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Synthesis and lipase-mediated stereoselective deacetylation of (±)-3-acetoxymethyl-3-alkyl-7-methoxychroman-4-ones

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Abstract—Six (±)-3-acetoxymethyl-3-alkyl-7-methoxychroman-4-ones have been synthesized in four steps starting with the coupling of resorcinol with corresponding aliphatic acid leading to the formation of 2,4-dihydroxyphenyl alkyl ketones, which upon monomethylation and hydroxymethylation, followed by acetylation afforded the racemic acetoxymethylated compounds in 17–30% overall yields. *Candida rugosa* lipase-catalyzed deacetylation of (±)-3-acetoxymethylchromanones in diisopropyl ether exhibited fairly moderate enantioselectivity.

1. Introduction

In the recent past, interest in the preparation of enantiomerically pure compounds has greatly increased. The arsenal available to synthetic organic chemists at present is rich in chiral building blocks and methods for their preparation and elaboration. The preparation of necessary chiral intermediates can usually be achieved either by asymmetric induction on an achiral compound or by kinetic resolution of a racemic mixture. Recently, enzymatic processes have extensively been used for the preparation of chiral intermediates and target molecules.[1] Among the different enzymatic processes, lipase-catalyzed acylations and deacylations represent an important class of enzymatic transformations in organic synthesis; this is attributed mainly to the low cost of lipases and their wide tolerance towards a variety of organic molecules.[2,3] In recent years, we have successfully used lipases from porcine pancreas; *Candida*, *Aspergillus* and *Pseudomonas* species for carrying out regio- and stereo-selective acylations/deacylations on polyphenolics,[4–6] carbohydrates[7,8] and polyols.[9]

Chroman-4-ones belong to the class of polyphenolics, and are widely distributed in the plant kingdom[10–13] and possess a variety of biological activities, viz anticonvulsant,[14] antimicrobial,[15] antiinflammatory,[16] antifungal,[17] 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.[11–13,18] However, no efficient synthetic methodologies are available either for the preparation of such chromanones in enantiomerically pure form or for resolution of their racemic mixtures.

We wish to report herein the synthesis of racemic 3-acetoxymethyl-3-alkylchromanones and their resolution by a lipase-catalyzed deacetylation reaction.

2. Results and discussion

Six racemic hydroxymethylchromanones **6a**–**6f** have been synthesized in three steps starting from the coupling of resorcinol (**1**) with the corresponding aliphatic acids **2a**–**2f** to afford 2,4-dihydroxyphenyl alkyl ketones **3a**–**3f** in 70–80% yields (Scheme 1).[19–22] The partial methylation of aryl alkyl ketones **3a**–**3f** leads to the formation of corresponding 2-hydroxy-4-methoxyphenyl alkyl ketones **4a**–**4f**[23–26] which on reaction with alkaline formaldehyde afforded (±)-hydroxymethylchromanones **6a**–**6f**. The alkaline hydroxymethylation of ketones **4a**–**4f** initially leads to the formation of geminal dihydroxymethylketones **5a**–**5f** which instantaneously cyclize to (±)-hydroxymethylchromanones **6a**–**6f**. The formation of intermediate geminal dihydroxymethylketones **5a**–**5f** has been confirmed by the isolation of 1,1-*bis*-hydroxymethylethyl 2-hydroxy-4-methoxyphenyl ketone (**5a**) formed during the hydroxymethylation of 2-hydroxy-4-methoxyphenyl ethyl ketone (**4a**). Acetylation of (±)-3-hydroxymethylchromanones **6a**–**6f** with acetic anhydride and pyridine in the presence of a catalytic amount of DMAP afforded the

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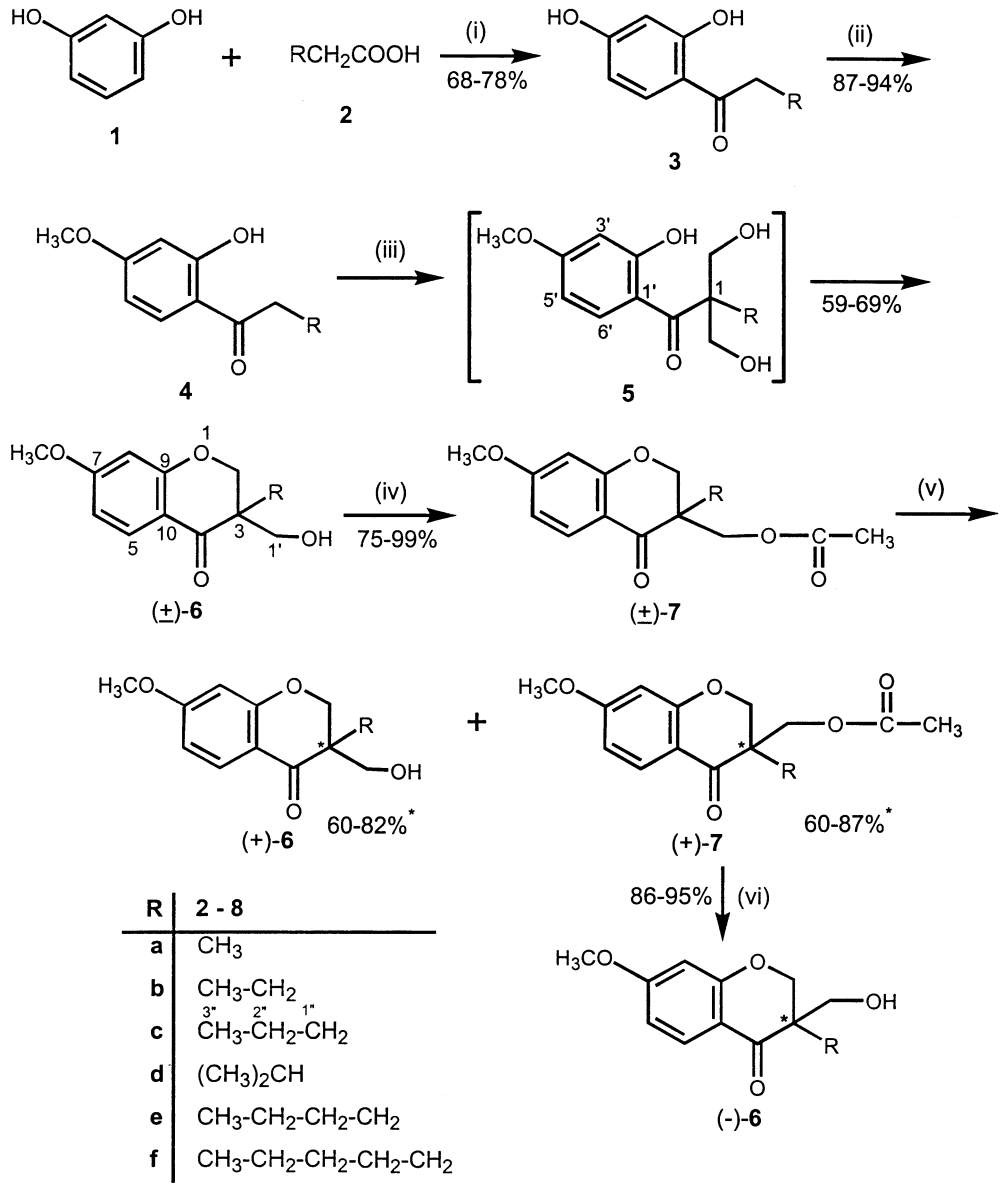

