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Enzymatic resolution of chroman-4-ol and its core analogues with *Burkholderia cepacia* lipase

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ABSTRACT

A convenient protocol for lipase resolution of chroman-4-ol and its analogues (six- and seven-membered rings with O, S, SO_2) has been elaborated. The structure of substrates has minor influence on the efficiency of resolution.

1. Introduction

Enzymes and cells in modern organic chemistry have been utilized in many popular synthetic strategies. Different substances are required in enantiomerically pure form for both scientific and industrial needs. Enzymatic resolution offers a simple fruitful path toward enantiomerically pure species.[1]

The use of lipases is one of the most developed enzymatic processes yielding asymmetric secondary alcohols, amines, and other substances.[2,3] Crude, purified, or immobilized lipases can be used in water, organic solvents, or ionic liquids in a straightforward manner. Recently, the efficacy of lipases was improved upon by ionic surfactant coating.[4] Coupling with a metal-based racemization step leads to the dynamic kinetic resolution of secondary alcohols with twice as high maximum yields in comparison to traditional kinetic resolution methods (100% vs 50%).[5,6] The former still requires development since more drastic reaction conditions can lead to unwanted side processes, decreasing the yields and purity of the final products. Finally, simple rules have been formulated for determining the absolute configuration of a secondary alcohol by observing the lipase selectivity.[7] These rules indicated that the lipase resolution is in addition an analytical method. The scope of lipase substrates that can be effectively separated in a routine and reliable manner therefore requires development.[8]

The enzymatic enantiomeric synthesis of chroman-4-ol (**1a**, X = O, *n* = 1) and thiochroman-4-ol was previously carried out via redox processes in *M. isabellina* and *Helminthosporium* fungus.[9] The resolution of racemic chroman-4-ol and its substituted analogues by lipase-catalyzed cross-acylation with vinylacetate was reported in the 1990s.[10,11] In the paper of Ramadas and Krupadanam,[11] the resolution was carried out with *Burkholderia cepacia* lipase (BCL) giving moderate to good ee values. In particular, the unsubstituted chroman-4-ol **1a** was obtained with 50% and 70% ee for acetylated (*R*)-(+)-**2a** and intact (*S*)-(−)-**1a** enantiomers, respectively, (Scheme 1B).

Herein we report a protocol which enables a better performance with ee ⩾94%. The key changes to the reported conditions were the use of *tert*-butylmethylether (TBME) as the solvent and carrying out the reaction at room temperature (23 °C). Furthermore, we used our optimized protocol for the kinetic resolution of the chroman-4-ol core **1** modifications. The steric properties were also varied. The difference in the electronic properties of sulfur and oxygen[12] could lead to a dramatic change in the substance reactivity. A general protocol for the lipase resolution of **1** to enantiomerically pure forms was also attempted.

The enantiomerically enriched substances obtained represent variations of the chroman-4-ol fragment. Chroman is the structural core of many natural products, such as the tocopherols, flavonoids, iso- and neoflavanoids. A major function of the latter compounds is their anti-oxidative activity,[13] which is important for the prevention of cancer[14] as well as aging in general. The 4-hydroxylated chroman was found in a number of natural products,[15] such as compounds **3** and **4**, which were recently extracted from the plants *B. zenkeri* and *T. yannanensis*, respectively, (Chart 1).[16]

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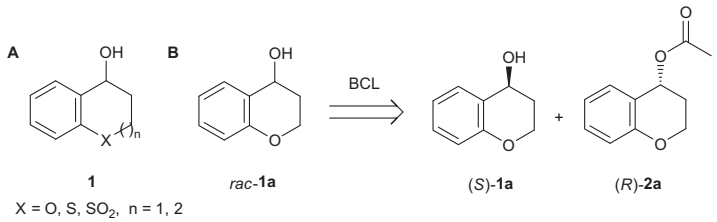


Scheme 1. (A) General structure of the chroman-4-ol analogues. (B) Lipase resolution of chroman-4-ol.

