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Enantioselective acylation of chroman-4-ols catalysed by lipase from *Pseudomonas cepecia* (Amano PS)

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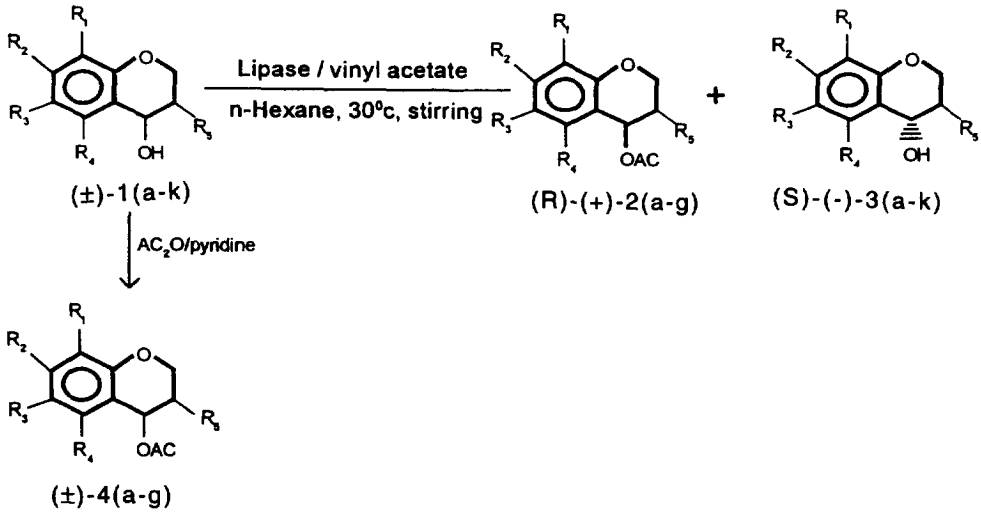
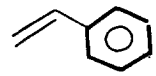
Abstract: Lipase Amano PS catalysed acylation of (±)-chroman-4-ols using vinyl acetate as the acyl donor in n-hexane gave (R)-(+)-chroman-4-ol acetates and (S)-(−)-chroman-4-ols in high enantiomeric excess. The relationship between the position of the substituents in the chroman-4-ol to the ee and the spatial characteristics of the enzyme active site are proposed. © 1997 Elsevier Science Ltd

Substituted chroman-4-ols are an important class of naturally occurring oxygen heterocyclics.[1] Natural chroman-4-ols and chroman-3-ols are homochiral.[1] Enzymes have simplified the route to homochiral compounds which have value as drugs, synthetic intermediates and chiral auxilliaries.[2] Among the enzymes, lipases are more extensively investigated as catalysts for either enantioselective acylation of racemic secondary and primary alcohols or enantioselective hydrolysis of racemic secondary or primary esters.[2] The active site conformation which accommodates the faster reacting enantiomer has been proposed for several lipases[3] and therefore it is possible to predict the absolute configuration of the products. Earlier Majeric *et al.*[4] reported the enantioselective acylation of unsubstituted chroman-4-ol **1a** and some 2,2-disubstituted chroman-4-ols with lipase from Candida cyclindracea (CCL) and proposed an active site model. In this paper we report the results of the kinetic resolution by enantioselective acylation of unsubstituted and 3,5,6,7,8-substituted chroman-4-ols with the lipase from *Pseudomonas cepecia* (Amano PS).



* Corresponding author.

		R1	R2	R3	R4	R5
(±) 1,2,3,	a	H	H	H	H	H
	b	H	H	Cl	H	H
	c	H	H	CH_3	H	H
	d	H	H	Br	H	H
	e	H	H	H	CH_3	H
	f	CH_3	H	H	H	H
	g	H	Cl	H	H	H
	h	H	OCH_3	H	H	H
	I	H	OCH_2-Ph	H	H	H
	j	CH_3	OCH_3	H	H	H
	k	H	H	H	H	

Racemic chroman-4-ols **1a–k** needed were obtained by the $NaBH_4$ reduction of chroman-4-ones.[5–10] Racemic chroman-4-ol acetates **4a–g** were obtained by acylation of **1a–g** with acetic anhydride and pyridine. *Pseudomonas cepecia* lipase (Amano PS) catalysed acylation of racemic chroman-4-ols **1a–k** were carried out with vinyl acetate as the acyl donor in n-hexane at 30°C and the progress of the reaction was monitored by TLC. The reaction was terminated at, or close to, 50% conversion, the enzyme filtered off and the product containing chroman-4-ol and its acetates were separated by column chromatography on silica gel. The ee of the product acetates **2a–g** and the alcohols **3a–k** were determined by chiral HPLC and are shown in Table 1. Good ees were observed for the acetates **2b, d, e, f, g** and the alcohols **3b, d, e, f, i, j**.

