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Candida rugosa lipase-mediated enantioselective acetylation studies on (±)-3-arylmethyl-3-hydroxymethyl-2,3-dihydro-1-benzopyran-4(*H*)-ones

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Candida rugosa lipase, catalyzed enantioselective acetylation reactions have been performed on novel (±)-3-arylmethyl-3-hydroxymethyl-2,3-dihydrobenzopyran-4-ones in diisopropyl ether. The *Candida rugosa* lipase-catalyzed acetylations exhibit the enantiomeric separation of the racemic compounds **5a-g**, the enantioselectivity of the reaction has been found to be highly dependent on the structure of the substrate. The enantiomeric excess (*ee*) values are determined by ^{1}H NMR spectral analysis of their *O*-acetylmandelic acid esters and highest enantiomeric excess obtained is 79% in case of **5c**.

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The stereo-controlled synthesis of a variety of complex organic molecules has been possible because of the tremendous developments in synthetic organic chemistry. There is a growing need to develop such synthetic processes, which are environmentally benign as well as, economically feasible. It is at this juncture that the use of enzymes comes in handy.

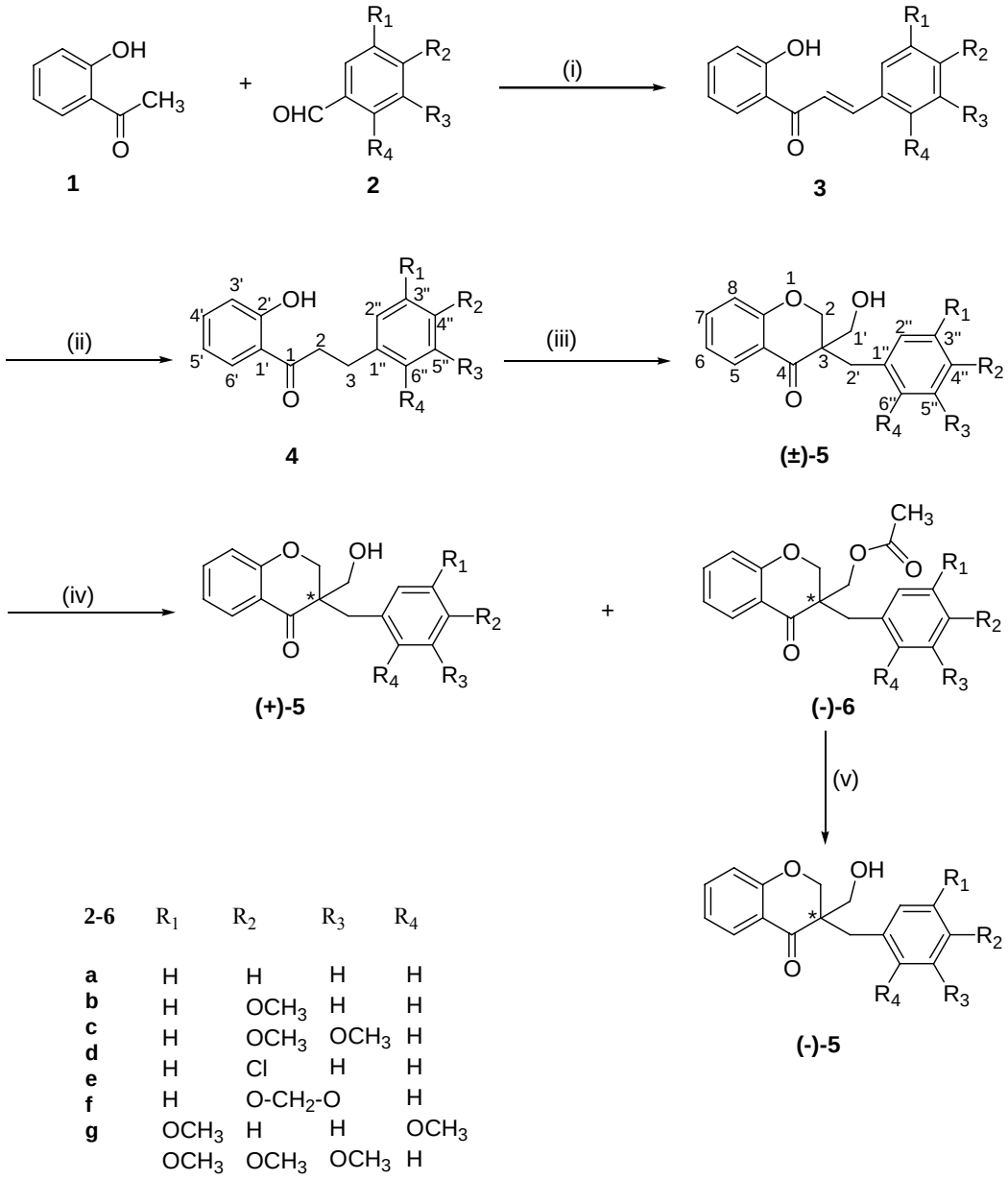
The explosion of interest in biocatalysis has come as a surprise to the generation of chemists and biologists who are struggling to accommodate a new methodology called "biotransformation". Enzymes have been increasingly exploited by chemists in the preparation of chiral synthones and target molecules because they can accelerate reactions specifically and selectively[1]. A large number of synthones of biologically active compounds, *i.e.* pharmaceuticals and agrochemicals, have been synthesized, using enzymes as catalysts[2-4]. The enzyme-assisted organic synthesis involves a relatively simple procedure and the products are obtained in a fairly high state of purity. Among the different enzymatic processes, lipase-catalyzed acylation and deacylation reactions represent an important class of enzymatic transformations in organic synthesis. This is due to their low cost and wide tolerance towards a variety of organic molecules[5,6]. Lipases from *Candida rugosa* (CRL), porcine pancreas (PPL), *Pseudomonas fluorescens* (PFL) and *Candida antarctica* (CAL) are the most extensively used enzymes for stereoselection.

In recent years, our group has been actively involved in the lipase catalyzed transformations on a variety of biologically important class of compounds, *i.e.* aryl alkyl ketones[7], hydroxymethylated phenolic compounds[8], polyacetoxy chalcones[9,10] and chromanones[11], and we were able to generate a variety of well-defined and functionalized compounds under mild reaction conditions. In the present paper, we have carried out studies involving *Candida rugosa* lipase (CRL)-catalyzed acetylation of (±)-3-arylmethyl-3-hydroxymethyl-2,3-dihydro-1-benzopyran-4(*H*)-ones **5a-g** to get optically enriched (+)-**5a-g**. These compounds, generally known as chromanones are widely distributed in the plant kingdom[12-15] and possess a variety of biological activities[16-22], *viz.* anticonvulsant[16], antimicrobial[17], antiinflammatory[18], antifungal[19], etc. Several chiral chromanones, substituted at C-2 and/or C-3 position(s) have been isolated from natural sources and quite a few of them are therapeutically useful[12-14,23]. The present studies provide a novel biocatalytic route for the synthesis of optically enriched chromanones, under mild reaction conditions as compared to corresponding chemical reactions which in turn require expensive chiral

chemicals such as chiral ligands, chiral auxiliaries and chiral reagents.

Results and Discussion

Seven *racemic* (±)-3-arylmethyl-3-hydroxymethyl-2,3-dihydro-1-benzopyran-4(*H*)-ones **5a-g** have been synthesized by the hydroxymethylation reaction on the corresponding 2'-hydroxydihydrochalcones[24-27] **4a-g**, which in turn were prepared by the catalytic hydrogenation of the corresponding 2'-hydroxy-chalcones[24,25,27-30] **3a-g** (**Scheme I)**. The physical and spectral data of the compounds **3a-g** compared well with those reported in the literature for these compounds[30]. Although all the dihydrochalcones are known in the literature but we were not able to locate their spectral data. The ^{1}H NMR and ^{13}C NMR spectral data of the compounds **4a-g** are given in **Tables I** and **II**. The hydroxymethylation reaction was done using formaldehyde (37%) in 0.5*N* sodium hydroxide at room temperature affording the corresponding *racemic* 3-arylmethyl-3-hydroxymethyl-2,3-dihydro-1-benzopyran-4(*H*)-ones **5a-g** in 63-68% yields[31]. All the synthesized compounds were fully characterized from their detailed spectral data.