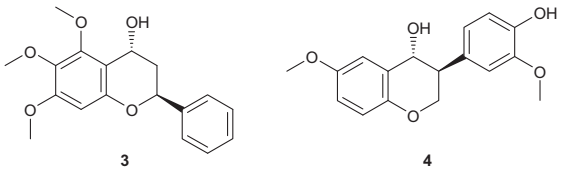


Chart 1. The structures of the chroman-4-ol based natural products **3** and **4**.

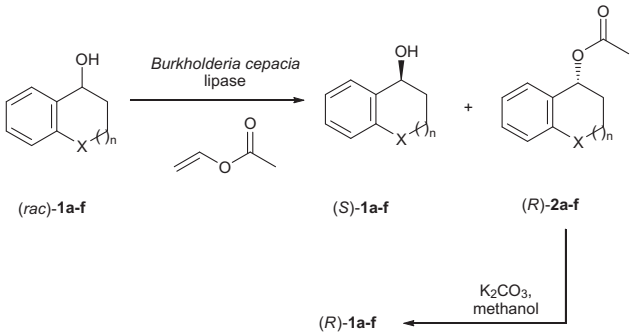
2. Results and discussion

Racemic alcohol **1a** (X = O, *n* = 1) was obtained by sodium borohydride reduction of chroman-4-one.[17] It was then subjected to the kinetic enzymatic resolution with BCL, with vinyl acetate as the acetyl donor (Scheme 2, entry 1). The use of TBME as the solvent led to 50% conversion after 14 h at room temperature as monitored by ^{1}H NMR spectroscopy. The alcohol (*S*)-**1a** and the ester (*R*)-**2a** were then separated on a silica gel column. The (*R*)-**2a** ester hydrolysis with potassium carbonate in methanol gave the second enantiomer (*R*)-**1a**. Both were subjected to conventional Mosher ester derivatization with MTPA chloroanhydride.[18] The ^{19}F NMR spectra of the derivatives showed (*S*)- and (*R*)-**1a** to possess an ee of ⩾94% and 95%, respectively.

Next we took a substrate with a larger heterocycle size. The corresponding homochromanol[19] **1b** (X = O, *n* = 2) was resolved with even better ee ⩾99% for both enantiomers after application of the reported protocol (Scheme 2, entry 2). These results inspired us to apply the BCL kinetic resolution to the thio-, homothiochromanols (X = S) and their dioxides (X = SO_2). Racemic thiochroman-4-ol **1c** was obtained according to the known pathway starting from thiophenol.[20] Our BCL kinetic resolution procedure gave the corresponding **1c** enantiomers with an ee of 95% (Scheme 2, entry 3).

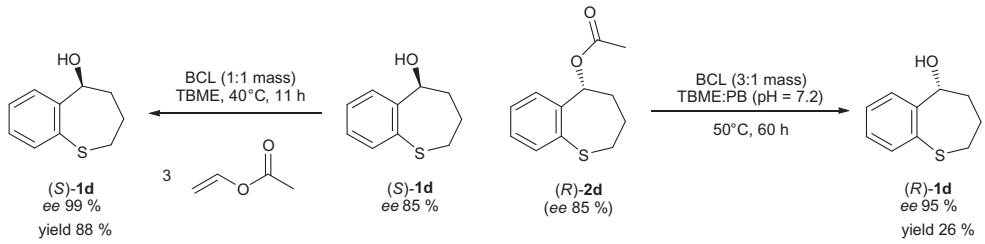
The racemic homothiochromanol **1d** was obtained by alkylation of thiophenol with butyrolactone, followed by cyclization and reduction of the carbonyl group. The BCL resolution efficacy for this substrate exhibited a significant drop. When the procedure was performed in an analogous manner to the previous substrates (1:10 mass amount of the enzyme, 23 °C, TBME), the conversion was only 2% after 14 h. We then attempted the reaction under more vigorous conditions (1:3 mass amount of the lipase, 40 °C) in different solvents. After 8 h, the conversion was found to be 15% in TBME, 4% in acetonitrile and 6% in THF, indicating that TBME gave the fastest reaction. We carried out the resolution in this solvent until 50% conversion was reached (after 50 h). The resulting resolution was only 85% ee for both enantiomers (*S*)-**1d** and (*R*)-**2d** (Scheme 2, entry 4).