However, in the case of reaction of 7-substituted chroman-4-ol **1h** and 7,8-disubstituted chroman-4-ols **1i,j**, the acetates **2h, i, j**, could not be isolated by column chromatography on silica gel as these compounds underwent elimination of AcOH under the acidic conditions of silica gel.

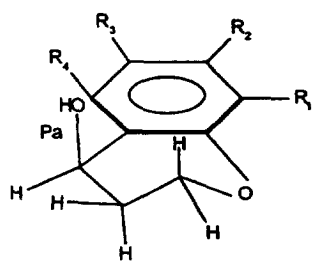
Elaborating on the ideas of Naemura *et al.*,[3] Majeric[4] proposed a cubic spaced active site model for the *Candida cylindracea* lipase (CCL) to explain the enantioselectivity in the acylation of chroman-4-ols. They considered that (R)-chroman-4-ols are the more reactive stereoisomers in this enantioselective acylation and that the 4-hydroxyl is accommodated into the active site in the less stable conformation wherein the hydroxyl is pseudoaxial. The aromatic ring of the chroman-4-ols and the C-2 substituted groups are accommodated in two hydrophobic pockets. They suggested that any substituent on the aromatic ring causes steric interactions with the enzyme active site leading to lowered reaction rates and extent of conversion.[4]

From the results of the present study, we consider that in the case of *Pseudomonas cepecia* lipase (Amano PS) the spatial configuration of the active site is similar to the other lipases such as CCL. The (R)-stereoisomer of chroman-4-ols reacts in the conformation shown in Figure 1a wherein the 4-hydroxyl is pseudoaxial. The enantioselective acylation of (5,6,7,8)-substituted chroman-4-ols is faster and the ee of the products higher indicating that the hydrophobic cavity accommodating the aromatic ring of the chroman-4-ols is larger relative to that in the CCL. Further the 3-substituted chroman-4-ol **1k** did not react at all indicating that the hydrophobic cavity accommodating C-2 and C-3 is smaller (Figure 2).

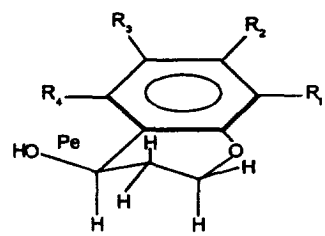
The CD spectra of **2c** and **3c** are shown in Figure 3. The acetates **2a–g** showed positive cotton effect bands at approx. 280 nm and approx. 230 nm while the alcohols **3a–j** showed negative cotton effect with bands at approx. 280 nm and approx. 230 nm (Table 2). Earlier Majeric *et al.* assigned the (R)-configuration to the acetate **2a** and the (S)-configuration to the alcohol **3a** from the helicity rules.[4] Therefore, the acetates **2a–g** are considered to be (R)- while the chroman-4-ols **3a–j** are (S)-configuration.

Table 1. Acylation of (±)-**1a–k** with lipase from *Pseudomonas cepecia* (Amano PS) in n-hexane

Racemic compd	Lipase	Reaction time (hr)	R-(+)-acetate **2a-g** Yield (%)	[α]$_D$ of (+)	S-(-) -alcohol **3a-k** R-(+) acetate	Yield (%)	[α]$_D$ of (-)	S-(-) alcohol
(±)-1 a	Amano PS	20	50	+40.2 (C 0.23)	51.2	50	-55.1 (C 2.41)	70.0
(±) -1 b	Amano PS	9	50	+120.9 (C 1.0)	89.1	50	-24.0 (C 1.0)	80.4
(±) -1 b	Lipase F (AP-15)	48	5	-	-	95	-	-
	Lipase A (Amano-6)	52	3	-	-	97	-	-
	Lipase AY(Amano-30)	72	5	-	-	95	-	-
	Lipase acylase	52	3	-	-	97	-	-
	(Amano - 300000)	48	2	-	-	98	-	-
	Lipase AK(Amano-20)	43	5	-	-	95	-	-
(±) -1 c	Amano PS	20	50	+112.2 (C 1.14)	60.1	50	-22.8 (C 1.46)	59.0
(±) -1 d	Amano PS	17	50	+105.3 (C 1.0)	85.0	50	-17.6 (C 1.0)	96.5
(±) -1 e	Amano PS	3	50	+136.0 (C 1.0)	87.2	50	-50.8 (C 1.0)	99.0
(±) -1 f	Amano PS	7	50	+106.2 (C 1.25)	97.0	50	-28.2 (C 1.0)	98.0
(±) -1 g	Amano PS	6	50	+180.0 (C 0.28)	97.0	50	-56.6 (C 0.93)	59.0
(±) -1 h	Amano PS	8	50	-	-	50	-16.9 (C 2.0)	42.0
(±) -1 i	Amano PS	11	50	-	-	50	-17.0 (C 1.0)	100
(±) -1 j	Amano PS	27	50	-	-	50	-84.6 (C 1.0)	100
(±) -1 k	Amano PS	96	-	-	-	100	-	-