R	2 - 8
a	CH_3
b	CH_3-CH_2
c	CH_3-CH_2-CH_2
d	$(CH_3)_2CH$
e	CH_3-CH_2-CH_2-CH_2
f	CH_3-CH_2-CH_2-CH_2-CH_2

Scheme 1. *Reagents and conditions*: (i) Fused $ZnCl_2$, 140–50°C; (ii) $(CH_3)_2SO_4$, dry acetone, anhyd. K_2CO_3, refluxing; (iii) 37%; HCHO, 0.5M NaOH, stirring at 25–28°C; (iv) Acetic anhydride, pyridine, dimethylaminopyridine, stirring at 25–28°C; (v) *Candida rugosa* lipase, diisopropyl ether, *n*-butanol, stirring at 35–38°C; (vi) MeOH-HCl, stirring at 25–28°C.

corresponding 3-acetoxymethylchromanones **7a**–**7f** in quantitative yields (Scheme 1). The molecular structure of (±)-3-ethyl-3-hydroxymethyl-7-methoxychromanone (**6b**) deduced on the basis of spectral analysis was further confirmed by single crystal X-ray diffraction studies. Schematic representation of the molecular structure of compound **6b** is shown in Fig. 1 and some of the crystallographic data are summarized in the Section 4. The X-ray crystallographic studies on hydroxymethylchromanone **6b** indicate that the compound exists in a conformation in which carbonyl group at C-4 position and hydroxymethyl group at C-3 position are *trans* (Fig. 1).

Our initial attempts of carrying out enantioselective acetylation of (±)-3-alkyl-3-hydroxymethyl-7-methoxychroman-4-ones **6a**–**6f** using different lipases from porcine pancreas (PPL), *Candida rugosa* (CRL) and *Candida antarctica* (CAL) as the biocatalysts and vinyl acetate as the acetylating agent were unsuccessful except in the case of reaction catalyzed by CRL. However, the rate of acetylation reaction catalyzed by CRL was too slow to be used for practical purposes. Thus, we undertook the screening of the enzymes PPL, CRL and CAL in tetrahydrofuran (THF), diisopropyl ether (DIPE) and dioxane in the presence of *n*-butanol (acetyl trap) for the enantioselective deacetylation of (±)-3-acetoxymethyl-3-alkyl-7-methoxychroman-4-ones **7a**–**7f**. The selection of solvents for the deacetylation reactions catalyzed by PPL, CRL and CAL was based on our earlier experiences.[4,6] While there was no reaction with PPL in THF and CAL in dioxane, the deacetylation reaction in the presence of CRL in DIPE proceeded satisfactorily (Table 1).

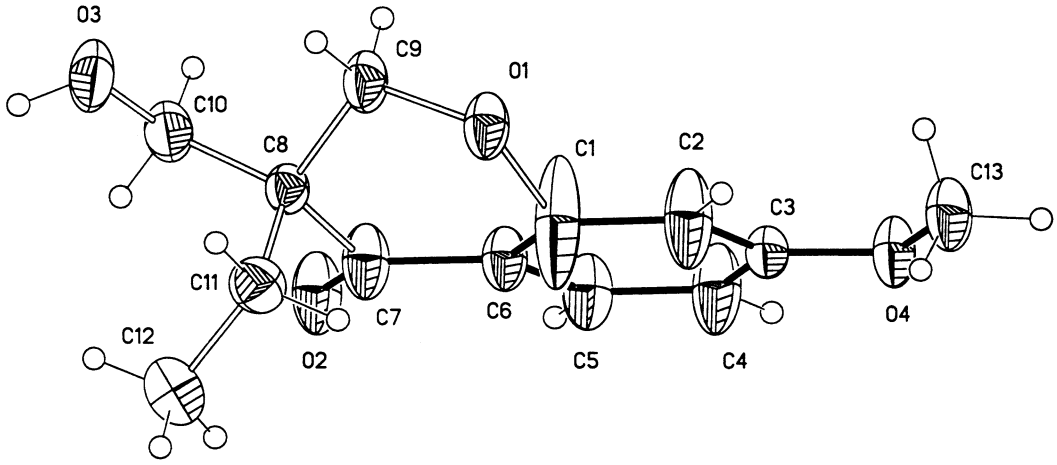

Figure 1. X-Ray crystal structure of (±)-**6b**.

In a typical reaction, the racemic 3-acetoxymethylchromanones **7a**–**7f** were incubated with CRL in DIPE in the presence of 3–4 equiv. of *n*-butanol and the reaction was monitored by HPLC and/or TLC. The reaction was stopped by filtering off the enzyme after about 45–50% conversion of the starting acetate to the deacetylated hydroxymethylchromanone. The deacetylated 3-hydroxymethylchromanones and the unreacted 3-acetoxymethylchromanones 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, deacetylated (+)-3-hydroxymethylchromanones **6a**–**6f** and unreacted (+)-3-acetoxymethylchromanones **7a**–**7f** were found to be optically active. Further, the unreacted (+)-acetoxymethylchromanones **7a**–**7f** recovered from the deacetylation reaction mediated by CRL were hydrolyzed chemically by stirring in methanolic-HCl. The chemical hydrolysis of (+)-**7a**–**7f** led to the formation of (−)-3-hydroxymethylchromanones **6a**–**6f**. The comparison of optical rotation values of the (+)-hydroxymethylchromanones **6a**–**6f** obtained by enzymatic deacetylation of (±)-3-acetoxymethylchromanones **7a**–**7f** with those of (−)-hydroxymethylchromanones **6a**–**6f** obtained by chemical deacetylation of (+)-**7a**–**7f** revealed that they are quite comparable and had opposite signs of rotation (cf. Section 4). All these reactions, when performed under identical conditions but without addition of the enzyme did not yield any product.