In order to complete the resolution, we took the reaction products and performed additional manipulations. Compound (*S*)-**1d** with 85% ee was subjected to the second resolution step with BCL (Scheme 3). After 11 h, we obtained the starting material with 99% ee. The acetyl-ester (*R*)-**2d** was also subjected to the lipase-catalyzed hydrolysis in the TBME-phosphate buffer mixture. The



Entry	Racemic Compound	X	n	temperature, °C	reaction time, hours	lipase, mass.	(*S*)-alcohol yield, %	(*S*)-alcohol *ee*, %	(*R*)-alcohol yield, %	(*R*)-alcohol *ee*, %
1	(±)-**1a**	O	1	23	14	1/10	47	94	43	95
2	(±)-**1b**	O	2	23	14	1/10	48	99	43	99
3	(±)-**1c**	S	1	23	14	1/10	47	95	40	95
4	(±)-**1d**	S	2	40	50	1/3	41	85	35	85
5	(±)-**1e**	SO_2	1	40	14	1/10	40	95	34	94
6	(±)-**1f**	SO_2	2	50	72	2/3	45	99	35	90

Scheme 2. Enzymatic resolution of enantiomeric chroman-4-ol and its analogues with BCL. The cross-acylation reactions were run until 50% conversion was reached.



Scheme 3. Second BCL kinetic resolution of the homothiochromanol enantiomers **1d** after the first acylation.

reaction gave only a barely detectable conversion after 12 h at 40 °C (the lipase was taken as 1:3 by mass). Therefore, we performed this procedure for 60 h at 50 °C and with an excess of the lipase (3:1 mass amount). A conversion of 26% was eventually achieved and the resulting alcohol (*R*)-**1d** was obtained with 95% ee.

We then carried out additional optimization for the sulfonic compounds **1e** and **1f** (X = SO_2, *n* = 1 and 2, respectively). The starting materials were obtained by peroxide oxidation of the thiochromanone and homothiochromanone, followed by borohydride reduction of the carbonyl function.[21] The racemic substances were subjected to BCL resolution under more drastic conditions (50 °C, 4 days) until 50% conversion was reached. Since, the substrates were less soluble in TBME, we employed larger amounts of this solvent. The resolution was still quite good, with the corresponding alcohols (*S*)- and (*R*)-**1e** being obtained in ee ⩾94% (Scheme 2, entry 5). For **1f**, the enantiomeric alcohols were obtained in ee ⩾90% (entry 6).

Alternatively, the kinetic resolution for the sulfonic species **1e** and **1f** can be performed in acetonitrile. These substrates are more soluble in this solvent. For **1e**, we carried out the resolution in acetonitrile under the same conditions as shown in Scheme 2 for the TBME reaction. We found that the conversion in acetonitrile (2.5 l/mol substrate) reached 46% only after 72 h, whereas in TBME (5 l/mol substrate) it was 50% after 14 h. A similar effect was expected for **1f**.

Finally, we obtained all of the desired enantiomers with ee values of 94–99% for (*S*)-**1a-1f** and 90–99% for (*R*)-**1a**–**1f**. Over the past two decades, a number of methods have been reported for the separation of chroman-4-ol **1a** and its thio-analogue **1b** employing chemical catalysis.[20,22] Mostly, these are based on a ketone–alcohol redox conversion on metallic catalysts,[22] but also enantioselective sylilation.[20] However, the lipase cross-acylation remains a powerful and robust method for the separation of such secondary alcohols.

In our hands BCL gave good results with chroman-4-ol core analogues such as homo-, thio-, and dioxothio- as well as chromanol itself. Complications were found in the case of the substrates **1f** and especially **1d**. In the last case, thiohomo modification of the initial chroman-4-ol structure led to a significant drop in the reaction conversion as well as the resolution. The saturated heterocycle in chroman-4-ol defines the 'medium'-substituent in the secondary alcohol structure when accommodated by the lipase binding pocket, whereas the large substituent is the phenyl-ring. Both an enlargement of the saturated cycle and substitution of the ring oxygen with sulfur in **1d**, led to complications in the enzyme-binding.