1a) Hydroxyl pseudo-axial



1b) Hydroxyl pseudo-equitorial

Figure 1. Conformers of chroman-4-ols.

Experimental

Melting points were determined in a sulfuric acid bath. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Gemini 200 MHz spectrometer and the chemical shifts are expressed in δ ppm. Optical rotations were measured on a JASCO J-20 polarimeter (Cell size 50 mm) in $CHCl_3$. Mass spectra were recorded on VG Micromass 7070 H spectrometer. CD spectra were record on JASCO J-20 spectropolarimeter.

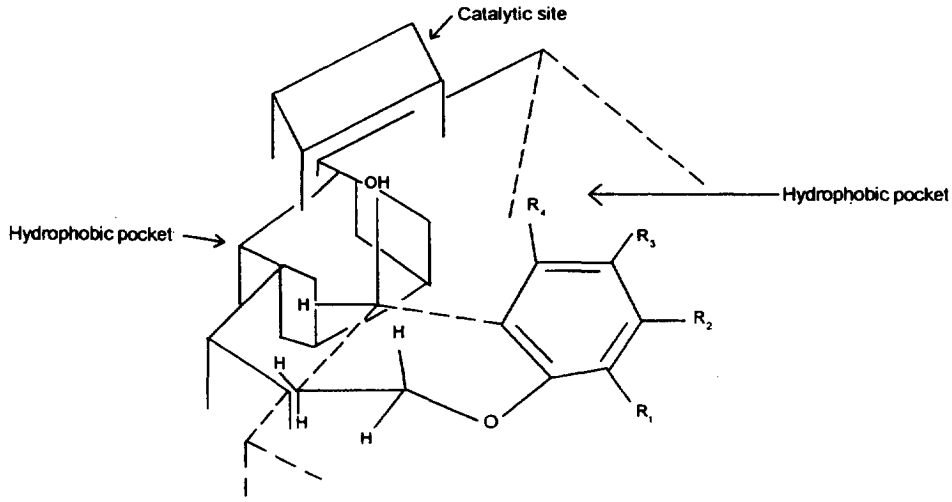


Figure 2. Active site model for Amano PS catalysed acylation of substituted chroman-4-ols.

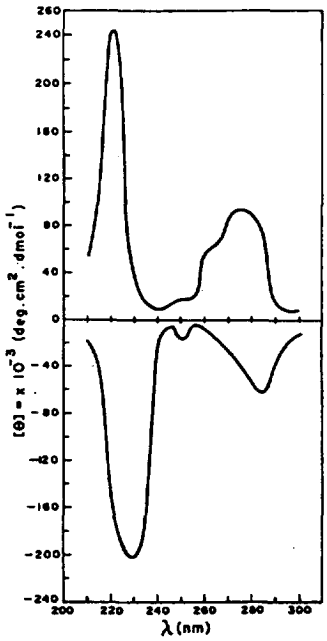


Figure 3. CD Spectra of 6-methyl chroman-4-ol-acetate **2c** and 6-methyl chroman-4-ol **3c** in MeCN.