In order to determine the enantiomeric excess (ee) of (+)-3-hydroxymethylchromanones **6a**–**6f**, the separation of two enantiomers of all the 12 compounds, i.e. (+)-**6a**–**6f** and (+)-**7a**–**7f** was attempted using chiral HPLC columns (chiracel OJ and chiracel OD). However, separation of enantiomers was not observed. The enantiomeric excess determination attempted by chiral shift ^{1}H NMR spectroscopy using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol [(+)-TFAE] shift reagent also failed as the separation of the signals in the ^{1}H NMR spectra of the racemic 3-hydroxymethylchromanones **6a**–**6f** was not observed. Finally, the enantiomeric excess of (+)-3-hydroxymethylchromanones **6a**–**6f** were determined by ^{1}H NMR spectral analysis of their *O*-acetylmandelic acid esters (Table 1). The synthesis of *O*-acetylmandelates was achieved by the reaction of (+)/(±) alcohols **6a**–**6f** with D-(−)-*O*-acetylmandelic acid in dichloromethane according to the procedure of Whitesell and Reynolds.[27]

It is noteworthy to mention that the rate of enzymatic deacetylation of acetoxymethylchromanones depends on the chain-length of the C-3 alkyl substituent (Table 1). The rate of the deacetylation reaction increases as the chain length of the C-3 alkyl group increases from C_1–C_5, except in the case of 3-*iso*propylchromanone **7d**. This may be because of the fact that the alkyl chain is branched in **7d**, which may increase the effective volume and thus slow its accommodation in the active site of the enzyme.

3. Conclusion

The present study has revealed fairly moderate enantioselective capabilities of CRL for the deacetylation of (±)-3-acetoxymethylchromanones **7a**–**7f** in diisopropyl ether. This investigation has also revealed that the rate of

Table 1. Enantioselective deacetylation of (±)-**7a**–**7f** catalyzed by *Candida rugosa* lipase in diisopropyl ether containing *n*-BuOH as the acyl trap at 35–38°C

Entry	Substrate	Reaction time (days)	Products (%yield)[a]	% ee
1	(±)-**7a**	8	(+)-**6a** (71) and (+)-**7a** (84)	(+)-**6a**:38
2	(±)-**7b**	8	(+)-**6b** (78) and (+)-**7b** (60)	(+)-**6b**:14
3	(±)-**7c**	6	(+)-**6c** (60) and (+)-**7c** (70)	(+)-**6c**:56
4	(±)-**7d**	10	(+)-**6d** (77) and (+)-**7d** (85)	(+)-**6d**:18
5	(±)-**7e**	5	(+)-**6e** (65) and (+)-**7e** (86)	(+)-**6e**:29
6	(±)-**7f**	5	(+)-**6f** (82) and (+)-**7f** (87)	(+)-**6f**:20

All these reactions, when performed under identical conditions, but without adding *Candida rugosa* lipase, did not yield any product.
[a] Yields are calculated by assuming corresponding single enantiomer as 100% in the starting (±)-3-acetoxymethylchromanones **7a**–**7f**.

deacetylation reaction catalyzed by CRL increases with the increase in lipophilicity of the substrate, i.e. the chain length of the C-3 alkyl group in (±)-**7a**–**7f**. As it is difficult 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.

4. Experimental

Melting points were determined on a Mettler FP62 instrument 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 either on a Cary 100 Bio- or on Beckmann DU-64 spectrophotometer. The optical rotations were measured with Bellingham Stanley AD 220 polarimeter. The ^{1}H- and ^{13}C NMR spectra were recorded on Bruker Advance-300 spectrometer at 300 and at 75 MHz, respectively using TMS as internal standard. The chemical shift values are on δ scale and the coupling constants (J) are in Hz. The EIMS and HRMS were recorded on a Jeol AX 505 W instrument at 70 eV in FAB (positive or negative ion mode) using NBA (3-nitrobenzyl alcohol) as matrix. The enzymes, porcine pancreatic lipase (PPL, Type II) and *Candida rugosa* lipase (CRL, Type VII) were purchased from Sigma Chemical Co. (USA) and used after storing in vacuo over P_2O_5 for 24 h. The *Candida antarctica* lipase immobilized on accurel was gifted by Novo Nordisk Co. and used as such. The organic solvents (THF and DIPE) used were distilled over activated molecular sieves (4 Å), while *n*-butanol was dried and distilled over ignited potassium carbonate. Analytical TLCs were performed on precoated Merck silica gel $60F_{254}$ plates; the spots were detected either by UV light, charring with 4% alcoholic H_2SO_4 or by spraying with 3% alcoholic $FeCl_3$ solution. Reactions were monitored at λ_{254} nm on a Shimadzu LC-10AS HPLC instrument with SPD-10A UV–Vis detector and Shimpack CLC-ODS (4.6×150 mm) reverse phase column; solvent system used was methanol–water (3:2) at a flow rate of 0.50 ml min^{-1}. (*S*)-(+)-*O*-Acetylmandelic acid (ee 99%) was purchased from Aldrich Chemical Co. (USA).

4.1. General procedure for the preparation of 2,4-dihydroxyphenyl alkyl ketones 3a–3f

Fused $ZnCl_2$ (0.15 mol, 20 g) and fatty acid **2a**–**2f** (0.15 mol) was heated slowly with stirring until the solution became homogeneous. Resorcinol **1** (0.1 mol, 11 g) was added and the reaction mixture stirred for 2 h at 140–150°C, cooled and poured over crushed ice containing hydrochloric acid (1:1). The solid that separated was filtered and washed repeatedly with water and sodium bicarbonate to afford the crude product, which was purified by column chromatography on silica gel using a gradient solvent system of petroleum ether–ethyl acetate to obtain the pure aryl alkyl ketones **3a**–**3f** in 70–80% yield, these were characterized on the basis of their physical and spectral data and by comparing them with the data reported in the literature.[19–22]