3. Conclusion

In conclusion, we have reported a convenient procedure for the enzymatic kinetic resolution of chroman-4-ol and its unsubstituted analogues. The resolution is based on a *Burcholderia cepacia* lipase catalyzed acylation of the alcohols with vinylacetate as the acetyl donor. We obtained the corresponding enantiomeric species with ee ⩾94% for chroman-4-ol itself and 90–99% for the rest of the structures examined. The observed resolution values showed good selectivity of the lipase toward (*R*)-substrates according to Kazlauskas's rule, despite the variation in the ring size and heteroatom nature. All of the compounds were obtained with high degrees of enantiomerical purity and can then be used elsewhere.

4. Experimental

4.1. General

All starting chemicals were supplied by Enamine Ltd or prepared according to the literature as mentioned in the main text. Amano-PS lipase from *Burkholderia cepacia* immobilized on diatomaceous earth was obtained from Amano Enzyme USA Co., Ltd.

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DRX 500 (at 500 and 126 MHz respectively) and ^{19}F NMR on Varian UNITY Plus 400 (at 376 MHz) spectrometers. Optical rotation values were measured on JASCO J-20 polarimeter with a 50 mm cell at 20 °C and 589 nm (sodium D-line). Chiral HPLC analysis was done at Agilent 1100 system equipped by Chiralpak® or Chiracel® (Chiral Technologies) analytical columns with cellulose-based stationary phase. The UV detection was performed at 215, 225, and 254 nm. Chemical purity of the obtained enantiomers was controlled by comparing their ^{1}H NMR spectra with that reported in the literature. Derivatization with α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) chloranhydride was carried out according to the literature.[13] The enantiomeric excess values were determined from the ^{19}F NMR spectra of the MTPA derivatives, or from chiral HPLC analysis. Absolute configurations of the alcohols obtained were determined by comparison of the specific rotation with the literature values and were consistent with Kazlauskas's rule.[7] The IR spectra were recorded on a Bruker Vertex 70 FTIR spectrometer in KBr; the absorption values are given in cm^{-1}. Substance purity was checked on an Agilent 1100 LC/MSD SL (chemical ionization) system to exceed 95%.

4.2. General procedure for enzymatic resolution of alcohols

To a solution of the racemic secondary alcohol (1 equiv, 0.29 mol) in TBME (800 ml per 1 mol of the alcohol; for **1e**–**f** 4.5 l per 1 mol), lipase (1:10 or 2:3 by mass to the alcohol) and vinyl-acetate (3 equiv) were added. The reaction was stirred (either at room temperature of 23 °C or at 50 °C) until 50% conversion was reached (^{1}H NMR monitoring). The lipase was filtered off and washed by the solvent twice. The filtrate was evaporated and subjected to chromatographic separation on silica gel with hexane–ethyl acetate gradient elution yielding (*S*)-**1** alcohol and (*R*)-**2** ester.

4.3. Resolution details and characterization of (*S*)-1 alcohols

(4*S*)-Chroman-4-ol (*S*)-**1a** was obtained using the general procedure at 23 °C, reaction time: 14 h. Yield; 47%. $[\alpha]_D^{20} = -56.0$ (*c* 1.4, EtOH) for 94% ee {literature $[\alpha]_D^{25} = -71.3$ (*c* 0.5, EtOH) for 99% ee}.[23]

(5*S*)-2,3,4,5-Tetrahydro-1-benzoxepin-5-ol (*S*)-**1b** was obtained using the general procedure at 23 °C, reaction time: 14 h. Yield; 48%. $[\alpha]_D^{20} = -18.4$ (*c* 0.7, $CHCl_3$) for 99% ee {literature $[\alpha]_D^{25} = -15.5$ (*c* 2.48, $CHCl_3$)}.[24]

(4*S*)-Thiochroman-4-ol (*S*)-**1c** was obtained using the general procedure at 23 °C, reaction time: 14 h. Yield; 47%. $[\alpha]_D^{20} = -104.5$ (*c* 1.5, $CHCl_3$) for 95% ee {literature $[\alpha]_D^{25} = -136.0$ (*c* 1.0, $CHCl_3$) for 99% ee}.[17]

(5*S*)-2,3,4,5-Tetrahydro-1-benzothiepin-5-ol (*S*)-**1d** was obtained using the general procedure at 23 °C, reaction time: 14 h. Yield 41%. Re-crystallized from hexane-chloroform 10:1. $[\alpha]_D^{20} = -91.3$ (*c* 2.9, EtOH) for 85% ee.

