studied (Table 2; note the relatively high catalyst loading used).

Table 1. Enzymatic kinetic resolution of alcohols **1a–d** through *Amano PS*-catalyzed acetylation.

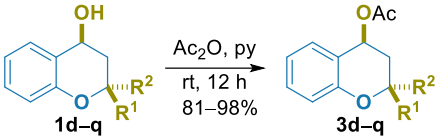


Entry	Chromanol	R	Enzymatic reaction time, h	Conversion, %	Yield of (2*R*,4*S*)-**1**, %[a,d]	*ee* of (2*R*,4*S*)-**1**, %[b,d]	Yield of (2*S*,4*R*)-**1**, %[a,c,e]	*ee* of (2*S*,4*R*)-**1**, %[b,e]
1	**1a**	Me	15	52	94 (84)	95 (99)	86 (71)	92 (99)
2	**1b**	*n*-Pr	144	54	97 (36)	96 (96)	86 (29)	79 (97)
3	**1c**	*n*-C_5H_{11}	168	52	96 (33)	98 (98)	91 (37)	86 (99)
4	**1d**	*i*-Pr	36	62	N/A	27	N/A	N/A

[a] Yields are given as values before recrystallization (in parentheses: values after recrystallization). [b] Optical purities are shown as values before recrystallization (in parentheses: values after recrystallization). [c] Yield is based on racemic **1a–d**. [d] (2*S*,4*S*)-isomer for R = *i*-Pr. [e] (2*R*,4*R*)-isomer for R = *i*-Pr.



Scheme 3. Synthesis of racemic chromanols **1b–q** (yields are given over two steps).

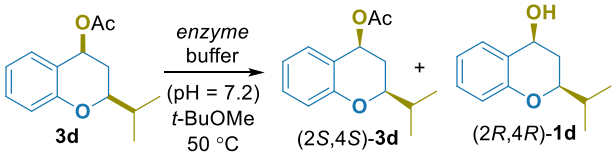


Scheme 4. Synthesis of racemic acetates **3d–q** (for R^1/R^2, see Scheme 3 or Table 3).

With these results in hands, we have applied the *PLE*-catalyzed hydrolysis protocol to all acetates **3d–q** (Table 3). As was anticipated, the reaction time increased with increasing the substituent size (see, for example, Entries 1–4 or 9–11). Notably, the presence of heteroatoms in the substituent(s) at the C-2 position decreased the reaction rate considerably (see Entries 5–7 and 12–14). Also, spirocyclic and (hetera)cycloalkyl-substituted substrates **3d–q** of similar substituent nature had comparable hydrolysis rates (see Entries 2/9, 3/10, 4/11, 5/12, or 6/13).

After the chromatographic separation of products (2*R*,4*S*)-**1d–j** / (*S*)-**1k–q** and (2*S*,4*R*)-**3d–j** / (*R*)-**3k–q**, alkaline hydrolysis of the latter compounds was performed upon action of K_2CO_3 in MeOH at rt. In this way, both enantiomers of *cis*-chromanols **1d–q** were obtained in 78–97% yields (based on racemic **3d–q**) with enantiomeric excess of 77–99% after recrystallization. Notably, the method was applicable for preparing up to 120 g of enantioenriched chromanols (2*R*,4*R*)-**1d–j** / (*R*)-**1k–q** and (2*S*,4*S*)-**1d–p** / (*S*)-**1k–q** in a single run, as demonstrated for compound **3k**.

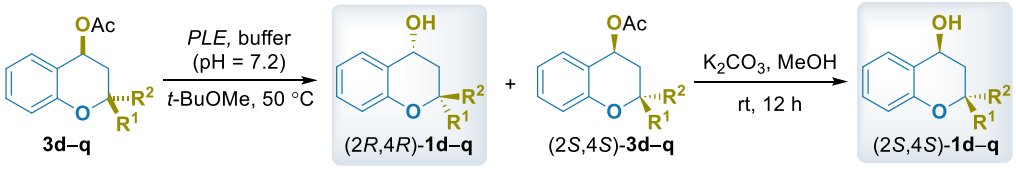
Table 2. Hydrolysis of racemic acetate **3d** using various enzymes as the catalysts.[a]

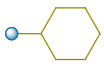
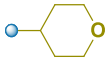


Entry	Enzyme	Reaction time, h	Conversion, %
1	*Amano-PS*	48	2
2	*Novozym 435*	48	1
3	*AS lipase*	24	4
4	*AYS lipase*	24	7
5	*PLE*	24	50

[a] 10 mg of enzyme per 1 mmol of **3d** was used.

Table 3. Enzymatic kinetic resolution of alcohols **1d–q** through *Amano PS*-catalyzed hydrolysis of acetates **3d–q**.