4.2. General procedure for the preparation of 2-hydroxy-4-methoxyphenyl alkyl ketones 4a–4f

To a stirred solution of 2,4-dihydroxyphenyl alkyl ketone **3a**–**3f** (0.05 mol) in dry acetone (100 ml) was added freshly ignited potassium carbonate (3 g), followed by the addition of dimethyl sulphate (0.055 mol). The reaction mixture was refluxed for 4–6 h and the progress of reaction was monitored by TLC. On completion, the reaction mixture was cooled, filtered and solvent removed under vacuum. Ice was added to the gummy residue and the resulting solid filtered, washed thoroughly with water, dried and purified by column chromatography on silica gel using a gradient solvent system of petroleum ether–ethyl acetate to obtain the pure ketones **4a**–**4f** in 85–90% yields, these were characterized on the basis of their physical and spectral data and by comparing them with the data reported in the literature.[20,23–26]

4.3. General procedure for the preparation of 3-alkyl-3-hydroxymethyl-7-methoxychroman-4-ones 6a–6f

A solution of 2-hydroxy-4-methoxyphenyl alkyl ketone **4a**–**4f** (0.016 mol) in sodium hydroxide (0.5 M, 4.0 equiv.) and formaldehyde (37%, 4.5 equiv.) was stirred at 25–28°C. The progress of the reaction was followed by TLC and on completion, was stopped by acidification with dilute hydrochloric acid. The product was extracted with ether (3×50 ml), the ethereal layers combined, washed with brine (3×25 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 (4:1) to afford pure hydroxymethylated chromanones **6a**–**6f** in 59–69% yields.

In a separate reaction of 2-hydroxy-4-methoxyphenyl ethyl ketone (**4a**) with alkaline formaldehyde, the reaction was stopped when about half of the starting ketone was consumed. The residue obtained after work-up of the reaction was purified by column chromatography on silica gel using a gradient solvent system of petroleum ether–ethyl acetate to afford three products, i.e. the starting ketone **4a**, hydroxymethylchromanone **6a** and bis-hydroxymethyl ketone **5a** in 40, 25 and 10% yields, respectively.

4.3.1. 1,1-Bis-hydroxymethylethyl 2-hydroxy-4-methoxyphenyl ketone (5a). It was obtained as a white crystalline solid (0.4 g) in 10% yield. Mp 84–86°C; R_f: 0.30 (petroleum ether–ethyl acetate, 5:3); $C_{12}H_{15}O_5$ ($[M-H]^+$ 239.0943, Calcd 239.0920); IR (Nujol): 3233(OH), 1620(C=O), 1463, 1274, 1227, 1119, 1033, 935, 809 and 612 cm^{-1}; UV (MeOH): 216, 279 and 316 nm; ^{1}H NMR (CD_3OD) δ: 1.42 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 3.95 (4H, s, 2×OCH_2), 6.45 (1H, d, J=2.5 Hz, C-3′H), 6.50 (1H, dd, J=2.5 and 9.0 Hz, C-5′H) and 8.04 (1H, d, J=9.0 Hz, C-6′H); ^{13}C NMR (CD_3OD) δ: 19.08(CH_3), 56.00 and 56.30 (2×OCH_2 and C-1), 66.93 (OCH_3), 102.44 (C-3′), 107.39 (C-5′), 114.53 (C-1′), 133.17 (C-6′), 166.53 and 166.84 (C-2′ and C-4′) and 209.88 (C=O); EIMS, *m/z* (% rel. int.): 240 ($[M]^+$, 20), 151 (100), 125 (40), 85 (15) and 73 (14).

4.3.2. (±)-3-Hydroxymethyl-7-methoxy-3-methylchroman-4-one (6a). It was obtained as a white amorphous solid (2.3 g) in 65% yield. Mp 76–77°C; R_f: 0.42 (petroleum ether–ethyl acetate, 7:3); $C_{12}H_{15}O_4$ ($[M+H]^+$ 223.0996, Calcd 223.0970); IR (KBr): 3442 (OH), 2966, 1657 (C═O), 1616, 1441, 1264, 1237, 1106, 1030, 951, 827 and 754 cm^{-1}; UV (MeOH): 212, 232, 272 and 311 nm; ^1H NMR ($CDCl_3$) δ: 1.22 (3H, s, CH_3), 2.36 (1H, br t, J=5.2 Hz, CH_2OH), 3.57 (1H, dd, J=5.2 and 11.3 Hz, C-1′H_α), 3.84 (3H, s, OCH_3), 3.91 (1H, dd, J=5.2 and 11.3 Hz, C-1′H_β), 4.15 (1H, d, J=11.3 Hz, C-2H_α), 4.49 (1H, d, J=11.3 Hz, C-2H_β), 6.40 (1H, d, J=2.0 Hz, C-8H), 6.59 (1H, dd, J=2.0 and 8.8 Hz, C-6H) and 7.82 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 16.55 (CH_3), 46.51 (C-3), 55.57 (OCH_3), 64.80 (C-1′), 73.68 (C-2), 100.50 (C-8), 110.21 (C-6), 113.71 (C-10), 129.18 (C-5), 163.29 (C-9), 166.13 (C-7) and 195.84 (C═O); EIMS, m/z (% rel. int.): 222 ($[M]^+$,40), 207 (4), 192 (16), 150 (100), 122 (37), 107 (15) and 79 (8).

4.3.3. (±)-3-Ethyl-3-hydroxymethyl-7-methoxychroman-4-one (6b). It was obtained as white needles (2.4 g) in 64% yield. Mp 85–88°C; R_f: 0.45 (petroleum ether–ethyl acetate, 7:3); $C_{13}H_{17}O_4$ ($[M+H]^+$ 237.1152, Calcd 237.1127); IR (Nujol): 3492 (OH), 2941, 1653 (C═O), 1612, 1437, 1386, 1262, 1199, 1045, 1020, 931, 828 and 758 cm^{-1}; UV (MeOH): 286 and 311 nm; ^1H NMR ($CDCl_3$) δ: 0.90 (3H, t,J=7.6 Hz, CH_3), 1.70 (2H, m, CH_2CH$_3$), 2.55 (1H, br s, OH), 3.54 (1H, d, J=13.9 Hz, C-1′H_α), 3.81 (3H, s, OCH_3), 3.93 (1H, d, J=13.9 Hz, C-1′H_β), 4.29 (1H, d, J=13.9 Hz, C-2H_α), 4.42 (1H, d, J=13.9 Hz, C-2H_β), 6.36 (1H, d, J=2.4 Hz, C-8H), 6.56 (1H, dd, J=2.4 and 8.8 Hz, C-6H) and 7.79 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 7.95 (CH_3), 22.96 (CH_2CH$_3$), 49.32 (C-3), 55.49 (OCH_3), 62.61 (C-1′), 71.47 (C-2), 100.33 (C-8), 110.07 (C-6), 113.88 (C-10), 129.01 (C-5), 163.17 (C-9), 166.03 (C-7) and 196.12 (C═O); EIMS, m/z (% rel. int.): 236 ($[M]^+$,25), 208 (43), 177 (14), 150 (100), 122 (32), 107 (12) and 79(6).