2-6	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	OCH_3	H	H
c	H	OCH_3	OCH_3	H
d	H	Cl	H	H
e	H	O-CH_2-O		H
f	OCH_3	H	H	OCH_3
g	OCH_3	OCH_3	OCH_3	H

Scheme I— Reagents and conditions: (i) $Ba(OH)_2$, ethanol, reflux; (ii) H_2, Pd/C, EtyOAc; (iii) 0.5 N NaOH, 37% HCHO, 28-30°C; (iv) *Candida rugosa* lipase, diisopropyl ether, vinyl acetate, stirring at 38-40°C; (v) MeOH-HCl, stirring at 25-28°C

Table I— ^{1}H NMR spectral data of dihydrochalcones **4a-g**

Compd	^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm)
4a (Colourless oil)	3.04 (2H, t, *J*=7.3 Hz, C-3H), 3.32 (2H, t, *J*=7.2 Hz, C-2H), 6.84-6.89 (1H, m, C-5'H), 6.98 (1H, d, *J*=8.4 Hz, C-3'H), 7.18-7.33 (5H, m, C-2"H, C-3"H, C-4"H, C-5"H and C-6"H), 7.42-7.48 (1H, m, C-4'H), 7.72-7.75 (1H, dd, *J*=8.0 and 1.5 Hz, C-6'H) and 12.30 (1H, s, chelated OH).
4b (m.p. 42°C)	3.01 (2H, t, *J*=7.9 Hz, C-3H), 3.28 (2H, t, *J*=7.9 Hz, C-2H), 3.79 (3H, s, OCH_3), 6.83-6.89 (3H, m, C-3"H, C-5"H, C-5'H), 6.96-6.99 (1H, m, C-3'H), 7.16 (2H, d, *J*=8.5 Hz, C-2"H and C-6"H), 7.43-7.48 (1H, m, C-4'H), 7.72-7.75 (1H, dd, *J*=8.5 and 1.5 Hz, C-6'H) and 12.31 (1H, s, chelated OH).
4c (m.p. 90-91°C)	3.02 (2H, t, *J*=7.5 Hz, C-3H), 3.32 (2H, t, *J*=7.3 Hz, C-2H), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.77-6.83 (3H, m, C-2"H, C-5"H and C-6"H), 6.85-6.91 (1H, m, C-5'H), 6.99 (1H, d, *J*= 12 Hz, C-3'H), 7.44 -7.50 (1H, m, C-4'H), 7.74-7.77 (1H, dd, *J*= 8.1 and 1.5 Hz, C-6'H) and 12.32 (1H, s, chelated OH).
4d (m.p. 60°C)	3.04 (2H, t, *J*=7.3 Hz, C-3H), 3.31 (2H, t, *J*=7.7 Hz, C-2H), 6.85-6.90 (1H, m, C-5'H), 6.97-7.00 (1H, m, C-3'H), 7.18 (2H, d, *J*= 8.4 Hz, C-2"H and C-6"H), 7.28 (2H, d, *J*=8.3 Hz, C-3"H and C-5"H), 7.43-7.49 (1H, m, C-4'H), 7.71-7.74 (1H, dd, *J*=7.7 and 1.5 Hz and C-6'H) and 12.34 (1H, s, chelated OH).
4e (m.p. 70-72°C)	2.99 (2H, brs, C-3H), 3.28 (2H, t, *J*=7.9 Hz, C-2H), 5.93 (2H, s, OCH_2O), 6.67-6.76 (3H, m, C-2"H, C-5"H and C-6"H), 6.85-6.90 (1H, m, C-5'H), 6.97-6.99 (1H, dd, *J*=7.9 and 0.9 Hz, C-3'H), 7.43-7.48 (1H, m, C-4'H), 7.72-7.76 (1H, dd, *J*=7.8 and 1.5 Hz, C-6'H) and 12.28 (1H, s, chelated OH).
4f (m.p. 47-48°C)	2.99 (2H, brs, C-3H), 3.23 (2H, brs, C-2H), 3.73 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 6.72-6.96 (5H, m, C-3'H, C-5'H, C-2"H, C-4"H and C-5"H), 7.41 (1H, brs, C-4'H), 7.74 (1H, brs, C-6'H) and 12.35 (1H, s, chelated OH).
4g (semisolid)	3.01 (2H, t, *J*=7.5 Hz, C-3H), 3.32 (2H, t, *J*=7.8 Hz, C-2H), 3.80 (3H, s, OCH_3), 3.85 (6H, s, 2 × OCH_3), 6.45 (2H, s, C-2"H and C-6"H), 6.88 (1H, t, *J*= 7.2 Hz C-5'H), 6.99 (1H, d, *J*=8.3 Hz, C-3'H), 7.44-7.50 (1H, m, C-4'H), 7.73-7.76 (1H, dd, *J*=8.4Hz, 0.9 Hz, C-6'H) and 12.28 (1H, s, chelated OH).

Table II— ^{13}C NMR spectral data of dihydrochalcones **4a-g**

Compd	C-1	C-2	C-3	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-1"	C-2"	C-3"	C-4"	C-5"	C-6"	OCH_3	OCH_2O
4a	205.79	40.43	30.45	141.14	162.90	118.99	136.74	119.33	130.23	119.71	128.80	129.02	126.74	129.02	128.80	-	-
4b	205.96	40.70	29.65	133.14	162.90	118.96	136.70	119.29	130.24	119.68	129.72	130.24	158.56	130.24	129.72	55.68	-
4c	203.95	39.03	28.51	132.05	161.22	117.31	135.09	117.65	128.58	118.06	110.60	147.74	146.32	110.18	118.92	54.69, 54.61	
4d	205.30	40.10	29.65	132.49	162.86	119.01	136.82	119.33	129.06	119.61	130.15	130.09	139.55	130.09	130.15	-	-
4e	203.40	40.67	30.20	134.89	162.89	118.99	136.75	119.31	130.20	119.70	109.28	148.14	147.68	108.74	121.57	-	101.28
4f	208.58	41.01	28.41	138.52	164.88	118.99	132.46	121.19	132.46	120.79	113.58	155.96	114.01	113.58	154.15	58.05, 58.11	
4g	206.21	40.98	31.39	137.53	163.34	119.73	137.21	119.43	130.63	120.18	106.41	154.16	147.52	154.16	106.41	56.99, 61.65	

Enzymatic enantioselective acetylations on (±)-**5a-g** were tried in the presence of porcine pancreatic lipase (PPL) in tetrahydrofuran and *Candida rugosa* lipase (CRL) in diisopropyl ether. The hydroxymethylated chromanones (±)-**5a-g** were found to be good substrates for *Candida rugosa* lipase (CRL) in diisopropyl ether based on the kinetics of the acetylation reaction, the reactions with porcine pancreatic lipase were extremely slow. The selection of the solvent for the acetylation reactions catalyzed by PPL and CRL was based on our earlier experiences. In a typical reaction, the (±)-3-hydroxymethylchromanone **5a-g** was incubated with CRL and vinyl acetate in diisopropyl ether at 38-40°C. The progress of the reaction was monitored on TLC and/or HPLC (methanol-water, 70:30) using a CL-column ODS (M), UV detector (254 nm) and at 0.5 mL min^{-1} flow rate, and the reaction was worked-up at about 45-50% conversion of the starting substrate into the 3-acetoxymethylchromanones **6a-g** by filtering off the enzyme. The enzymatic reaction products *viz.* (-)-**6a-g** and the unreacted hydroxymethylchromanones (+)-**5a-g** were separated by column chromatography on silica gel with a gradient solvent system of petroleum ether - ethyl acetate and their optical rotations were measured, both series of these compounds were found

to be optically active (**Tables III** and **IV**). Further, the enzymatically obtained acetoxymethylchromanones (-)-**6a-g** were deacetylated chemically by stirring with MeOH-HCl to obtain the (-)-hydroxymethylchromanones **5a-g**. The optical rotation values, $[\alpha]_D^{25}$ of (-)-hydroxymethylchromanones obtained by chemical deacetylation of the enzymatically acetylated chromanones **6a-g** and those of the unreacted (+)-hydroxymethylchromanones **5a-g** were of opposite signs and were quite comparable **(Table IV)**, which indicates the optical enrichment during the biocatalytic reaction. All these reactions when performed under identical conditions but without addition of the enzyme did not yield any product.