The second resolution step was performed as follows; alcohol (*S*)-**1d** (0.80 g, 4.4 mmol; ee = 85%) obtained in the general procedure was dissolved in 7 ml of TBME (1.5 l per 1 mol of the alcohol). Next, the lipase (0.80 g, 1:1 by mass to the alcohol) was added followed by vinyl acetate (1.0 ml, 13.2 mmol, 3 equiv). The mixture was stirred for 11 h at 40 °C at which point the desired conversion was reached (^{1}H NMR). The lipase was filtered off, washed twice, and the resulting filtrate was concentrated under reduced pressure, after which it was subjected to chromatographic separation on silica gel (hexane—ethyl acetate gradient elution) to give 0.71 g of (*S*)-**1d** (yield 88%). $[\alpha]_D^{20} = -98.1$ (*c* 3.2, $CHCl_3$) for 99% ee. Mp = 42 °C. ^{1}H NMR ($CDCl_3$), δ: 7.45–7.52 (2H, m), 7.31 (1H, t, *J* = 7.3 Hz), 7.17 (1H, t, *J* = 7.0 Hz), 5.22 (1H, d, *J* = 9.1 Hz), 2.80–2.95 (1H, br s), 2.75–2.81 (1H, m), 2.63 (1H, t, *J* = 9.4 Hz), 2.06–2.22 (2H, m), 1.96–2.06 (1H, m), 1.76–1.88 (1H, m). ^{13}C NMR ($CDCl_3$), δ: 28.4 (CH_2), 33.5 (CH_2), 35.4 (CH_2), 73.4 (CH), 125.8 (CH), 126.9 (CH), 128.2 (CH), 132.8 (C), 133.5 (CH), 148.3 (C). IR bands: 3296, 2922.

(4*S*)-1,1-Dioxo-3,4-dihydro-2*H*-thiochromen-4-ol (*S*)-**1e** was obtained using the general procedure at 50 °C, reaction time: 96 h. Yield; 40%. $[\alpha]_D^{20} = +5.1$ (*c* 1.41, $CHCl_3$) for 95% ee {literature $[\alpha]_D^{25} = +5.1$ (*c* 1.0, $CHCl_3$) for 99% ee}.[17]

(5*S*)-1,1-Dioxo-2,3,4,5-tetrahydro-1-benzothiepin-5-ol (*S*)-**1f** was obtained using the general procedure at 50 °C, reaction time: 72 h. Yield; 45%. Mp = 148 °C. ^{1}H NMR (DMSO-d_6), δ: 7.91 (1H, d, *J* = 7.9 Hz), 7.88 (1H, d, *J* = 7.9 Hz), 7.73 (1H, t, *J* = 7.5 Hz), 7.50 (1H, t, *J* = 7.5 Hz), 5.73 (1H, s), 5.26 (1H, d, *J* = 10.3 Hz), 3.41 (1H, d, *J* = 14.0 Hz), 3.19 (1H, t, *J* = 13.8 Hz), 2.22 (1H, q, *J* = 13.3 Hz), 2.13 (1H, d, *J* = 13.3 Hz), 2.01 (1H, d, *J* = 13.5 Hz), 1.55 (1H, q, *J* = 12.2 Hz). ^{13}C NMR (DMSO-d_6), δ: 22.7 (CH_2), 37.1 (CH_2), 54.2 (CH_2), 69.4 (CH), 126.2 (CH), 127.0 (CH), 127.4 (CH), 134.2 (CH), 137.2 (C), 145.5 (C). IR bands: 3496, 2925, 2869. $[\alpha]_D^{20} = -32.8$ (*c* 1.4, $CHCl_3$) for 99% ee.