4.3.4. (±)-3-Hydroxymethyl-7-methoxy-3-propylchroman-4-one (6c). It was obtained as a colourless viscous oil (2.7 g) in 69% yield. R_f: 0.45 (petroleum ether–ethyl acetate, 7:3); $C_{14}H_{19}O_4$ ($[M+H]^+$ 251.1263, Calcd 251.1283); IR (thin film): 3455(OH), 2960, 1669(C═O), 1608, 1440, 1387, 1245, 1162, 1105, 1029, 947, 837 and 772 cm^{-1}; UV (MeOH): 212, 232, 272 and 311 nm; ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz, CH_3), 1.32 (2H, m, C-2″H), 1.62 (2H, m, C-1″H), 2.51 (1H, br s, OH), 3.56 (1H, d, J=11.5 Hz, C-1′H_α), 3.83 (3H, s, OCH_3), 3.96 (1H, d, J=11.5 Hz, C-1′H_β), 4.31 (1H, d, J=11.5 Hz, C-2H_α), 4.46 (1H, d, J=11.5 Hz, C-2H_β), 6.39 (1H, d, J=2.0 Hz, C-8H), 6.57 (1H, dd, J=2.0 and 8.7 Hz, C-6H) and 7.80 (1H, d, J=8.7 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 14.97 (CH_3), 17.38 (C-2″), 33.07 (C-1″), 49.94 (C-3), 56.00 (OCH_3), 63.57 (C-1′), 72.40 (C-2), 100.86 (C-8), 110.58 (C-6), 114.45 (C-10), 129.54 (C-5), 163.70 (C-9), 166.52 (C-7) and 196.50 (C═O); EIMS, m/z (% rel. int.): 250 ($[M]^+$,10), 220 (12), 208 (100), 190 (28), 177 (24), 150 (98), 122 (36), 107 (15) and 79 (8).

4.3.5. (±)-3-Hydroxymethyl-3-isopropyl-7-methoxychroman-4-one (6d). It was obtained as white plates (2.4 g) in 59% yield. Mp 74–76°C; R_f: 0.40 (petroleum ether–ethyl acetate, 7:3); $C_{14}H_{19}O_4$ ($[M+H]^+$ 251.1268, Calcd 251.1283); IR (KBr): 3458 (OH), 2970, 1661 (C═O), 1610, 1575, 1437, 1264, 1164, 1026, 921, 823 and 771 cm^{-1}; UV (MeOH): 212, 232, 272 and 311 nm; ^1H NMR ($CDCl_3$) δ: 0.91 and 1.00 (6H, 2d, 3H each, J=7.0 Hz each, CH (CH_3)$_2$), 2.23–2.30 (2H, m, CH(CH$_3$)$_2$ and OH), 3.48 (1H, d, J=11.7 Hz, C-1′H_α), 3.83 (3H, s, OCH_3), 4.07 (1H, d, J=11.7 Hz, C-1′H_β), 4.48 (2H, br s, C-2H_α and C-2H_β), 6.37 (1H, d, J=2.3 Hz, C-8H), 6.58 (1H, dd, J=2.3 and 8.8 Hz, C-6H) and 7.82 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 17.22 and 17.49 (2×CH_3), 28.09 (CH(CH$_3$)$_2$), 51.94 (C-3), 55.57 (OCH_3), 61.27 (C-1′), 70.51 (C-2), 100.37 (C-8), 110.06 (C-6), 114.65 (C-10), 129.06 (C-5), 163.26 (C-9), 166.07 (C-7) and 196.46 (C═O); EIMS m/z (% rel. int.): 250 ($[M]^+$,17), 219 (19), 208 (78), 190 (16), 177 (27), 150 (100), 122 (34), 107 (15) and 79 (9).

4.3.6. (±)-3-Butyl-3-hydroxymethyl-7-methoxychroman-4-one (6e). It was obtained as a colourless viscous oil (2.9 g) in 68% yield. R_f: 0.52 (petroleum ether–ethyl acetate, 7:3); $C_{15}H_{21}O_4$ ($[M+H]^+$ 265.1419, Calcd 265.1440); IR (thin film): 3456 (OH), 2935, 1670 (C═O), 1608, 1440, 1387, 1257, 1163, 1107, 1030, 940, 837 and 694 cm^{-1}; UV (MeOH): 212, 232, 273 and 311 nm; ^1H NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.7 Hz, CH_3), 1.29 (4H, m, C-2″H and C-3″H), 1.66 (2H, m, C-1″H), 2.48 (1H, br s, OH), 3.57 (1H, dd, J=3.6 and 11.5 Hz, C-1′H_α), 3.84 (3H, s, OCH_3), 3.96 (1H, dd, J=3.6 and 11.5 Hz, C-1′H_β), 4.32 (1H, d, J=11.5 Hz, C-2H_α), 4.38 (1H, d, J=11.5 Hz, C-2H_β), 6.40 (1H, d, J=2.3 Hz, C-8H), 6.59 (1H, dd, J=2.3 and 8.8 Hz, C-6H) and 7.83 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 13.60 (CH_3), 23.06, 25.53 and 30.02 (C-1″, C-2″ and C-3″), 49.36 (C-3), 55.31 (OCH_3), 62.75 (C-1′), 71.93 (C-2), 100.27 (C-8), 109.86 (C-6), 113.95 (C-10), 128.91 (C-5), 163.11 (C-9), 165.82 (C-7) and 195.50 (C═O); EIMS, m/z (% rel. int.): 264 ($[M]^+$,6), 233 (9), 208 (100), 190 (30), 177 (25), 150 (75), 122 (25), 107 (12) and 79 (6).