The enantiomeric excess values of (+)-3-hydroxymethylchromanones **5a-g** were determined by ^{1}H NMR spectral analysis of their *O*-acetylmandelic acid esters **(Table III)**. The synthesis of *O*-acetylmandelates was achieved by the reaction of (+)/(±) alcohols **5a-g** with (*S*)-(+)-*O*-acetylmandelic acid in dichloromethane according to the procedure of Whitesell *et.al*[32]. The results of *ee* determination indicated that the nature and extent of substitution in the C-3 benzyl moiety affects the extent of enantioselection (**Table III**). The 3-benzyl-3-hydroxymethyl-1-benzopyran-4(*H*)-one **5a**, which lacks any substitution in the C-3 benzyl moiety, has extremely low and the least *ee* value (4%) among the seven compounds studied. Among monosubstitued benzyl derivatives, the one having an electron withdrawing group, *viz.* chloro at the *para* position has a lower *ee* value; thus 3-(4'-chlorobenzyl)-3-hydroxymethyl-1-benzopyran-4(*H*)-one **5d** showed *ee* value of 10% only, while presence of electron donating group at the *para* position causes more than three times higher *ee* value as 3-hydroxymethyl-3-(4'-methoxybenzyl)-1-benzopyran-4(*H*)-one **5b** shows *ee* of 33%. The number of + I directing groups (OMe groups) in the C-3 benzyl moiety has great influence on *ee* values. Thus, both 3-(3',4'-dimethoxybenzyl)-3-hydroxymethyl-1-benzopyran-4(*H*)-one **5c** and 3-hydroxymethyl-3-(3',4'-methylenedioxbenzyl)-1-benzopyran-4(*H*)-one **5e** show quite high *ee* values of 79% and 65%, respectively. Similarly 3-hydroxymethyl-3-(3',4',5'-trimethoxybenzyl)-1-benzopyran-4(*H*)-one **5g** having

Table III—Enantioselective acetylation of **(±)-5a-g** catalyzed by *Candida rugosa* lipase in diisopropyl ether at 38-40°C[a]

Entry	Substrate	Reaction time (hr)	Product (% yield)[b]	% *ee* of **(+)-5a-g**
1	(±)-**5a**	8	(+)-**5a** (62) and (-)-**6a** (66)	4
2	(±)-**5b**	5	(+)-**5b** (65) and (-)-**6b** (68)	33
3	(±)-**5c**	6	(+)-**5c** (67) and (-)-**6c** (66)	79
4	(±)-**5d**	7	(+)-**5d** (62) and (-)-**6d** (64)	10
5	(±)-**5e**	8	(+)-**5e** (60) and (-)-**6e** (65)	65
6	(±)-**5f**	7	(+)-**5f** (65) and (-)-**6f** (67)	8
7	(±)-**5g**	8	(+)-**5g** (64) and (-)-**6g** (66)	59

[a]All these reactions, when performed under identical conditions, but without adding *Candida rugosa* lipase, did not yield any product.
[b]Yields are calculated by assuming corresponding single enantiomer as 100% in the starting (±)-3-acetoxymethylchromanones **5a-g**

Table IV—Optical rotation values ($[\alpha]_D^{25}$ in $CHCl_3$) of CRL-catalyzed acetylated products, *i.e.* (-)-3-acetoxymethyldihydrobenzopyranones **6a-g**, and the recovered, unreacted (+)-3-hydroxymethyldihydrobenzopyranones **5a-g**, and chemically deacetylated products (-)-3-hydroxymethyldihydrobenzopyranones **5a-g**

$[\alpha]_D^{25}$ Values of the 3-acetoxymethyl-dihydrobenzopyranones **6a-g** obtained by enzymatic acetylation of *racemic* **5a-g**	$[\alpha]_D^{25}$ Values of the recovered, unreacted 3-hydroxymethyl -dihydrobenzopyranones **5a-g**	$[\alpha]_D^{25}$ Values of the 3-hydroxymethyl-dihydrobenzopyranones **5a-g** obtained by chemical deacetylation of enzymatically obtained acetates **(-)-6a-g**
6a: (-) 8.00	**5a**: (+) 6.00	**5a**: (-) 7.20
6b: (-) 9.60	**5b**: (+) 14.25	**5b**: (-) 12.00
6c: (-) 12.40	**5c**: (+) 7.08	**5c**: (-) 9.42
6d: (-) 15.00	**5d**: (+) 8.90	**5d**: (-) 11.50
6e: (-) 6.06	**5e**: (+) 9.09	**5e**: (-) 10.80
6f: (-) 11.25	**5f**: (+) 15.00	**5f**: (-) 13.42
6g: (-) 7.05	**5g**: (+) 8.15	**5g**: (-) 10.35

three methoxy groups in the benzyl moiety shows *ee* of 59%, the *ee* value is lower in this case than in **5c** and **5e** despite the presence of three methoxy groups, probably because of the steric factors. It is further shown from these studies that the presence of a $-OCH_3$ group at the C-4 position in the benzyl moiety is necessary for better enantioselection. Though the compound 3-(2',5'-dimethoxybenzyl)-3-hydroxymethyl-1-benzopyran-4(*H*)-one **5f** contains two methoxy groups, but it shows a very low value of *ee* (8%) than the compound **5c** which contains two methoxy groups at the C-3 and C-4 positions in the benzyl moiety because the compound **5f** lacks the C-4' methoxy group. Out of fourteen compounds made, three compounds **5a**, **5d** and **5e** are known in the literature[31].

Conclusion

To conclude, the present study has shown interesting and potentially useful enantioselective capabilities of *Candida rugosa* lipase for the enantiomeric separation of *racemic* 3-arylmethyl-3-hydroxymethyl-2,3-dihydro-1-benzopyran-4(*H*)-ones **5a-g**. Further, as it is not that easy to synthesize such compounds in enantiomerically enriched forms by purely chemical methods, the biocatalytic approach reported herein may find utility in the synthesis of optically enriched compounds of this class.