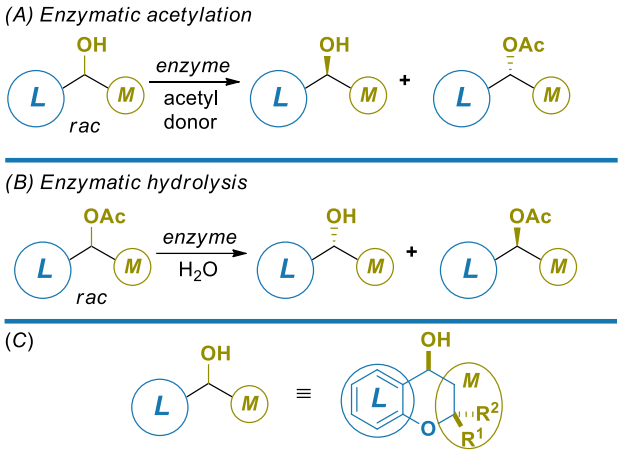


Entry	Acetate	R^1	R^2	Enzymatic reaction time, d[a]	Conversion, %	(2*R*,4*R*)-**1d–j** / (*R*)-**1k–q**		(2*S*,4*S*)-**1d–j** / (*S*)-**1k–q**	
						Yield, %[b]	*ee*, %[c]	Yield, %[b, d]	*ee*, %[c]
1	**3d**		H	8	48	96 (73)	99 (99)	90 (70)	86 (99)
2	**3e**		H	6	49	86 (61)	99 (99)	78 (55)	90 (99)
3	**3f**		H	7	49	92 (79)	91 (99)	88 (72)	86 (99)
4	**3g**		H	11	47	90 (76)	99 (99)	86 (74)	77 (99)
5	**3h**		H	28	48	87	99	89	91
6	**3i**		H	41	49	87 (71)	97 (99)	85 (67)	93 (95)

7	**3j**		H	46	49	84 (72)	98 (98)	82 (68)	91 (92)
8	**3k**	Me	Me	4	49	96 (73)	94 (99)	88 (70)	89 (99)
9	**3l**			6	51	86 (71)	91 (99)	78 (63)	96 (99)
10	**3m**			14	51	93 (82)	92 (99)	87 (74)	96 (99)
11	**3n**			21	51	97 (86)	89 (95)	92 (81)	95 (99)
12	**3o**			17	52	90	77	82	85
13	**3p**			34	51	97	88	92	99
14	**3q**			39	51	95	96	92	97

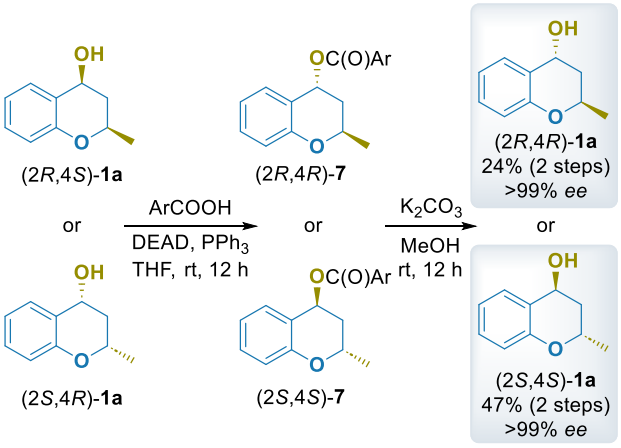
[a] 2 mg of *PLE* per 1 mmol of **3d–q** was used. [b] Yields are given as values before recrystallization (in parentheses: values after recrystallization). [c] Optical purities are shown as values before recrystallization (in parentheses: values after recrystallization). [d] Yield is based on racemic **3d–q**.

Absolute configuration of products **1a–q** followed the well-known Kazlauskas rule (Scheme 5), which is explained by specific orientation of the secondary alcohol in the enzyme's active site.[28] This result was confirmed by comparison of specific rotation values ($[\alpha]_D$) for the known compounds (*e.g.*, **1a**, **1b**, **1k**) with those reported in the literature.



Scheme 5. Illustration of the Kazlauskas rule for enzymatic acetylation (*A*) and enzymatic hydrolysis (*B*), as well as its application to chromanols **1a–q** (*C*). *L* and *M* – large- and medium-sized substituents, respectively.