4.3.7. (±)-3-Hydroxymethyl-7-methoxy-3-pentylchroman-4-one (6f). It was obtained as a colourless viscous oil (2.7 g) in 60% yield. R_f: 0.56 (petroleum ether–ethyl acetate, 7:3); $C_{16}H_{23}O_4$ ($[M+H]^+$ 279.1625, Calcd 279.1596); IR (thin film): 3459 (OH), 2933, 1673 (C═O), 1607, 1441, 1387, 1257, 1163, 1030, 945, 837 and 694 cm^{-1}; UV (MeOH): 213, 232, 273 and 311 nm; ^1H NMR ($CDCl_3$) δ: 0.85 (3H, t, J=6.7 Hz, CH_3), 1.27 (6H, m, C-2″H, C-3″H and C-4″H), 1.64 (2H, m, C-1″H), 2.52 (1H, br s, OH), 3.56 (1H, dd, J=4.3 and 11.5 Hz, C-1′H_α), 3.84(3H, s, OCH_3), 3.95 (1H, dd, J=4.3 and 11.5 Hz, C-1′H_β), 4.31 (1H, d, J=11.6 Hz, C-2H_α), 4.44 (1H, d, J=11.6 Hz, C-2H_β), 6.39 (1H, d, J=2.3 Hz, C-8H), 6.58 (1H, dd, J=2.3 and 8.8 Hz, C-6H) and 7.81 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 14.31 (CH_3), 22.78, 23.61, 30.72 and 32.69 (C-1″, C-2″, C-3″ and C-4″), 49.85 (C-3), 55.99 (OCH_3), 63.61 (C-1′), 72.35 (C-2), 100.91 (C-8), 110.57 (C-6), 114.47 (C-10), 129.56 (C-5), 163.70 (C-9), 166.54 (C-7) and 196.57 (C═O); EIMS, m/z (% rel. int.): 278 ($[M]^+$,4), 247 (6), 208 (100), 190 (32), 177 (24), 150 (65), 122 (25), 107 (10) and 79 (6).

4.4. General procedure of acetylation of (±)-hydroxymethylchromanones 6a–6f: preparation of (±)-acetoxymethylchromanones 7a–7f

To a solution of hydroxymethylchromanone **6a–6f** (0.01 mol) in acetic anhydride (1.1 equiv.) and pyridine (2 equiv.), was added a catalytic amount of 4-*N,N*-dimethylaminopyridine and the reaction mixture stirred at 25–28°C for 18 h. The reaction was worked-up by addition of ice-cold water and aqueous reaction mixture extracted with ethyl acetate (3×15 ml). The combined ethyl acetate layers were washed with sodium bicarbonate and concentrated to afford the corresponding acetoxymethylchromanones **7a–7f** in 75–99% yields.

4.4.1. (±)-3-Acetoxymethyl-7-methoxy-3-methylchroman-4-one (7a). It was obtained as a colourless viscous oil (2.4 g) in 92% yield. R_f: 0.70 (petroleum ether–ethyl acetate, 4:1); $C_{14}H_{17}O_5$ ($[M+H]^+$ 265.1062, Calcd 265.1076); IR (Nujol): 2940, 1744 ($OCOCH_3$), 1681 (C=O), 1611, 1577, 1440, 1394, 1237, 1161, 1040, 952 and 838 cm^{-1}; UV (MeOH): 212, 234, 273 and 311 nm; ^1H NMR ($CDCl_3$) δ: 1.22 (3H, s, CH_3), 2.04 (3H, s, $OCOCH_3$), 3.83 (3H, s, OCH_3), 4.15 and 4.19 (2H, 2d, 1H each, J=11.0 and 11.3 Hz, C-1′H_α and C-2H_α), 4.36 and 4.45 (2H, 2d, 1H each, J=11.0 and 11.3 Hz, C-1′H_β and C-2H_β), 6.41 (1H, d, J=2.2 Hz, C-8H), 6.60 (1H, dd, J=2.2 and 8.8 Hz, C-6H) and 7.83 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 16.81 (CH_3), 21.04 ($OCO\mathit{C}H_3$), 45.29 (C-3), 56.00 (OCH_3), 65.56 (C-1′), 73.84 (C-2), 100.98 (C-8), 110.73 (C-6), 114.06 (C-10), 129.83 (C-5), 163.54 (C-9), 166.45 (C-7), 171.00 ($O\mathit{C}OCH_3$) and 193.01 (C=O); EIMS, *m/z* (% rel. int.): 264 ($[M]^+$, 35), 191 (7), 150 (100), 122 (23), 107 (6) and 43 (6).

4.4.2. (±)-3-Acetoxymethyl-3-ethyl-7-methoxychroman-4-one (7b). It was obtained as a colourless viscous oil (2.1 g) in 76% yield. R_f: 0.70 (petroleum ether–ethyl acetate, 4:1); $C_{15}H_{19}O_5$ ($[M+H]^+$ 279.1226, Calcd 279.1232); IR (Nujol): 2923, 1733 ($OCOCH_3$), 1675 (C=O), 1612, 1460, 1384, 1234, 1161, 1092, 1051 and 926 cm^{-1}; UV (MeOH): 219, 231, 273 and 309 nm; ^1H NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.6 Hz, CH_3), 1.76 (2H, q, J=7.6 Hz, CH_2CH_3), 2.01 (3H, s, $OCOCH_3$), 3.84 (3H, s, OCH_3), 4.22, 4.34, 4.41 and 4.43 (4H, 4d, 1H each, J=11.4, 11.5, 11.5 and 11.4 Hz, C-1′H_α, C-1′H_β, C-2H_α and C-2H_β), 6.40 (1H, d, J=2.3 Hz, C-8H), 6.60 (1H, dd, J=2.3 and 8.8 Hz, C-6H) and 7.84 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 6.80 (CH_3), 19.42 ($OCO\mathit{C}H_3$), 22.29 ($\mathit{C}H_2CH_3$), 46.59 (C-3), 54.30 (OCH_3), 62.35 (C-1′), 70.88 (C-2), 99.20 (C-8), 108.90 (C-6), 112.68 (C-10), 128.06 (C-5), 161.68 (C-9), 164.65 (C-7), 169.40 ($O\mathit{C}OCH_3$) and 190.99 (C=O); EIMS, *m/z* (% rel. int.): 278 ($[M]^+$,20), 250 (23), 190 (30), 150 (100), 122 (25), 107 (8) and 43 (10).