Progress of the acylation was monitered by TLC on silica gel ACME and column chromatography was done on 'Finer than 200 mesh' silica gel ACME. The chiral HPLC of racemic (±)-**1a–k** was done on chiracel 0D column (25×0.46 cm, Daicel, Japan) under following conditions: flow rate 0.5 ml/min 10% isopropanol in n-hexane as the eluent. The retention times (min) are (±)-**1a** 18.3 and 23.8, (±)-**1b** 13.0 and 14.1, (±)-**1c** 15.7 and 17.9, (±)-**1d** 13.2 and 16.1, (±)-**1e** 11.7 and 15.9, (±)-**1f** 13.5 and 16.9, (±)-**1g** 12.9 and 15.8, (±)-**1h** 22.0 and 27.6, (+)-**1i** 28.2 and 30.0, (±)-**1j** 21.7 and 23.3. The chiral HPLC of the resolved alcohols **3a–j** was done on chiracel OD column (25×0.45 cm, Daicel, Japan) under the following conditions: flow rate 0.5 ml/min with 10% isopropanol in n-hexane as the eluent. The retention times are (−)-**3a** 18.5 and 23.9, (−)-**3b** 13.2 and 14.7, (−)-**3c** 15.8 and 18.0,

Table 2. CD Spectral data of **2a–g** and **3a–j**

Compd No.	Acetates R	Θ (deg.cm^2.d.mol^{-1}	Compd No.	Alcohols S	Θ (deg. cm^2.d.mol^{-1})
2a	(+) 228nm	(+) 79x10^{-3}	3a	(-)228 nm	(-) 200x10^{-3}
	(+) 280nm	(+) 239x10^{-3}		(-)280 nm	(-) 48x10^{-3}
2b	(+) 230nm	(+) 85x10^{-3}	3b	(-)232 nm	(-) 239x10^{-3}
	(+) 290nm	(+) 231x10^{-3}		(-)290 nm	(-) 79x10^{-3}
2c	(+) 228nm	(+) 51x10^{-3}	3c	(-)230 nm	(-) 139x10^{-3}
	(+) 285nm	(+) 139x10^{-3}		(-)285 nm	(-) 39x10^{-3}
2b	(+) 228nm	(+) 86x10^{-3}	3d	(-)238 nm	(-) 240x10^{-3}
	(+) 287nm	(+) 186x10^{-3}		(-)285 nm	(-) 50x10^{-3}
2e	(+) 231nm	(+) 55x10^{-3}	3e	(-)234 nm	(-) 226x10^{-3}
	(+) 284nm	(+) 232x10^{-3}		(-)276 nm	(-) 43x10^{-3}
2f	(+)254nm	(+) 37x10^{-3}	3f	(-)233 nm	(-) 234x10^{-3}
	(+)285nm	(+) 237x10^{-3}		(-)279 nm	(-) 52x10^{-3}
2g	(+)236nm	(+) 45x10^{-3}	3g	(-)233 nm	(-) 239x10^{-3}
	(+)283nm	(+) 234x10^{-3}		(-)275 nm	(-) 47x10^{-3}
			3h	(-)229 nm	(-) 249x10^{-3}
				(-)262 nm	(-) 27x10^{-3}
			3i	(-)236 nm	(-) 220x10^{-3}
				(-)263 nm	(-) 39x10^{-3}
			3j	(-)243 nm	(-) 246x10^{-3}
				(-)279 nm	(-) 33x10^{-3}

(−)-**3d** 13.8 and 15.2, (−)-**3e** 11.7 and 13.9, (−)-**3f** 13.9 and 17.1, (−)-**3g** 13.0 and 16.1, (−)-**3h** 22.1 and 27.8, (−)-**3i** 28.4 and 30.1, (−)-**3j** 22.2 and 23.5. The chiral HPLC of resolved acetate (+)-**2a–g** was done on chiracel OJ column (25×0.46 cm, Daicel, Japan) under the following conditions: flow rate 0.8 ml/min 5% isopropanol in n-hexane as the eluent. The retention times are (+)-**2a** 32.4 and 34.9, (+)-**2b** 10.3 and 12.9, (+)-**2c** 13.4 and 18.5, (+)-**2d** 11.2 and 12.4, (+)-**2g** 9.4 and 10.7.

Chroman-4-ols (±)-**1a–k** are synthesized by the reduction of the corresponding chroman-4-ones using $NaBH_4$ as per the literature procedure.[5–10] Their ^{1}H- and ^{13}C-NMR spectral data are given below.

Chroman-4-ol (±)-1a

IR: 3375 cm^{-1} (OH). UV 219 nm (log ε 3.9). ^{1}H-NMR ($CDCl_3$): δ 4.15 (m, 2H, OCH_2), 1.95 (m, 2H, CH_2), 4.60 (t, J=2 Hz, 1H, H-4), 3.0 (bs, 1H, OH), 6.82 (m, 2H, H-5,H-8), 7.20 (m, 2H, H-6). ^{13}C-NMR ($CDCl_3$): 62.0 (C-2), 37.1 (C-3), 63.0 (C-4), 124.4 (C-4a), 130.0 (C-5), 121.0 (C-6), 130.0 (C-7), 117.0 (C-8), 135.0 (C-8a). MS (m/z) 150 (100), 121 (75), 105 (20), 77 (25) and 51 (20).