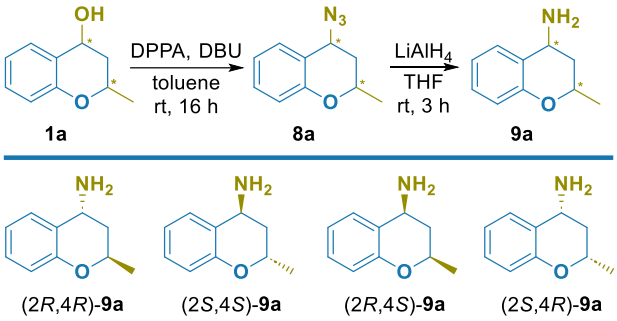
To demonstrate the synthetic utility of synthesized chromanols **1a–q**, we have performed some transformations with methyl-substituted derivatives **1a** and **1k** as the model compounds. In particular, the Mitsunobu reaction of (2*R*,4*S*)-**1a** and (2*S*,4*R*)-**1a** with *p*-nitrobenzoic acid, followed by alkaline hydrolysis of esters **7**, yielded the *trans* isomers (2*R*,4*R*)-**1a** and (2*S*,4*S*)-**1a** in 24–47% yield over two steps (Scheme 6). In other words, all four theoretically possible stereoisomers of chromanol **1a** could be obtained in optically pure form.



Scheme 6. Synthesis of *trans* isomers (2*R*,4*R*)-**1a** and (2*S*,4*S*)-**1a** (Ar = 4-nitrophenyl).

Moreover, the Mitsunobu reaction of alcohols (2*R*,4*S*)-**1a**, (2*S*,4*R*)-**1a**, (2*R*,4*R*)-**1a** and (2*S*,4*S*)-**1a** with diphenyl phosphoryl azide (DPPA) yielded azides **8a** in 80–91%, which were further reduced with $LiAlH_4$ to give enantioenriched primary amines **9a** (64–72% yield, isolated as hydrochlorides) (Scheme 7). Since amine is the most popular functional group in medicinal chemistry,[29] chiral compounds **9** are especially valuable as building blocks for early drug discovery programs.

Table 4. Synthesis of enantioenriched amines **9a**.



Entry	Alcohol **1**	R^2	Products **8** / **9**	Yield of **8**, %	Yield / *ee* of **9**, %[a]
1	(2*R*,4*S*)-**1a**	H	(2*R*,4*R*)-**8a/9a**	87	64 / 98
2	(2*S*,4*R*)-**1a**	H	(2*S*,4*S*)-**8a/9a**	91	70 / 99
3	(2*R*,4*R*)-**1a**	H	(2*R*,4*S*)-**8a/9a**	80	70 / 98
4	(2*S*,4*S*)-**1a**	H	(2*S*,4*R*)-**8a/9a**	87	72 / 99

[a] Isolated as hydrochlorides.

Conclusion

Enzymatic kinetic resolution is a very efficient method for the multigram synthesis of enantioenriched *cis*-2-(hetera)cyclo)alkyl-substituted chroman-4-ols. The substituent(s) at the C-2 position had a crucial impact on the enzymatic reaction rate (that decreased with increasing the substituent size) and defined the choice of the most appropriate protocol. In particular, for *n*-alkyl-substituted derivatives, enzymatic acetylation catalyzed by *Amano PS* lipase was very efficient, and the target (2*R*,4*S*) and (2*S*,4*R*) enantiomers were obtained with over 96% *ee*. For the compounds with α-branched substituents (i.e., isopropyl or (hetera)cycloalkyl) as well as 2,2-disubstituted counterparts, *PLE*-catalyzed enzymatic hydrolysis of pre-synthesized acetates should be used. In this way, (2*R*,4*R*) / (*R*) and (2*S*,4*S*) / (*S*) enantiomers were synthesized with 77–99% *ee*. Notably, both protocols were amenable to the multigram preparation of the target enantioenriched chromanols (up to 120 g in a single run). The synthetic utility of the synthesized intermediates was demonstrated by the Mitsunobu configuration inversion, this enabling access to all possible stereoisomers of 2-(hetera)cyclo)-alkylsubstituted chroman-4-ols. In addition to that, their transformation into enantioenriched primary amines – valuable sp^3-enriched *O*–heterocyclic building blocks for drug discovery – was performed.

Supporting Information

The authors have cited additional references within the Supporting Information.[30–48]

Acknowledgements

The work was supported by Enamine Ltd. The authors thank Prof. Andriy A. Tolmachov for his encouragement and support, and all the brave people of Ukraine for making this publication possible.

Conflict of Interest

Most authors are employees, trainees, or consulting scientists of Enamine Ltd. which offers the compounds described in this paper in the company's catalog.