Experimental Section

General. Melting points were determined on a sulphuric acid bath and are uncorrected. The IR spectra were recorded either on a Perkin-Elmer model 2000 FT-IR or RXI FT-IR spectrophotometer. The UV spectra were recorded on a Cary 100 Biospectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75.5 MHz, respectively using TMS as internal standard. The chemical shift values are on δ scale and the coupling constant values (*J*) are in Hz. The HRMS were recorded on a JMS-AX 505 W instrument at 70 eV in FAB (positive or negative ion mode) using HEDS (*bis*-hydroxyethyldisulphide) doped with sodium ions and NBA (3-nitrobenzylalcohol) as matrix. Optical rotation values were measured on a Bellingham Stanley ADP 220 polarimeter. HPLC runs were performed on a Shimadzu LC-10AS HPLC instrument with SPD-10A UV-Vis detector using a CL-column-ODS(M), UV detector (254 nm) and at 0.5 mL min^{-1} flow rate. Analytical TLCs were performed on precoated Merck silica gel $60F_{254}$ plates; the spots were detected either under UV light, charring with 10% alcoholic H_2SO_4 or by spraying with 5% alcoholic $FeCl_3$ solution. The enzymes, porcine pancreatic lipase (PPL, Type II) and *Candida rugosa* lipase (CRL, Type VII) were purchased from Sigma and Aldrich Chemical Co. (USA), respectively and used after storing *in vacuo* over P_2O_5 for 24 hr. The organic solvents (THF and DIPE) used were dried and distilled over molecular sieves (4Å) prior to their use. (*S*)-(+)-*O*-Acetylmandelic acid (*ee* 99%) was purchased from Aldrich Chemical Co. (USA).

Preparation of 1,3-diphenylpropenones (chalcones 3a-g). To a solution of *o*-hydroxyacetophenone (1.36 g, 10 mmoles) and substituted benzaldehyde (**2a-g**, 10 mmoles) in dry ethanol (20 mL) was added freshly fused barium hydroxide (0.20 g) and the contents refluxed for 6-7 hr. The progress of the reaction was monitored by TLC (petroleum ether-ethyl acetate, 4:1). After completion, the reaction mixture was poured onto crushed ice and the *p*H of the solution was made acidic using dilute hydrochloric acid. The solid obtained was filtered, dried and recrystallized from ethanol to give yellow needles of **3a-g** in 70-86% yields; these were characterized on the basis of their physical and spectral data and by comparing them with the data reported in the literature[24,25,28-30].

Preparation of 1,3-diphenylpropanones 4a-g. To a solution of **3a-g** (1 g, 3.5-4.5 mmoles) in dry ethyl acetate (15 mL) taken in the reaction bottle of atmospheric pressure hydrogenation apparatus, palladium-charcoal (10%, 0.1 g) was added. The air was displaced with hydrogen and the mixture was shaken for 1 hr. The progress of the reaction was monitored by TLC (petroleum ether-ethyl acetate, 4:1). After completion, palladium-charcoal was filtered and ethyl acetate was removed under vacuum. The solid obtained was purified using column chromatography to obtain **4a-g** in 72-82% yields; these were characterized on the basis of their physical and spectral data[24-27].

Preparation of 3-arylmethyl-3-hydroxymethyl-1-benzopyran-4(*H*)-ones 5a-g. A solution of **4a-g** (0.5 g, 1.6-2.2 mmoles) in sodium hydroxide (0.5 N, 4.0 equiv.) and formaldehyde (37%, 4.5 equiv.) was stirred at 25-28ºC. The progress of the reaction was monitored by TLC (checked in petroleum ether-ethyl acetate, 3:2). On completion, reaction was stopped by

acidification with dilute hydrochloric acid. The product was extracted with ether (2 × 30 mL), the ethereal layer combined, washed with brine (2 × 30 mL), dried over sodium sulfate and the solvent removed under vacuum to afford a gummy residue, which was purified by column chromatography on silica gel using a gradient solvent system of petroleum ether-ethyl acetate (3:2) to afford pure hydroxymethylated chromanones **5a-g** in 63-68 % yields.

(±) -3-Benzyl-3-hydroxymethyl-1-benzopyran-4(*H*)-one 5a: It was obtained as thick colourless oil (0.384 g) in 65% yield, R_f 0.30 (petroleum ether-ethyl acetate, 3:2); IR (nujol): 3465 (OH), 2924, 1681 (C=O), 1606, 1478, 1304, 1213, 1144, 1036, 941 and 760 cm^{-1}; UV (MeOH): 322, 250, 241 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 (1H, brs, CH_2OH), 2.96 (1H, d, J = 13.4 Hz, C-2'H_α), 3.03 (1H, d, J = 13.4 Hz, C-2'H_β), 3.55 (1H, d, J = 11.5 Hz, C-1'H_α), 3.71 (1H, d, J = 11.5 Hz, C-1'H_β), 4.15 (1H, d, J = 11.7 Hz, C-2H_α), 4.23 (1H, d, J = 11.7 Hz, C-2H_β), 7.02-7.09 (2H, m, C-6H and C-8H), 7.22-7.34 (5H, m, C-2"H, C-3"H, C-4"H, C-5"H and C-6"H), 7.50-7.55 (1H, m, C-7H), 7.94 (1H, dd, J = 7.8 and 1.7 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 35.52 ($C$$H_2$Ph) 50.58 (C-3), 62.58 ($C$$H_2$OH), 70.48 (C-2), 118.26 (C-6), 121.70 (C-1"), 122.13 (C-8), 127.39 (C-4"), 128.02 (C-7), 128.81 (C-3" and C-5"), 131.04 (C-2" and C-6"), 135.26 (C-10), 136.75 (C-5), 152.00 (C-9), 198.34 (C=O); HRMS: Calcd for $C_{17}H_{16}O_3Na$ $[M+Na]^+$ 291.0997. Found 291.0996.

(±)-3-Hydroxymethyl-3-(4'-methoxybenzyl)-1-benzopyran-4(*H*)-one 5b: It was obtained as a white solid (0.394 g) in 68% yield, m.p. 84 °C; R_f 0.30 (petroleum ether-ethyl acetate, 3:2); IR (nujol): 3406 (OH), 2908, 2871, 1678 (C=O), 1604, 1511, 1474, 1309, 1278, 1178, 1143, 1024, 946, 847, 763 cm^{-1}; UV (MeOH): 321, 251, 239 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (1H, d, J = 13.7 Hz, C-2'H_α), 2.95 (1H, d, J = 13.7 Hz, C-2'H_β), 3.52 (1H, d, J = 11.5 Hz, C-1'H_α), 3.72 (1H, d, J = 11.5 Hz, C-1'H_β), 3.78 (3H, s, OCH_3), 4.14 (1H, d, J = 11.7 Hz, C-2H_α), 4.23 (1H, d, J = 11.7 Hz, C-2H_β), 6.83 (2H, d, J = 11.5 Hz, C-2"H and C-6"H), 6.99-7.06 (2H, m, C-6H and C-8H), 7.16 (2H, d, J = 11.4 Hz, C-3"H and C-5"H), 7.47-7.52 (1H, m, C-7H), 7.91 (1H, dd, J = 7.8 and 1.6 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 36.17 ($C$$H_2$Ph), 52.21 (C-3), 57.04 (OCH_3), 63.98 ($C$$H_2$OH), 71.98 (C-2), 115.65 (C-3" and C-5"), 119.66 (C-6), 121.77 (C-1'), 123.49 (C-8), 128.63 (C-10), 129.40 (C-7), 133.43 (C-2" and C-6"), 138.09 (C-5), 160.45 (C-4'), 163.15 (C-9), 199.71 (C=O); HRMS: Calcd for $C_{18}H_{18}O_4Na$ $[M+Na]^+$ 321.1103. Found 321.1131.