4.4. General procedure for the hydrolysis of (*R*)-2 acetyl esters

To a solution of the corresponding (*R*)-**2** (1 equiv, 0.16 mol) in methanol (300 ml), potassium carbonate (3 equiv) was added. The mixture was stirred for 3 h at room temperature (23 °C). Next, the mixture was filtered off and the filtrate was concentrated under reduced pressure. Water (300 ml) was then added to the residue and this was extracted by ethyl acetate (3 × 200 ml). The organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Resulting crude material was purified by either vacuum distillation for (*R*)-**1a** and (*R*)-**1d**, or re-crystallization to give pure (*R*)-**1** alcohol.

4.5. Details and characterization of (*R*)-1 alcohols

(4*R*)-Chroman-4-ol (*R*)-**1a**. Yield; 43%. $[\alpha]_D^{20} = +65.5$ (*c* 3.0, EtOH) for 95% ee {literature $[\alpha]_D^{20} = +70.2$ (*c* 1.0, EtOH) for 99% ee}.[25]

(5*R*)-2,3,4,5-Tetrahydro-1-benzoxepin-5-ol (*R*)-**1b** was re-crystallized from hexane. Yield; 43%. Mp = 73 °C. IR bands: 3465, 2956, 2867. $[\alpha]_D^{20} = +13.5$ (*c* 1.0, EtOH) for 99% ee {literature $[\alpha]_D^{25} = -15.5$ (*c* 2.5, $CHCl_3$) for the (*S*)-isomer}.[18]

(4*R*)-Thiochroman-4-ol (*R*)-**1c** was re-crystallized from hexane. Yield; 40%. $[\alpha]_D^{20} = +117.5$ (*c* 1.2, $CHCl_3$) for 95% ee {literature $[\alpha]_D^{25} = +143.0$ (*c* 1.0, $CHCl_3$) for 98% ee}.[26]

(5*R*)-2,3,4,5-Tetrahydro-1-benzothiepin-5-ol (*R*)-**1d**. Yield; 35%. Re-crystallized from hexane-chloroform (10:1). Mp = 39 °C. IR bands: 3289, 2919, 2856 cm^{-1}. $[\alpha]_D^{20} = +83.5$ (*c* 5.7, EtOH) for 85% ee.

Otherwise the synthesis was performed as following. Acetate (*R*)-**2d** (0.51 g, 2.3 mmol) obtained in Section 4.2 was dissolved in TBME (4 ml). The lipase (1.5 g, 3:1 by mass to the acetate) and phosphate buffer (4 ml, pH = 7.2, 50 mM KH_2PO_4) were then added and the mixture was stirred for 60 h at 50 °C. The resulting mixture contained 26% of the hydrolyzed product (^{1}H NMR). The mixture was then filtered from the solid lipase, the organic layer was separated, and the aqueous layer was extracted by TBME (3 × 5 ml). The organic fractions were dried over sodium sulfate, the crude mixture was concentrated in vacuo, and then separated on silica gel (hexane—ethyl acetate gradient elution) to give 0.070 g (13%) of the desired alcohol (*R*)-**1d** with 95% ee. $[\alpha]_D^{20} = +97.8$ (*c* 3.2, $CHCl_3$).

(4*R*)-1,1-Dioxo-3,4-dihydro-2*H*-thiochromen-4-ol (*R*)-**1e** was re-crystallized from hexane—isopropanol (10:1). Mp = 91 °C. Yield—34%. IR bands: 3455, 2977, 2924. $[\alpha]_D^{20} = -7.0$ (*c* 1.3, $CHCl_3$) for 94% ee {literature $[\alpha]_D^{25} = +5.1$ (*c* 1.0, $CHCl_3$) for 99% ee of the (*S*)-isomer}.[17]

(5*R*)-1,1-Dioxo-2,3,4,5-tetrahydro-1-benzothiepin-5-ol (*R*)-**1f** was re-crystallized from hexane–isopropanol (10:1). Yield—35%. Mp = 146 °C. IR bands: 3496, 2925. $[\alpha]_D^{20} = +34.8$ (*c* 1.4, $CHCl_3$) for 90% ee.

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