Experimental section

General

The solvents were purified according to the standard procedures.[49] All the starting materials were available commercially and obtained from Enamine Ltd. or UORSY. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR), on Agilent ProPulse 600 spectrometer (at 500 MHz for ^{1}H and 151 MHz for ^{13}C) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. For ^{19}F NMR CCl_3F was used as internal standards. Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

General procedure for the synthesis of chroman-4-ones 6

1-(2-Hydroxyphenyl)ethan-1-one (**4**) (15 g, 110 mmol, 1 eq) was dissolved in MeOH (150 mL) and the corresponding aldehyde or ketone (121 mmol, 1.1 eq) was added. Next, pyrrolidine (18.2 mL, 220 mmol, 2 eq) was carefully added dropwise to the reaction mixture at 30–40 °C, and the mixture was then stirred at 50 °C overnight. Afterward, all volatiles were evaporated in *vacuo*, and the residue was purified by column chromatography on silica gel using *n*-hexane – THF (10/1, v/v) as the eluent to afford the corresponding 2-(hetero)cycloalkyl- and spirocyclic chroman-4-ones.

General procedure for the synthesis of racemic chroman-4-ols 1

$NaBH_4$ (3.78 g, 100 mmol, 1 eq) was carefully added to the solution of corresponding chroman-4-one **6** (100 mmol, 1 eq) in MeOH (75 mL) and THF (75 mL) at 0 °C, and the mixture was stirred at rt overnight. Then, NH_4Cl (5.9 g, 110 mmol, 1.1 eq) was added, and the mixture was evaporated in *vacuo*. The residue was diluted with H_2O (100 mL), extracted with *t*-BuOMe (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The pure product was obtained after recrystallization from hexane.

General procedure for the synthesis of racemic acetates 3

Corresponding chroman-4-ol **1** (44.5 mmol, 1 eq) was dissolved in pyridine (100 mL), and Ac_2O (5 mL, 53.4 mmol, 1.2 eq) was added dropwise at 0 °C. The resulting solution was stirred at rt overnight. Then, the reaction mixture was evaporated in *vacuo*. The residue was diluted with H_2O (200 mL), extracted with *t*-BuOMe (3 × 50 mL), washed with water (5 × 50 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was purified by column chromatography on silica gel using *n*-hexane – THF (10/1, v/v) as the eluent to afford the pure product.

General procedure for the enzymatic resolution of racemic chroman-4-ols 1a–c

Isopropenyl acetate (13.5 mL, 123 mmol, 2 eq) and *Amano-PS lipase* (1.2 g, 1/10 w/w) were added to a solution of chroman-4-ols **1b** or **1c** (61.4 mmol, 1 eq) in *t*-BuOMe (150 mL), and the resulting mixture was stirred at 50 °C until the conversion of reaction was approximately 50%. The reaction progress was monitored by ^{1}H NMR spectroscopy. Then, the lipase was filtered out and washed with *t*-BuOMe. The filtrate was evaporated in *vacuo* to give a mixture of the alcohol and acetate. This mixture was separated by column chromatography on silica gel using *n*-hexane – THF (10/1, v/v) as the eluent to afford pure products (2*R*,4*S*)-**1a–c** and (2*R*,4*S*)-**3a–c**.

General procedure for the enzymatic resolution of racemic acetates 3d–q

To a solution of racemic acetate **3d–q** (41.8 mmol, 1 eq) in a mixture of *t*-BuOMe (100 mL) and a phosphate buffer (pH = 7.2, 100 mL), *PLE* (84 mg) was added. The mixture was stirred at 50 °C until the conversion of reaction was approximately 50%. When the pH of the reaction mixture decreased below 6.0, a saturated solution of KOH was added to adjust the pH back to 7.2. The reaction progress was monitored by ^{1}H NMR spectroscopy. Afterward, the lipase was filtered and washed with *t*-BuOMe. The filtrate was separated, and the organic layer was dried over Na_2SO_4 and evaporated in vacuo to afford a mixture of the alcohol and acetate. This mixture was separated by column chromatography on silica gel using *n*-hexane – THF (10/1, v/v) as the eluent to afford pure products (2*R*,4*R*)-**1d–j** / (*R*)-1**k–q** and (2*S*,4*S*)-**3d–j** / (*S*)-**3k–q**.

Keywords: kinetic resolution • enzymes • chiral compounds • chromanes • oxygen heterocycles

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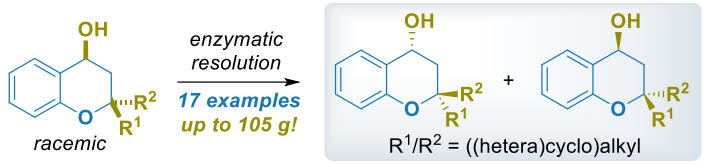
Enzymatic Resolution



An expedient approach to the multigram preparation of enantioenriched 2-((hetera)cyclo)alkylchromanols and their spirocyclic analogs based on their enzymatic acylation or enzymatic hydrolysis of the corresponding acetates is described. Utility of the obtained intermediates for the preparation of chiral sp^3-enriched building blocks valuable to drug discovery is demonstrated.

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