(±)-3-(3',4'-Dimethoxybenzyl)-3-hydroxymethyl-1-benzopyran-4(*H*)-one 5c: It was obtained as yellow oil (0.394 g) in 68% yield, R_f 0.30 (petroleum ether-ethyl acetate, 3:2); IR (nujol): 3406 (OH), 2908, 2872, 1676 (C=O), 1604, 1511, 1474, 1278, 1178, 1024, 946, 847, 763 cm^{-1}; UV (MeOH): 320, 251, 213 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.91 (1H, d, J = 13.8 Hz, C-2'H_α), 2.97 (1H, d, J = 13.8 Hz, C-2'H_β), 3.56 (1H, d, J = 11.1 Hz, C-1'H_α), 3.71 (1H, d, J = 10.8 Hz, C-1'H_β), 3.89 (6H, s, 2 × OCH_3), 4.16 (1H, d, J = 11.7 Hz, C-2H_α), 4.24 (1H, d, J = 11.7 Hz, C-2H_β), 6.45-6.75 (3H, m, C-2"H, C-5"H and C-6"H), 7.00-7.10 (2H, m, C-6H and C-8H), 7.48-7.54 (1H, m, C-7H), 7.90-7.93 (1H, dd, J = 7.8 and 1.8 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 34.86 ($C$$H_2$Ph), 50.41 (C-3), 55.93 (2 × OCH_3), 62.31 ($C$$H_2$OH), 70.27 (C-2), 111.11 (C-6'), 113.81 (C-5"), 117.93 (C-2"), 120.00 (C-1"), 121.76 (C-8), 122.85 (C-6), 127.39 (C-10), 127.59 (C-7), 136.38 (C-5), 148.08 and 148.76 (C-3" and C-4"), 161.38 (C-9), 198.02 (C=O); HRMS: Calcd for $C_{19}H_{20}O_5Na$ $[M+Na]^+$ 351.1208. Found 351.1214.

(±)-3-(4'-Chlorobenzyl)-3-hydroxymethyl-1-benzopyran-4(*H*)-one 5d: It was obtained as a colorless viscous oil (0.364 g) in 63% yield, R_f 0.30 (petroleum ether-ethyl acetate, 3:2); IR (nujol): 3448 (OH), 2930, 2362, 1681 (C=O), 1606, 1478, 1304, 1213, 1091, 1037, 1016, 941, 841, 759 cm^{-1}; UV (MeOH): 324, 248, 246 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (1H, brs, CH_2OH), 2.93 (1H, d, J = 13.5 Hz, C-2'H_α), 3.02 (1H, d, J = 13.5 Hz, C-2'H_β), 3.56 (1H, d, J = 11.5 Hz, C-1'H_α), 3.63 (1H, d, J = 11.5 Hz, C-1'H_β), 4.09 (1H, d, J = 11.8 Hz, C-2H_α), 4.21 (1H, d, J = 11.8 Hz, C-2H_β), 7.01-7.09 (2H, m, C-6H and C-8H), 7.20-7.29 (4H, m, C-2"H, C-3"H, C-5"H and C-6"H), 7.50-7.55 (1H, m, C-7H), 7.92 (1H, dd, J = 7.8 and 1.6 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 34.71 ($C$$H_2$Ph), 50.43 (C-3), 62.33 ($C$$H_2$OH), 70.37 (C-2), 118.24 (C-6), 120.00 (C-1"), 120.17 (C-8), 122.23 (C-7), 127.99 (C-3" and C-5"), 128.91 (C-2" and C-6"), 131.00 (C-4"), 133.78 (C-10), 136.83 (C-5), 161.63 (C-9), 198.12 (C=O); HRMS: Calcd for $C_{17}H_{15}ClO_3$ $[M+H]^+$ 303.0788. Found 303.0824.

(±)-3-Hydroxymethyl-3-(3',4'-methylenedioxybenzyl)-1-benzopyran-4(*H*)-one 5e: It was obtained as an off white semisolid (0.386 g) in 66% yield, R_f 0.35 (petroleum ether-ethyl acetate, 3:2); IR (nujol): 3435 (OH), 2924, 1681 (C=O), 1606, 1480, 1304, 1247,

1096, 1038, 930, 762 cm^{-1}; UV (MeOH): 320, 289, 248, 215, 212 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 2.77 (1H, brs, CH_2OH), 2.87 (1H, d, *J* = 13.7 Hz, C-2'H_α), 2.95 (1H, d, *J* = 13.7 Hz, C-2'H_β), 3.56 (1H, d, *J* = 11.5 Hz, C-1'H_α), 3.69 (1H, d, *J* = 11.5 Hz, C-1'H_β), 4.15 (1H, d, *J* = 11.8 Hz, C-2H_α), 4.22 (1H, d, *J* = 11.8 Hz, C-2H_β), 5.93 (2H, s, OCH_2O), 6.70-6.79 (3H, m, C-2"H, C-5"H and C-6"H), 7.00-7.08 (2H, m, C-6H and C-8H), 7.49-7.55 (1H, m, C-7H), 7.92 (1H, dd, *J* = 7.8 and 1.4 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 35.16 (CH_2Ph), 50.61 (C-3), 62.49 (CH_2OH), 70.44 (C-2), 101.34 (OCH_2O), 108.53 (C-6"), 111.30 (C-5"), 118.22 (C-2"), 120.22 (C-1"), 122.10 (C-8), 124.13 (C-6), 127.97 (C-7), 128.75 (C-10), 136.71 (C-5), 146.97 and 148.04 (C-3" and C-4"), 161.68 (C-9), 198.31 (C=O); HRMS: Calcd for $C_{18}H_{16}O_5Na$ $[M+Na]^+$ 335.0895. Found 335.0897.

(±)-**3-(2',5'-Dimethoxybenzyl)-3-hydroxymethyl-1-benzopyran-4(*H*)-one 5f**: It was obtained as a viscous oil (0.366 g) in 64% yield, R_f 0.30 (petroleum ether-ethyl acetate, 3:2); IR (nujol): 3401 (OH), 2923, 2852, 1686 (C=O), 1603, 1499, 1447, 1369, 1223, 1178, 1024, 910 cm^{-1}; UV (MeOH): 290 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (1H, d, *J* = 13.7 Hz, C-2'H_α), 3.20 (1H, d, *J* = 13.7 Hz, C-2'H_β), 3.63 (1H, d, *J* = 12.1 Hz, C-1'H_α), 3.72 (6H, s, 2 × OCH_3), 3.82 (1H, d, *J* = 12.1 Hz, C-1'H_β), 4.40 (1H, d, *J* = 12.0 Hz, C-2H_α), 4.45 (1H, d, *J* = 12.0 Hz, C-2H_β), 6.59-6.78 (3H, m, C-3"H, C-4"H and C-6"H), 6.95-7.05 (2H, m, C-6H and C-8H), 7.47 (1H, t, *J* = 7.2 Hz, C-7H), 7.90 (1H, d, *J* = 7.9 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.08 (CH_2Ph), 48.10 (C-3), 51.59 (2 × OCH_3), 62.78 (CH_2OH), 72.76 (C-2), 111.58 (C-2"), 113.17 (C-5"), 117.75 (C-4"), 118.67 (C-8), 120.77 (C-1"), 121.81 (C-6), 125.46 (C-10), 127.84 (C-7), 136.17 (C-5), 152.36 and 153.79 (C-3" and C-6"), 161.49 (C-9), 195.95 (C=O); HRMS: Calcd for $C_{19}H_{20}O_5Na$ $[M+Na]^+$ 351.1208. Found 351.1200.

(±)-3-Hydroxymethyl-3-(3',4',5'-trimethoxybenzyl)-1-benzopyran-4(*H*)-one 5g: It was obtained as viscous oil (0.368 g) in 65% yield, R_f 0.33 (petroleum ether-ethyl acetate, 3:2); IR (nujol): 3500 (OH), 2937, 2839, 1682 (C=O), 1605, 1591, 1507, 1463, 1302, 1240, 1184, 1125, 1037, 939, 850, 762 cm^{-1}; UV (MeOH): 320 and 219 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 2.94 (2H, s, C-2'H), 3.59 (1H, d, *J* = 11.2 Hz, C-1'H_α), 3.73 (1H, d, *J* = 11.2 Hz, C-1'H_β), 3.83 (9H, s, 3 × OCH_3), 4.20 (1H, d, *J* = 11.3 Hz, C-2H_α), 4.25 (1H, d, *J* = 11.3 Hz, C-2H_β), 6.49 (2H, s, C-2"H and C-6"H), 6.99-7.06 (2H, m, C-6H and C-8H), 7.48-7.53 (1H, m, C-7H), 7.91 (1H, d, *J* = 7.9 Hz, C-5H); ^{13}C NMR (75.5 MHz): δ 35.97 (CH_2Ph), 50.69 (C-3), 56.53 (3 × OCH_3), 62.74 (CH_2OH), 70.72 (C-2), 108.12 (C-2" and C-6"), 118.12 (C-8), 120.37 (C-1"), 122.09 (C-6), 127.88 (C-7), 130.96 (C-10), 136.70 (C-5), 153.39 (C-3", C-4" and C-5"), 161.69 (C-9), 198.10 (C=O); HRMS: Calcd for $C_{20}H_{22}O_6Na$ $[M+Na]^+$ 381.1314. Found 381.1289.