6-Chloro-chroman-4-ol (±)-1b

IR: 3352 cm^{-1} (OH). UV 286 nm (log ε 3.1), 231 nm (log ε 3.8). ^{1}H-NMR ($CDCl_3$): δ 4.18 (m, 2H, $0CH_2$), 2.00 (m, 2H, CH_2), 4.65 (bs, 1H, H-4), 1.90 (bs, 1H, 0H), 7.20 (d, J=2 Hz, 1H, H-5), 7.08 (dd, J=10, 2 Hz, 1H, H-7) 6.70 (d, J=10 Hz, 1H, H-8). ^{13}C-NMR ($CDCl_3$): 62.1 (C-2), 30.3 (C-3), 63.3 (C-4), 125.7 (C-4a), 130.0 (C-5), 125.2 (C-6), 129.2 (C-7), 118.5 (C-8), 153.3 (C-8a). MS (m/z) 184 (90), 165 (20), 156 (70), 107 (20), 103 (20), 75 (20), 63 (25) and 39 (20).

*6-Methyl chroman-4-ol (±)-**1c***

IR: 3348 cm^{-1} (OH). UV 283 nm (log ε 3.4), 217 nm (log ε 3.7). ^{1}H-NMR ($CDCl_3$): δ 4.15 (m, 2H, OCH_2), 1.98 (m, 2H, CH_2), 4.60 (t, J=2 Hz, 1H, H-4), 2.40 (bs, 1H, OH), 7.02 (d, J=2 Hz, 1H, H-5), 6.95 (dd, J=10, 2Hz, 1H, H-7), 6.60 (d, J=10 Hz, 1H, H-8), 2.26 (bs, 3H CH_3). ^{13}C-NMR ($CDCl_3$): 62.0 (C-2), 31.0 (C-3), 63.0 (C-4), 124.0 (C-4a), 130.2 (C-5), 130.0 (C-6), 130.0 (C-7), 117.0 (C-8), 152.3 (C-8a), 20.1 (CH_3). MS (m/z) 164 (100), 149 (70), 135 (80, 121 (25), 107 (30), 91 (20), 77 (30) and 51 (20).

*6-Bromo chroman-4-ol (±)-**1d***

IR: 3389 cm^{-1} (OH). UV 286 nm (log ε 3.0), 230 nm (log ε 3.1). ^{1}H-NMR ($CDCl_3$): δ 4.25 (m, 2H, OCH_2), 2.05 (m, 2H, CH_2), 4.75 (m, 1H, H-4), 1.75 (bs, 1H, OH), 7.44 (d, J=2 Hz, 1H, H-5), 7.28 (dd, J=10, 2 Hz, 1H, H-7), 6.72 (d, J=10 Hz, 1H, H-8). ^{13}C-NMR ($CDCl_3$): 62.0 (C-2), 30.3 (C-3), 62.7 (C-4), 126.2 (C-4a), 132.4 (C-5), 112.3 (C-6), 132.1 132.1 (C-7), 119.0 (C-8), 153.8 (C-8a). MS (m/z) 228 (100), 211 (25), 200 (75), 149 (75), 131 (20), 107 (40), 103 (15), 91 (15) and 63 (30).

*5-Methyl chroman-4-ol (±)-**1e***

IR: 3334 cm^{-1} (OH). UV 283 nm (log ε 3.7), 220 nm (log ε 3.0). ^{1}H-NMR ($CDCl_3$): δ 4.24 (m, 2H, OCH_2), 2.10 (m, 2H, CH_2), 4.70 (bs, 1H, H-4), 1.65 (bs, 1H, OH), 6.74 (dd, J=10, 2 Hz, 1H, H-6), 6.74 (dd, J=10, 2 Hz, 1H, H-7), 7.00 (m, 1H, H-8), 2.20 (m, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 62.0 (C-2), 31.0 (C-3), 62.2 (C-4), 123.8, (C-4a), 126.3 (C-5), 127.3 (C-6), 131.0 (C-7), 120 (C-8), 153.0 (C-8a), 160.0 (CH_3).