4.4.3. (±)-3-Acetoxymethyl-7-methoxy-3-propylchroman-4-one (7c). It was obtained as an off-white viscous oil (2.2 g) in 75% yield. R_f: 0.72 (petroleum ether–ethyl acetate, 4:1); $C_{16}H_{21}O_5$ ($[M+H]^+$ 293.1363, Calcd 293.1389); IR (Nujol): 2959, 1745($OCOCH_3$), 1681(C=O), 1610, 1464, 1236, 1161, 1039, 946 and 736 cm^{-1}; UV (MeOH): 213, 230, 269 and 309 nm; ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.2 Hz, CH_3), 1.32 (2H, m, C-2″H), 1.67 (2H, m, C-1″H), 2.03 (3H, s, $OCOCH_3$), 3.83 (3H, s, OCH_3), 4.21, 4.33, 4.40 and 4.44 (4H, 4d, 1H each, J=11.4 Hz each, C-1′H_α, C-1′H_β, C-2H_α and C-2H_β), 6.40 (1H, d, J=2.3 Hz, C-8H), 6.60 (1H, dd, J=2.3 and 8.8 Hz, C-6H), 7.84 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 14.92 (CH_3), 17.36 (C-2″), 21.08 ($OCO\mathit{C}H_3$), 33.45 (C-1″), 48.31 (C-3), 55.97 (OCH_3), 64.45 (C-1′), 72.80 (C-2), 100.94 (C-8), 110.60 (C-6), 114.43 (C-10), 129.78 (C-5), 163.42 (C-9), 166.37 (C-7), 171.06 ($O\mathit{C}OCH_3$) and 192.73 (C=O); EIMS, *m/z* (% rel. int.): 292 ($[M]^+$,5), 250 (44), 190 (100), 150 (96), 122(26), 107 (8) and 43 (9).

4.4.4. (±)-3-Acetoxymethyl-3-isopropyl-7-methoxychroman-4-one (7d). It was obtained as a white solid (1.1 g) in 96% yield. Mp 65–66°C; R_f: 0.65 (petroleum ether–ethyl acetate, 4:1); $C_{16}H_{21}O_5$ ($[M+H]^+$ 293.1365, Calcd 293.1389); IR (KBr): 2970, 1735 ($OCOCH_3$), 1676 (C=O), 1611, 1435, 1386, 1235, 1162, 1019, 927, 834 and 685 cm^{-1}; UV (MeOH): 210, 235, 272 and 312 nm; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.92 and 1.06 (6H, 2d, 3H each, J=7.0 Hz each, $CH(C\mathit{H}_3)_2$), 2.01 (3H, s, $OCOCH_3$), 2.21 (1H, m, C$\mathit{H}(CH_3)_2$), 3.82 (3H, s, OCH_3), 4.18, 4.42 and 4.52 (4H, 3d of 1H, 1H and 2H, respectively, J=11.3, 11.3 and 11.8 Hz, C-1′H_α, C-1′H_β, C-2H_α and C-2H_β), 6.39 (1H, d, J=2.3 Hz, C-8H), 6.59 (1H, dd, J=2.3 and 8.8 Hz, C-6H) and 7.85 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 17.44 and 18.37 (2×CH_3), 21.14 ($OCO\mathit{C}H_3$), 28.94 ($\mathit{C}H(CH_3)_2$), 50.52 (C-3), 55.98 (OCH_3), 62.81 (C-1′), 70.97 (C-2), 100.86 (C-8), 110.48 (C-6), 114.83 (C-10), 129.86 (C-5), 163.46 (C-9), 166.26 (C-7), 171.14 ($O\mathit{C}OCH_3$) and 192.85 (C=O); EIMS, *m/z* (% rel. int.): 292 ($[M]^+$,10), 250 (29), 190 (62), 150 (100), 122 (21), 107 (10) and 43 (12).

4.4.5. (±)-3-Acetoxymethyl-3-butyl-7-methoxychroman-4-one (7e). It was obtained as a white solid (1.0 g) in 96% yield. Mp 81–83°C; R_f: 0.75 (petroleum ether–ethyl acetate, 4:1); $C_{17}H_{23}O_5$ ($[M+H]^+$ 307.1537, Calcd 307.1545); IR (Nujol): 2937, 1731 ($OCOCH_3$), 1673 (C=O), 1611, 1442, 1396, 1240, 1107, 1035, 948, 851 and 748 cm^{-1}; UV (MeOH): 211, 234, 273 and 311 nm; ^1H NMR ($CDCl_3$) δ: 0.63 (3H, t, J=6.8 Hz, CH_3), 1.07 (4H, m, C-2″H and C-3″H), 1.45 (2H, t, J=8.0 Hz, C-1″H), 1.80 (3H, s, $OCOCH_3$), 3.60 (3H, s, OCH_3), 3.98, 4.10 and 4.20 (4H, 3d of 1H, 1H and 2H, respectively, J=11.4 Hz each, C-1′H_α, C-1′H_β, C-2H_α and C-2H_β), 6.17 (1H, d, J=1.7 Hz, C-8H), 6.36 (1H, dd, J=1.7 and 8.8 Hz, C-6H) and 7.61 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 12.39 (CH_3), 19.32 ($OCO\mathit{C}H_3$), 21.82 (C-3″), 24.32 and 29.16 (C-1″ and C-2″), 46.44 (C-3), 54.22 (OCH_3), 62.65 (C-1′), 71.02 (C-2), 99.19 (C-8), 108.84 (C-6), 112.65 (C-10), 128.01 (C-5), 161.65 (C-9), 164.60 (C-7), 169.26 ($O\mathit{C}OCH_3$) and 190.98 (C=O); EIMS, *m/z* (% rel. int.): 306 ($[M]^+$, 4), 250 (40), 190 (100), 150 (86), 122 (25), 107 (7) and 43 (11).

4.4.6. (±)-3-Acetoxymethyl-7-methoxy-3-pentylchroman-4-one (7f). It was obtained as a colourless viscous oil (3.2 g) in 99% yield. R_f: 0.75 (petroleum ether–ethyl acetate, 4:1); $C_{18}H_{25}O_5$ ($[M+H]^+$ 321.1712, Calcd 321.1702); IR (KBr): 2932, 1744 ($OCOCH_3$), 1678 (C=O), 1611, 1441, 1238, 1107, 1038, 948 and 837 cm^{-1}; UV (MeOH): 232 and

267 nm; ^{1}H NMR ($CDCl_3$) δ: 0.84 (3H, t, J=6.9 Hz, CH_3), 1.25 (6H, m, C-2″H, C-3″H and C-4″H), 1.67 (2H, m, C-1″H), 2.03 (3H, s, $OCOCH_3$), 3.84 (3H, s, OCH_3), 4.20, 4.33 and 4.43 (4H, 3d of 1H, 1H and 2H, respectively, J=11.4 Hz each, C-1′H_α, C-1′H_β, C-2H_α and C-2H_β), 6.40 (1H, d, J=2.3 Hz, C-8H), 6.60 (1H, dd, J=2.3 and 8.8 Hz, C-6H) and 7.84 (1H, d, J=8.8 Hz, C-5H); ^{13}C NMR ($CDCl_3$) δ: 14.29 (CH_3), 21.11 ($OCOCH_3$), 22.71, 23.59, 31.12 and 32.63 (C-1″, C-2″, C-3″ and C-4″), 48.21 (C-3), 55.99 (OCH_3), 64.39 (C-1′), 72.75 (C-2), 100.9 (C-8), 110.60 (C-6), 114.38 (C-10), 129.78 (C-5), 163.39 (C-9), 166.33 (C-7), 171.08 ($OCOCH_3$) and 192.76 (C=O); EIMS, *m/z* (% rel. int.): 320 ($[M]^+$,4), 250 (35), 190 (100), 150 (67), 122 (20), 107 (11) and 43 (12).