General procedure for enzymatic acetylation of (±)-3-benzyl-3-hydroxymethyl-benzopyran-4(*H*)-ones 5a-g. To a solution of the (±)-hydroxymethyl-chromanone **5a-g** (0.3 g, 0.8-1.1 mmoles) in anhydrous diisopropyl ether (5 mL), vinyl acetate (1.1 equiv.) was added, followed by the addition of *Candida rugosa* lipase (0.150 g). The suspension was stirred at 38-40ºC in an incubator and progress of the reaction was monitored periodically by HPLC and/or TLC. After about 45-50% conversion of the starting material into the product, the reaction was quenched by filtering off the enzyme and the solvent evaporated to dryness *in vacuo* to afford a gummy residue, which was purified by column chromatography on silica gel using a gradient solvent system of petroleum ether and ethyl acetate. Optically enriched (-)-3-acetoxymethyl-3-benzyl-benzopyran-4(*H*)-ones **6a-g** and the (+)-3-benzyl-3-hydroxymethyl-benzopyran-4(*H*)-ones **5a-g** were isolated in 64-68% and 64-67% yield (yields were calculated by assuming single enantiomer as 100% in the starting (±)-**5a-g**), respectively. The (+)-hydroxymethylchromanones **5a-g** and (-)-acetoxymethylchromanones **6a-g** were identified on the basis of their spectral data.

(-)-3-Acetoxymethyl-3-benzyl-1-benzopyran-4(*H*)-one 6a: It was obtained as a colourless oil (0.114 g) in 66% yield, R_f 0.35 (petroleum ether-ethyl acetate, 4:1); IR (nujol): 1748 ($COCH_3$), 1678 (C=O), 1606, 1477, 1306, 1283, 1088, 1045, 939, 854, 795, 764 cm^{-1}; UV (MeOH): 321, 244, 218, 212 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (3H, s, $COCH_3$), 2.88 (1H, d, *J* = 13.8 Hz, C-2'H_α), 3.12 (1H, d, *J* = 13.8 Hz, C-2'H_β), 4.07 (1H, d, *J* = 11.4 Hz, C-1'H_α), 4.29 (1H, d, *J* = 11.7 Hz, C-2H_α), 4.40 (1H, d, *J* = 11.8 Hz, C-2H_β), 4.48 (1H, d, *J* = 11.4 Hz, C-1'H_β), 7.00-7.09 (2H, m, C-6H and C-8H), 7.14-7.33 (5H, m, C-2"H, C-3"H, C-4"H, C-5"H and C-6"H), 7.48-7.54 (1H, m, C-7H), 7.95 (1H, dd, *J* = 7.9 and 1.6 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.44 ($OCOCH_3$), 36.10 (CH_2Ph), 48.84 (C-3), 63.34 (CH_2OAc), 70.46

(C-2), 117.57 (C-6), 119.89 (C-1"), 121.57 (C-8), 125.33 (C-4"), 126.88 (C-7), 128.24 (C-3" and C-5"), 130.14 (C-2" and C-6"), 134.46 (C-10), 135.81 (C-5), 160.80 (C-9), 170.24 (*C*OCH$_3$), 193.05 (C=O); HRMS: Calcd for $C_{19}H_{18}O_4Na$ [M+Na]$^+$ 333.1103. Found 333.1096.

(-)-3-Acetoxymethyl-3-(4'-methoxybenzyl)-1-benzopyran-4(*H*)-one 6b: It was obtained as a yellowish oil (0.116 g) in 68% yield, R_f 0.40 (petroleum ether-ethyl acetate, 4:1); IR (nujol): 1744 (COCH$_3$), 1689 (C=O), 1607, 1513, 1477, 1244, 1038, 764 cm^{-1}; UV (MeOH): 322, 252, 218, 214 nm; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.00 (3H, s, COCH$_3$), 2.82 (1H, d, J = 14.1 Hz, C-2'H$_\alpha$), 3.06 (1H, d, J = 14.1 Hz, C-2'H$_\beta$), 3.78 (3H, s, OCH$_3$), 4.05 (1H, d, J = 11.4 Hz, C-1' H$_\alpha$), 4.29 (1H, d, J = 11.7 Hz, C-2H$_\alpha$), 4.40 (1H, d, J = 11.7 Hz, C-2H$_\beta$), 4.47 (1H, d, J = 11.4 Hz, C-1'H$_\beta$), 6.82 (2H, d, J = 14.3 Hz, C-2"H and C-6"H), 6.99-7.09 (4H, m, C-6H, C-8H, C-3"H and C-5"H), 7.48-7.54 (1H, m, C-7H), 7.93-7.97 (1H, dd, J = 7.8 and 1.6 Hz, C-5H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 20.46 (CO*C*H$_3$), 35.26 (*C*H$_2$Ph), 48.95 (C-3), 54.97 (O*C*H$_3$), 63.35 (*C*H$_2$OAc), 70.45 (C-2), 113.66 (C-2" and C-6"), 117.56 (C-6), 119.91 (C-1"), 121.53 (C-8), 126.29 (C-10), 127.59 (C-7), 131.14 (C-3" and C-5"), 135.77 (C-5), 158.47 (C-4"), 160.83 (C-9), 170.27 (*C*OCH$_3$), 193.20 (C=O); HRMS: Calcd for $C_{20}H_{20}O_5Na$ [M+Na]$^+$ 363.1208. Found 363.1218.

(-)-3-Acetoxymethyl-3-(3',4'-dimethoxybenzyl)-1-benzopyran-4(*H*)-one 6c: It was obtained as a colourless oil (0.111 g) in 66% yield, R_f 0.34 (petroleum ether- ethyl acetate, 4:1); IR (nujol): 1746 (COCH$_3$), 1689 (C=O), 1607, 1513, 1477, 1244, 1038, 764 cm^{-1}; UV (MeOH): 315, 258, 218, 210 nm; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.01 (3H, s, COCH$_3$), 2.82 (1H, d, J = 14.1 Hz, C-2'H$_\alpha$), 3.08 (1H, d, J = 14.0 Hz, C-2'H$_\beta$), 3.87 (6H, s, 2 × OCH$_3$), 4.10 (1H, d, J = 11.1 Hz, C-1'H$_\alpha$), 4.31 (1H, d, J = 11.4 Hz, C-2H$_\alpha$), 4.41 (1H, d, J = 11.7 Hz, C-2H$_\beta$), 4.48 (1H, d, J = 11.7 Hz, C-1'H$_\beta$), 6.25-6.65 (3H, m, C-2"H, C-5"H and C-6"H), 6.99-7.23 (2H, m, C-6H and C-8H), 7.49-7.52 (1H, m, C-7H), 7.93-7.96 (1H, dd, J = 7.8 and 1.8 Hz, C-5H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 20.77 (CO*C*H$_3$), 36.12 (*C*H$_2$Ph), 49.31 (C-3), 55.94 (2 × OCH$_3$), 63.67 (*C*H$_2$OAc), 70.90 (C-2), 111.19 (C-6"), 113.57 (C-5"), 117.24 (C-2"), 118.00 (C-1"), 121.89 (C-8), 122.66 (C-6), 127.15 (C-10), 127.84 (C-7), 136.14 (C-5), 148.24 and 148.81 (C-3" and C-4"), 161.23 (C-9), 170.74 (*C*OCH$_3$), 198.12 (C=O); HRMS: Calcd for $C_{21}H_{22}O_6Na$ [M+Na]$^+$ 393.1314. Found 393.1328.