*8-Methyl chroman-4-ol (±)-**1f***

IR: 3299 cm^{-1} (OH). UV 227 nm (log ε 4.6), 220 nm ε 4.4), ^{1}H-NMR ($CDCl_3$): δ 4.20 (m, 2H, OCH_2), 2.02 (m, 2H, CH_2), 4.70 (bs, 1H, H-4), 1.72 (bs, 1H, OH), 7.21 (m, 2H, CH_2), 4.70 (bs, 1H, H-4), 1.72 (bs, 1H, OH), 7.21 (m 1H, H-5) 6.64 (m, 1H, H-6) 6.64 (m, 1H, H-7), 2.28 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 61.6 (C-2), 30.9 (C-3), 62.9 (C-4), 123.8 (C-4a), 129.0 (C-5), 129.9 (C-6), 130.1 (C-7), 116.7 (C-8), 152.2 (C-8a), 20.4 (CH_3).

*7-Chloro chroman-4-ol (±)-**1g***

IR: 3297 cm^{-1} (OH). UV 287 nm (log ε 3.1), 221 nm (log ε 3.2). ^{1}H-NMR ($CDCl_3$): δ 4.18 (m, 2H, OCH_2), 2.00 (m, 2H, CH_2), 4.68 (bs, 1H, H-4), 1.68 (bs, 1H, OH), 7.12 (d, J=10 Hz, 1H, OH), 7.12 (d, J=10 Hz, 1H, H-5), 6.80 (m 1H, H-6), 6.80 (m, 1H, H-8). ^{13}C-NMR ($CDCl_3$): 62.0 (C-2), 30.8 (C-3), 62.9 (c-4), 122.2 (C-4a), 130.5 (C-5), 121.0 (C-6), 130.1 (C-7), 96.3 (C-8), 154.1 (C-8a). MS (m/z) 184 (96), 65 (35), 55 (100), 149 (95), 131 (10), 130 (5), 91 (10), 75 (20), 63 (15) and 51 (20).

*7-Methoxy chroman-4-ol (±)-**1h***

IR: 3336 cm^{-1} (OH). UV 227 nm (log ε 4.5), 225 nm (log ε 4.6). ^{1}H-NMR ($CDCl_3$): δ 4.48 (m, 2H, OCH_2), 2.05 (m, 2H, CH_2), 4.75 (bs, 1H, OH), 7.20 (d, J=10 Hz, 1H, H-5), 6.52 (dd, J=10, 2Hz, 1H, H-6), 6.38 (d, J=2 Hz, 1H, H-8), 3.80 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$) 61.7 (C-2), 30,8 (C-3), 62.0 (C-4), 130.8 (C-4a), 131.0 (C-5), 116.8 (C-6), 130.9 (C-7), 101.1 (C-8), 155.5 (C-8a), 55.1 (OCH_3).

*7-Benzyloxy chroman-4-ol (±)-**1i***

IR: 3364 cm^{-1} (OH). UV 256 nm (log ε 3.4), 230 nm (log ε 3.8). ^{1}H-NMR ($CDCl_3$): δ 4.18 (m, 2H, OCH_2), 2.00 (m, 2H, CH_2), 4.63 (bs, 1H, H-4), 1.52 (bs, 1H, OH), 7.10 (d, J=10 Hz, 1H, H-5), 6.47 (dd, J=10, 2 Hz, 1H, H-6), 6.32 (d, J=2 Hz, 1H, H-8), 4.95 (s, 2H, OCH_2), 7.30 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$): 61.7 (C-2), 30.8 (C-3), 61.7 (C-4), 117.1 (C-4a), 128.4 (C-5), 108.3 (C-6), 159.7 (C-7), 102.3 (C-8), 155.5 (C-8a), 69.7 (OCH_2), 127.2, 128.4 136.8, 130.5 (Ph).

*7-Methoxy 8-methyl chroman-4-ol (±)-**1j***

IR: 3375 cm^{-1} (OH). UV 283 nm (log ε 3.0), 209, 209 nm (log ε 3.3). ^{1}H-NMR ($CDCl_3$): δ 4.38 (m, 2H, OCH_2), 4.80 (bs, 1H, H-4), 1.75 (d, J=6 Hz, 1H, OH), 7.15 (d, J=10 Hz, 1H, H-5), 6.55 (d,

J=10 Hz, 1H, H-6), 3.90 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$); 61.9 (C-2), 30.9 (C-3), 63.4 (C-4), 117,3 (C-4a), 127.0 (C-5), 103.1 (C-6), 153.1 (C-7), 113.7 (C-8), 158.3 (C-8a), 55.7 (OCH_3), 8.0 (CH_3).