4.5. General procedure of enzymatic deacetylation of (±)-3-acetoxymethyl-3-alkyl-7-methoxychroman-4-ones 7a–7f

To a solution of (±)-acetoxymethylchromanone (**7a–7f**, 1.0 mmol) in anhydrous diisopropyl ether (15 ml), *n*-butanol (3–4 equiv.) was added, followed by the addition of *Candida rugosa* lipase (200 mg). The suspension was stirred at 35–38°C 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–ethyl acetate to afford optically enriched (+)-3-alkyl-3-hydroxymethyl-7-methoxychroman-4-ones **6a–6f** and (+)-3-acetoxymethyl-3-alkyl-7-methoxychroman-4-ones **7a–7f** in 60–82 and 60–87% yields (yields were calculated by assuming single enantiomer as 100% in starting (±)-**7a–7f**), respectively. The (+)-hydroxymethylchromanones **6a–6f** and (+)-acetoxymethylchromanones **7a–7f** were identified on the basis of their spectral data, which were found identical with the spectral data of the corresponding racemic compounds, i.e. (±)-**6a–6f** and (±)-**7a–7f**, respectively as reported above. The optical rotation values of (+)-3-hydroxymethylchromanones **6a–6f** and (+)-3-acetoxymethylchromanones **7a–7f** were found to be: (+)-**6a** +9.0° (*c* 0.66, $CHCl_3$), (+)-**6b** +23.4° (*c* 0.68, $CHCl_3$), (+)-**6c** +12.0° (*c* 0.66, $CHCl_3$), (+)-**6d** +12.2° (*c* 0.81, $CHCl_3$), (+)-**6e** +12.0° (*c* 0.66, $CHCl_3$), (+)-**6f** +13.0° (*c* 0.66, $CHCl_3$), (+)-**7a** +18.0° (*c* 0.66, $CHCl_3$), (+)-**7b** +22.8° (*c* 0.70, $CHCl_3$), (+)-**7c** +27.0° (*c* 0.66, $CHCl_3$), (+)-**7d** +18.0° (*c* 0.66, $CHCl_3$), (+)-**7e**+12.0° (*c* 0.66, $CHCl_3$) and (+)-**7f** +21.0° (*c* 0.66, $CHCl_3$).

4.6. General procedure for chemical deacetylation of unreacted, recovered acetates (+)-7a–7f

The (+)-acetoxymethylchroman-4-one **7a–7f** (100 mg) was dissolved in MeOH (5 ml) containing 2–3 drops of hydrochloric acid. The reaction mixture was stirred for 4 h at 25–28°C and quenched by the addition of ice-cold water (5 ml). The reaction mixture was extracted with ethyl acetate (2×10 ml), combined ethyl acetate layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to afford the (−)-hydroxymethylchroman-4-ones **6a–6f** in 86–95 yields. The (−)-hydroxymethylchromanones **6a–6f** were identified on the basis of their spectroscopic data, which were found identical with the spectroscopic data of corresponding (+)- and (±)-hydroxymethylchromanones reported above. The optical rotation values of (−)-3-hydroxymethylchromanones **6a–6f** were found to be: (−)-**6a** −10.6° ($CHCl_3$), (−)-**6b** −25.3° ($CHCl_3$), (−)-**6c** −12.9° ($CHCl_3$), (−)-**6d** −9.5° ($CHCl_3$), (−)-**6e** −13.0° ($CHCl_3$) and (−)-**6f** −16.4° ($CHCl_3$).

4.7. General procedure for the preparation of *O*-acetylmandelates of (+)/(±)-3-alkyl-3-hydroxymethylchromanones 6a–6f

To a solution of (+)/(±)-3-hydroxymethylchromanone **6a–6f** (0.25 mmol), catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine and D-(−)-*O*-acetylmandelic acid (0.25 mmol) in CH_2Cl_2 (5 ml) at 0°C, dicyclohexylcarbodiimide (0.25 mmol 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 25°C for an additional 15–20 h. The *N*,*N*-dicyclohexyl urea formed during the reaction was removed by filteration 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 ^{1}H NMR spectra of *O*-acetylmandelates of (±)-alcohols **6a–6f** 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 ^{1}H NMR spectra of the *O*-acetylmandelates of (+)-**6a–6f** gives a measure of their diastereomeric compositions, which are directly related to the enantiomeric compositions of the enzymatically deacetylated (+)-3-hydroxymethylchromanones (Table 1). The maximum ee of 56% was observed for (+)-3-hydroxymethyl-7-methoxy-3-propylchroman-4-one (**6c**).

4.8. X-Ray crystallography

The crystallographic measurements on (±)-3-ethyl-3-hydroxymethyl-7-methoxychroman-4-one (**6b**) were made using a Siemens SMART area-detector diffractometer. Graphite monochromated MoK_α radiation was used for data collection. The structure was solved using SHELXTL-PLUS[28] and refined with SHELXL-96.[29]

Crystal data of compound **6b**. $C_{13}H_{16}O_4$, M=236.26, T=180(2) K, λ=0.71073 Å, orthorhombic a=7.7656 (4), b=7.0204(3), c=21.0668(11) Å, β=90°, V=1148.51(10) Å^3, space group *pnma*, Z=4, D_x=1.366 Mg m^{-3}, μ=0.101 mm^{-1}, F(000)=504. Crystal size 0.48×0.44×0.22 mm; θ range for data collection 1.93–25.50°; index range $-9 < h < 10$, $-6 < k < 9$, $-27 < l < 28$; reflections collected 5899; independent reflections 1166 [$R_{(int)}$=0.0430]; refinement method full-matrix least squares on F^2; data/restraints/parameters 1166:0:125; goodness-of-fit on F^2 1.045; $R(F)$ [$I > 2(I)$] = 0.0616; $wR2$=0.1462 (for 846 reflections); largest diff. peak and hole 0.357 and −0.358 eÅ^{-3}.

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