(-)-3-Acetoxymethyl-3-(4'-chlorobenzyl)-1-benzopyran-4(*H*)-one 6d: It was obtained as a colourless oil (0.109 g) in 64% yield, R_f 0.35 (petroleum ether-ethyl acetate, 4:1); IR (nujol): 1748 (COCH$_3$), 1678 (C=O), 1606, 1477, 1325, 1226, 1088, 1045, 939, 795, 764 cm^{-1}; UV (MeOH): 321, 251, 213, 201 nm; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.01 (3H, s, COCH$_3$), 2.86 (1H, d, J = 13.9 Hz, C-2'H$_\alpha$), 3.10 (1H, d, J = 13.9 Hz, C-2'H$_\beta$), 4.08 (1H, d, J = 11.4 Hz, C-1'H$_\alpha$), 4.26 (1H, d, J = 11.8 Hz, C-2H$_\alpha$), 4.40 (1H, d, J = 11.8 Hz, C-2H$_\beta$), 4.44 (1H, d, J = 11.4 Hz, C-1'H$_\beta$), 6.99-7.10 (4H, m, C-2"H, C-3"H, C-5"H and C-6"H), 7.24-7.27 (2H, m, C-6H and C-8H), 7.49-7.54 (1H, m, C-7H), 7.92-7.95 (1H, dd, J = 7.8 and 1.6 Hz, C-5H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 20.42 (CO*C*H$_3$), 35.43 (*C*H$_2$Ph), 48.81 (C-3), 63.16 (*C*H$_2$OAc), 70.51 (C-2), 117.59 (C-6), 119.81 (C-1"), 121.69 (C-8), 127.60 (C-7), 128.38 (C-3" and C-5"), 131.42 (C-2" and C-6"), 130.13 (C-4"), 133.02 (C-10), 135.93 (C-5), 160.75 (C-9), 170.17 (*C*OCH$_3$), 192.71 (C=O); HRMS: Calcd for $C_{19}H_{17}ClO_4Na$ [M+Na]$^+$ 367.0713. Found 367.0706.

(-)-3-Acetoxymethyl-3-(3',4'-methylenedioxybenzyl)-1-benzopyran-4(*H*)-one 6e: It was obtained as a colourless oil (0.111 g) in 65% yield, R_f 0.40 (petroleum ether-ethyl acetate, 4:1); IR (nujol): 1744 (COCH$_3$), 1689 (C=O), 1606, 1481, 1445, 1242, 1147, 1100, 1039, 929, 821, 762 cm^{-1}; UV (MeOH): 319, 247, 214, 202 nm; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.01 (3H, s, COCH$_3$), 2.80 (1H, d, J = 14.0 Hz, C-2'H$_\alpha$), 3.05 (1H, d, J = 14.0 Hz, C-2'H$_\beta$), 4.08 (1H, d, J = 11.4 Hz, C-1' H$_\alpha$), 4.29 (1H, d, J = 11.8 Hz, C-2H$_\alpha$), 4.39 (1H, d, J = 11.8 Hz, C-2H$_\beta$), 4.46 (1H, d, J = 11.4 Hz, C-1' H$_\beta$), 5.93 (2H, s, OCH$_2$O), 6.58-6.74 (3H, m, C-2"H, C-5"H and C-6"H), 6.99-7.09 (2H, m, C-6H and C-8H), 7.48-7.54 (1H, m, C-7H), 7.93-7.96 (1H, dd, J = 7.8 and 1.67 Hz, C-5H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 20.45 (CO*C*H$_3$), 35.77 (*C*H$_2$Ph), 48.94 (C-3), 63.29 (*C*H$_2$OAc), 70.48 (C-2), 100.76 (O*C*H$_2$O), 107.98, 110.38 and 117.57 (C-2", C-5" and C-6"), 119.88 and 121.58 (C-6 and C-8), 120.42 (C-1") 127.61 (C-7), 127.94 (C-10), 135.80 (C-5), 146.47 (C-4"), 147.44 (C-3"), 160.80 (C-9), 170.24 (*C*OCH$_3$), 193.04 (C=O); HRMS: Calcd for $C_{20}H_{18}O_6Na$ [M+Na]$^+$ 377.1001. Found 377.0986.

(-)-3-Acetoxymethyl-3-(2',5'-dimethoxybenzyl)-1-benzopyran-4(*H*)-one 6f: It was obtained as a viscous oil (0.113 g) in 67% yield, R_f 0.34 (petroleum

ether-ethyl acetate, 4:1); IR (nujol): 1742 ($COCH_3$), 1635 (C=O), 1607, 1490, 1450, 1379, 1228, 1157, 1042, 762 cm^{-1}; UV (MeOH): 295, 255 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 1.99 (3H, s, $COCH_3$), 2.90 (1H, d, J = 13.5 Hz, C-2'H_α), 3.20 (1H, d, J = 13.5 Hz, C-2'H_β), 3.65 and 3.73 (6H, 2s, 2 × OCH_3), 4.14 (1H, d, J = 11.6 Hz, C-1' H_α), 4.33 (1H, d, J = 11.8 Hz, C-2H_α), 4.37 (1H, d, J = 12.6 Hz, C-2H_β), 4.45 (1H, d, J = 11.4 Hz, C-1'H_β), 6.73 (3H, s, C-3"H, C-4"H and C-6"H), 6.97-7.06 (2H, m, C-6H and C-8H), 7.47 (1H, t, J = 7.6 Hz, C-7H), 7.92 (1H, d, J = 7.7 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.11 ($CO\mathit{C}H_3$), 30.01 ($\mathit{C}H_2Ph$), 49.99 (C-3), 55.79 (2 × OCH_3), 64.41 ($\mathit{C}H_2OAc$), 71.87 (C-2), 111.48 (C-6"), 113.17 (C-4"), 118.16 (C-3"), 118.73 (C-6), 120.87 (C-1"), 121.92 (C-8), 124.95 (C-10), 128.09 (C-7), 136.12 (C-5), 152.55 (C-5"), 153.59 (C-2"), 161.46 (C-9), 170.94 ($\mathit{C}OCH_3$), 193.54 (C=O); HRMS: Calcd for $C_{21}H_{22}O_6Na$ $[M+Na]^+$ 393.1314. Found 393.1317.

(-)-3-Acetoxymethyl-3-(3',4',5'-trimethoxybenzyl)-1-benzopyran-4(*H*)-one 6g: It was obtained as a yellowish oil (0.110g) in 66% yield, R_f 0.34 (petroleum ether-ethyl acetate, 4:1); IR (nujol): 1744 ($COCH_3$), 1690 (C=O), 1606, 1507, 1479, 1238, 1040, 763 cm^{-1}; UV (MeOH): 321, 216 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (3H, s, $COCH_3$), 2.80 (1H, d, J = 13.8 Hz, C-2'H_α), 3.09 (1H, d, J = 13.9 Hz, C-2'H_β), 3.82 (9H, s, 3 × OCH_3), 4.15 (1H, d, J = 11.4 Hz, C-1'H_α), 4.34 (1H, d, J = 11.7 Hz, C-2H_α), 4.42 (1H, d, J = 11.9 Hz, C-2H_β), 4.48 (1H, d, J = 11.7 Hz, C-1'H_β), 6.34 (2H, s, C-2"H and C-6"H), 6.99-7.09 (2H, m, C-6H and C-8H), 7.51 (1H, t, C-7H), 7.93 (1H, d, J = 7.7 Hz, C-5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.09 ($CO\mathit{C}H_3$), 37.23 (C-2'), 49.61 (C-3), 56.55 (3 × OCH_3), 64.17 ($\mathit{C}H_2OAc$), 71.35 (C-2), 107.9 (C-2" and C-6"), 118.26 (C-8), 120.67 (C-1"), 122.24 (C-6), 128.15 (C-7), 130.75 (C-10), 135.25 (C-5), 136.49 (C-3", C-4" and C-5"), 161.47 (C-9), 170.86 ($\mathit{C}OCH_3$), 193.72 (C=O); HRMS: Calcd for $C_{22}H_{24}O_7Na$ $[M+Na]^+$ 423.1420. Found 423.1423.