*3-Benzilidine 6-chloro chroman-4-ol (±)-**1k***

IR: 3274 cm^{-1} (OH). UV 284 nm (log ε 3.0), 220 nm (log ε 3.1). ^{1}H-NMR ($CDCl_3$): δ 4.85 (s, 2H, OCH_2), 5.15 (d, J=8 Hz, 1H, H-4), 1.90 (bs, 1H, OH), 7.10–7.50 (m, 1H, H-5), 7.10–7.50 (m, 1H, H-7), 6.74 (d, J=9 Hz, 1H, H-8), 6.90 (1H, =CH), 7.10–7.50 (m, 5H, Ph).

*Chroman-4-ol acetate (±)-**4a***

UV 277 nm (log ε 3.5), 219 nm (log ε 3.7). ^{1}H-NMR ($CDCl_3$): δ 4.25 (m, 2H, OCH_2), 2.15 (m, 2H, CH_2), 5.90 (t, J=2 Hz, 1H, H-4), 2.08 (s, 3H, O–CO–CH_3), 6.80 (m, 1H, H-5), 7.20 (m, 1H, H-6), 7.20 (m, 1H, H-7), 6.80 (m, 1H, H-8). ^{13}C-NMR ($CDCl_3$): 61.7 (C-2), 27.9 (C-3), 64.9 (C-4), 120.1 (C-4a), 130.5 (C-5), 120.4 (C-6), 130.0 (C-7), 116 (C-8), 155.2 (C-8a), 170.4 (O–CO–CH_3), 20.9 (CH_3). MS (m/z) 192 (30), 150 (30) 131 (100), 105 (50) 77 (40), 51 (20) and 43 (50).

*6-Chloro chroman-4-ol acetate (±)-**4b***

UV: 288 nm (log ε 3.9), 230 (log ε 3.8) ^{1}H-NMR ($CDCl_3$): δ 4.25 (m, 2H, OCH_2), 2.15 (m, 2H, CH_2), 5.85 (t, J=2 Hz, 1H, H-4), 2.10 (s, 3H, O–CO–CH_3), 7.22 (d, J=2.5 Hz, 1H, H-5) 7.15 (dd, J=10, 2 Hz, 1H, H-7) 6.75 (d, J=10 Hz, 1H, H-8). ^{13}C-NMR ($CDCl_3$): 62.0 (C-2), 27.7 (C-3), 64.5 (C-4), 125.1 (C-4a), 130.1 (C-5), 121.6 (C-6), 129.9 (C-7), 118.4 (C-8), 153.9 (C-8a), 170.3 (O–CO–CH_3), 20.9 (CH_3).

*6-Methyl chroman-4-ol acetate (±)-**4c***

UV 284 nm (log ε 3.4), 220 nm (log ε 2.9). ^{1}H-NMR ($CDCl_3$): 4.15 (m, 2H, OCH_2), 2.10 (m, 2H, CH_2), 5.84 (t, J=2 Hz, 1H, H-4), 2.05 (s, 3H, O–CO–CH_3), 7.0 (t, J=2.5 Hz, 1H, H-5), 2.22 (s,3H, CH_3), 6.95 (dd, J=10, 2 Hz, 1H, H-7), 6.68 (t, J=10 Hz, 1H, H-8). ^{13}C-NMR ($CDCl_3$): 61.2 (C-2), 27.7 (C-3), 64.7 (C-4), 119.4 (c-4a) 130.4 (C-5), 129.0 (C-6), 130.2 (C-7), 116.3 (C-8), 152.7 (C-8a), 169.8 (O–CO–CH_3), 19.5 (CH_3), 20.3 (6-CH_3). MS (m/z) 206 (40), 164 (40), 149 (15), 145 (100), 131 (10), 119 (35), 91 (30), 77 (25) and 51 (10).

*6-Bromo chroman-4-ol acetate (±)-**4d***

UV 289 nm (log ε 3.7), 230 nm (log ε 3.8). ^{1}H-NMR ($CDCl_3$): δ 4.25 (m, 2H, OCH_2), 2.15 (m, 2H, CH_2), 5.85 (t, J=2 Hz, 1H, H-4), 2.10 (s, 3H, O–CO–CH_3), 7.38 (t, J=2.5 Hz, 1H, H-5), 7.30 (dd, J=10, 2Hz, 1H, H-7), 6.70 (d, J=10 Hz, 1H, H-8). ^{13}C-NMR ($CDCl_3$): 62.1 (C-2), 27.7 (C-3), 64.4 (C-4), 122.2 (C-4a), 133.0 (C-5), 112.3 (C-6), 133.0 (C-7), 119.0 (C-8), 154.4 (C-8a), 170.4 (O–CO–CH_3), 21.0 (CH_3). MS (m/z) 270 (4), 220 (45), 211 (90), 149 (45), 149 (45), 149 (45), 137 (95), 103 (40), 77 (45) and 51 (40).

*5-Methyl chroman-4-ol acetate (±)-**4e***

UV 282 nm (log ε 3.1), 231 nm (log ε 3.4). ^{1}H-NMR ($CDCl_3$): δ 4.30 (m, 2H, OCH_2), 2.15 (m, 2H, CH_2), 5.92 (t, J=2 Hz, 1H, H-4), 2.80 (s, 3H, O–CO–CH_3), 2.20 (s, 3H, CH_3), 7.10 (m, 1H, H-6) 6.80 (dd, J=9.9. 2 Hz, 1H, H-7), 7.10 (m, 1H, H-8).

*8-Methyl chroman-4-ol acetate (±)-**4f***

UV 285 nm (log ε 3.9), 221 nm (log ε 4.1). ^{1}H-NMR ($CDCl_3$): δ 4.18 (m, 2H, OCH_2), 2.10 (m, 2H, CH_2), 5.85 (t, J=2 Hz, 1H, H-4), 2.05 (s, 2H, –O–CO–CH_3), 6.62 (m, 1H, H-5), 7.10 (m, 1H, H-6), 6.62 (m, 1H, H-7), 2.22 (s, 3H, CH_3).

*7-Chloro chroman-4-ol acetate (±)-**4g***

UV 286 nm (log ε 3.6), 232 nm (log ε 3.8). ^{1}H-NMR ($CDCl_3$): δ 4.20 (m, J=2 Hz, 2H, OCH_2), 2.05 (m, 2H, CH_2), 5.80 (t, J=2 Hz, 1H, H-4), 2.00 (s, 3H, O–CO–CH_3), 7.12 (1H, H-5), 6.75 (1H, H-6), 6.75 (1H, H-8).

General procedure for the lipase mediated enantioselective acylation of chroman-4-ols ***1a–k***

Chroman-4-ol (250 mg) was dissolved in n-hexane (50 ml). To this solution lipase Amano PS (250 mg) was added and the suspension was thermostated at 30°C. After a few minutes vinyl acetate (5 ml) was added and the reaction mixture stirred on a magnetic stirrer and monitored by TLC. After about 50% conversion, the lipase was filtered off, hexane evaporated and the resulting gum chromatographed on silica gel by eluting with chloroform:n-hexane 3:7 v/v. Acetates **2a–g** and alcohols **3a–k** were obtained (Table 1).

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References

1. G. P. Ellis, Ed., *Chromones, Chromanones, and Chromones,* John Wiley & Sons Ltd, New York, **1977**.
2. Roberts, S. M.; Wiggins, K.; Casy K.; and Phythian, S.; *Preparative Biotransformations of Whole Cell and Isolated Enzymes in Organic Synthesis,* John Wiley & Sons Ltd, New York, **1993**.
3. Naemura, K.; Fukuda, R.; Konishi, M.; Hirose, K.; and Tobe, Y.; *J. Chem. Soc. Perkin Trans I,* **1994**, 1253.
4. Majeric, M.; Gelo-Pujic, M.; Sunjic, V.; Levai. A.; Sebox, P.; and Timar, T.; *Tetrahedron: Asymmetry,* **1995**, *6,* 937.
5. Parham, W. E.; and Huestis, L. D.; *J. Am. Chem. Soc.*, **1962**, *84,* 813.
6. Thakar, G. P.; Janaki, N.; and Subba Rao, B. C.; *Indian. J. Chem.*, **1965**, *3*(2), 74.
7. Clark-Lewis, J. W.; and Megarry, E. J.; *Aust. J. Chem.*, **1973**, *26,* 819.
8. Ibrahim, A. R.; Yusuf, J.; and Abul-Hajj, Y. J.; *J. Nat. Prod.*, **1990**, *53,* 1471.
9. Willhalm, B.; Thomas, A. F.; and Gautschi, F.; *Tetrahedron,* **1964**, *20,* 1185.
10. Pratap, R.; Gupta, R. C.; and Anand, N.; *Indian J. Chem.*, **1981**, *20B,* 1063.

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