General procedure for chemical deacetylation of enzymatically obtained acetates (-)-6a-g. The (-)-acetoxymethylchromanones **6a-g** (0.075 g, 0.20-0.24 mmoles) were dissolved in methanol (5 mL) containing 1-2 drops of hydrochloric acid. The reaction mixture was stirred for 4 hr at 25-28º C and quenched by the addition of ice-cold water (5 mL), extracted with ethyl acetate (2 × 10 mL) and the combined ethyl acetate layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to afford the (-)-hydroxymethylchromanones **5a-g** in 85-96% yields. These were identified on the basis of their spectroscopic data, which were found identical with the spectroscopic data of the corresponding (+)- and (±)-hydroxymethylchromanones **5a-g** reported earlier.

General procedure for the preparation of *O*-acetylmandelates of (+)/(±)-3-arylmethyl-3-hydroxymethylbenzopyran-4-ones 5a-g. To a solution of the (+)/(±)-3-arylmethyl-3-hydroxymethylchromanones **5a-g** (0.020 g, 0.06-0.07 mmoles), catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine and (*S*)-(+)-*O*-acetylmandelic acid (0.06-0.07 mmoles) in CH_2Cl_2 (5 mL) at 0ºC, dicyclohexylcarbodiimide (0.25 mmoles in 1 mL CH_2Cl_2) was added with the help of a syringe in 35-40 min. The reaction was then allowed to proceed at 25ºC for an additional 15-20 hr. The *N*,*N* –dicyclohexyl urea formed during the reaction was removed by filtration and the resulting solution was washed successively with 0.5N HCl (5 mL), 2N Na_2CO_3 (5 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, concentrated and the product isolated after purification by column chromatography or PTLC in quantitative yields. The ^1H NMR spectra of *O*-acetylmandelates of (±)-alcohols **5a-g** exhibited baseline resolution of the signals of diastereomeric protons of the *O*-acetylmandelic acid moiety, which resonated between δ 5.80 and 5.90. The integration of these signals in the ^1H NMR spectra of the *O*-acetylmandelates of **(+)-5a-g** gave a measure of their diastereomeric compositions, which are directly related to the enantiomeric compositions of the enzymatically acetylated 3-hydroxymethyl-chromanones **(Table I)**. The maximum *ee* of 79% was observed for (+)-3-(3',4'-dimethoxybenzyl)-3-hydroxymethyl-1-benzopyran-4(*H*)-one **5c**.

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References

1 Drauz K & Waldman H Eds; *Enzyme Catalysis in Organic Synthesis*, Vols 1 and 2, (VCH, Weinheim), **1994**.
2 Faber K, *Biotransformations in Organic Chemistry*, 4th edition, (Springer, New York), **2000**.
3 Santaniello E, Ferraboschi P, Griesenti P & Manzocchi A, *Chem Rev*, 92, **1992**, 1071.
4 Roberts S M, *J Chem Soc, Perkin Trans I*, **2000**, 611.
5 Waldman H & Sebastian D, *Chem Rev*, 94, **1994**, 911.
6 Roberts S M, *J Chem Soc, Perkin Trans I*, **1999**, 1.

7 Prasad A K, Pati H N, Azim A, Trikha S & Poonam, *Bioorg Med Chem*, 7, **1999**, 1973.
8 Parmar V S, Prasad A K, Pati H N, Kumar R, Azim A, Roy S & Errington W, *Bioorg Chem*, 27, **1999**, 119.
9 Parmar V S, Khanduri C H, Tyagi O D, Prasad A K, Gupta S, Bisht K S, Pati H N & Sharma N K, *Indian J Chem*, 31B, **1992**, 925.
10 Bisht K S, Kumar A, Kumar N & Parmar V S, *Pure Appl Chem*, 68, **1996**, 749.
11 Poonam, Prasad A K, Azim A, Kumar R, Jain S C, Parmar V S, Olsen C E & Errington W, *Tetrahedron*, 57, **2001**, 7395.
12 *Chromenes, Chromanones and Chromones*, edited by G P Ellis, (Wiley, New York), **1977**.
13 Calmarini O L & Stodola F H, *J Org Chem*, 30, **1965**, 112.
14 Boechler P & Tamm C, *Tetrahedron Lett*, **1967**, 3479.
15 Tamm C, Boehner B & Zuencher W, *Helv Chim Acta*, 55, **1972**, 510.
16 Mehta A C & Razdan R K, *Ger Offen*, 2, 209, 854, **1972**; *Chem Abstr*, 77, **1972**, 151933.
17 Schering A-G, *Brit Pat*, 1, 250, 340, **1971**; *Chem Abstr*, 76, **1972**, 3684.
18 Cignarella G, Grella G & Curzu M M, *Synthesis*, **1980**, 825.
19 AlNakib T, Bezjak V, Meegan M J & Chandy R, *Eur J Med Chem*, **1990**, *25*, 455; *Chem Abstr*, 113, **1990**, 231160.
20 Edenharder R, Speth C, Decker M, Kolodziej H, Kayser O & Platt K L, *Mutation Research,* 345, **1995**, 57.
21 Cohen N, Bizzaro F T, May W P, Toth K, Lee F K, Heslin P H, Holland G W, Kwoh S C & Franco L S, *Bioorg Med Chem Lett*, *4*, **1994**, 2883.
22 Ward F E, Garling D L, Buckler R T, Lawler D M & Cummings D P, *J Med Chem*, *24,* **1981**, 1073.
23 McGahren W J, Ellestad G A, Morton G O & Kunstmann M P, *J Org Chem*, 37, **1972**, 1636.
24 Chen C I, Lin Y Y & Lin Y C, *T'ai-wan K'o Hsueh*, 28, **1974**, 40; *Chem Abstr*, 83, **1975**, 42971.
25 Chatterjea J N, Shaw S C, Lal P K & Singh R P, *J Indian Chem Soc*, 56, **1979**, 1006.
26 Dhawan D & Grover S K, *Synth Commun*, 22, **1992**, 2405.
27 Kirkiacharian S, Tongo H G, Bastide J, Bastide P, Grenie M M, *Eur J Med Chem*, 24, **1989**, 541; *Chem Abstr*, 113, **1990**, 40230.
28 Joshi U K, Kelkar R M & Paradkar M V, *Indian J Chem*, 22B, **1983**, 1151.
29 Manna F, Chimenti F, Bolasco A, Bizzarri B, Botta M, Tafi A, Filippelli A & Rossi S, *Bioorg Med Chem Lett*, 10, **2000**, 1883.
30 Stoyanov E V, Champavier Y, Simon A & Basly J P, *Bioorg Med Chem Lett*, 12, **2002**, 2685.
31 Kirkiacharian S & Alovlov M, *Comptes Rendus de l'Academie Sciences, Series II,* 299, **1984**, 187; *Chem Abstr*, 102, **1985**, 45656.
32 Whitesell J K & Reynolds D, *J Org Chem*, 48, **1983**, 3548.