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Baker's yeast catalysed enantioselective reduction of chroman-4-ones

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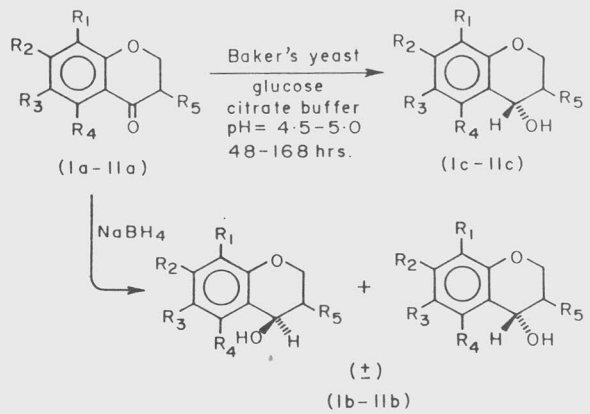
Substituted chroman-4-ones **1a-10a** on catalytic reduction with Baker's Yeast give (*S*)-chroman-4-ols **1c-11c** with high enantioselectivity. The absolute configuration has been determined by specific rotation and CD spectra.

The enantioselective reduction of carbonyl compounds using bio-catalysts such as isolated pure enzymes or whole cells such as yeasts, bacteria and fungi continue to attract the attention of synthetic organic chemists[1,2]. Whole cell yeast catalysed reactions are particularly attractive in this respect as yeast is readily and cheaply available bio-catalyst and the use of whole cells obviates the need for the addition of expensive co-factors. It is now known that, in general, the Baker's yeast catalysed enantioselective reduction of carbonyl compounds proceed in accordance with the Prelog's rule[3]. Earlier, (*S*)-chorman-4-ol **1c** was obtained by the lipase catalysed kinetic resolution of racemic chroman-4-ol **1b**[4].

Substituted chroman-4-ones, a class of oxygen heterocyclics, are common among natural products and are extensively used as synthetic intermediates[5]. Earlier Holl *et al.*[6] studied the *Mortierella isabellina* catalysed reduction of chroman-4-one **1a** and thiochroman-4-one and the products are (*S*)-chroman-4-ol **1c** and (*S*)-thiochroman-4-ol in 84% ee and 88% ee respectively. There are no reports in the literature regarding the enantioselective reduction of chroman-4-ones using Baker's yeast. We report herein the bio-reduction of several substituted chroman-4-ones **1a-10a** using Baker's yeast (Scheme I).



1 a,b,c = $R_1, R_2, R_3, R_4, R_5 = H$
2 a,b,c = $R_1, R_2, R_4, R_5 = H$; $R_3 = Cl$
3 a,b,c = $R_1, R_2, R_4, R_5 = H$; $R_3 = CH_3$
4 a,b,c = $R_1, R_2, R_3, R_5 = H$; $R_4 = CH_3$
5 a,b,c = $R_2, R_3, R_4, R_5 = H$; $R_1 = CH_3$
6 a,b,c = $R_1, R_3, R_4, R_5 = H$; $R_2 = OCH_3$
7 a,b,c = $R_3, R_4, R_5 = H$; $R_1 = CH_3$, $R_2 = OCH_3$
8 a,b,c = $R_1, R_2, R_4, R_5 = H$; $R_3 = Br$
9 a,b,c = $R_1, R_3, R_4, R_5 = H$; $R_2 = Cl$
10 a,b,c = $R_1, R_3, R_4, R_5 = H$; $R_2 = CH_2O$-
11 a,b,c = $R_1, R_2, R_4 = H$; $R_3 = Cl$; R_5 =

Scheme I

In a typical experiment, chroman-4-ones **1a-10a** (0.3 mol) dissolved in ethanol (5 mL) was slowly added during 24 hr to a citrate buffer 0.05 *M* (300 ml) containing Baker's yeast beads immobilised in calcium alginate[7] and stirred at RT for 48-168 hr, maintaining. *p*H of the reaction mixture at 4.5-5.0 by the addition of ammonia. The reduction was monitored by TLC by comparison with authentic racemic chroman-4-ols **1b-10b**. When there is no further increase in the product concentration, the supernatant solution was decanted, extracted with ethyl acetate and column chromatographed on silica gel. The yields of **1c-10c** was 30-40% (Table I). Racemic **1b-10b** needed to monitor the bio-

Table I—Characterization data of (*S*)-chroman-4-ols **1c-10c**

Compd	Reaction time (hr)	% of Chemical yield	% of ee (from chiral HPLC)	Specific rotation (in $CHCl_3$)	CD data	$\theta \times 10^{-3}$ (deg.cm^2.d. mol^{-1})
1c	48	30	88.4	-40.00 (c, 0.5%)	(-)228 nm (-)280 nm	(-) 220×10^{-3} (-) 48×10^{-3}
2c	96	40	73.3	-30.30 (c, 0.33%)	(-)232 nm (-)240 nm	(-) 293×10^{-3} (-) 79×10^{-3}
3c	72	34	44.2	-2.70 (c, 2%)	(-)230 nm (-)285 nm	(-) 210×10^{-3} (-) 59×10^{-3}
4c	168	37	32.5	-28.04 (c, 0.97%)	(-)234 nm (-)270 nm	(-) 200×10^{-3} (-) 25×10^{-3}
5c	72	36	10.3	-2.00 (c, 0.5%)	(-)233 nm (-)279 nm	(-) 234×10^{-3} (-) 52×10^{-3}
6c	96	30	74.1	-8.80 (c, 0.05%)	(-)229nm (-)262 nm	(-) 249×10^{-3} (-) 27×10^{-3}
7c	48	30	25.0	-8.46 (c, 0.26%)	(-)243 nm (-)274 nm	(-) 246×10^{-3} (-) 33×10^{-3}
9c	48	30	53.1	-25.00 (c, 1%)	(-)233 nm (-)275 nm	(-) 236×10^{-3} (-) 47×10^{-3}
10c	168	35	65.8	-9.00 (c, 1%)	(-)236 nm (-) 203 nm	(-) 220×10^{-3} (-) 39×10^{-3}

reduction were obtained by the $NaBH_4$ reduction of **1a-10a** using reported method[8].

The absolute configuration of the Baker's yeast reduction products **1c-10c** as *S* is determined from specific rotation and CD spectra. Earlier Maja *et al.*[4] reported the CD spectral data for **1c**. It showed negative cotton effect with bands at 228 and 280 nm. **1c-10c** showed negative CD spectral bands similar to the reported for **1c** (Table I). The % ee of the (*S*)-chroman-4-ols is determined by chiral HPLC. Table I gives the % chemical yields, % ee, specific rotation and CD spectral data of Baker's yeast reduction products. Good enantioselectivity was observed for unsubstituted chroman-4-one **1a** and 6- and 7-substituted chroman-4-ones **2a, 6a, 8a**. The bio-reduction of prochiral chroman-4-ones proceed in accordance with Prelog's rule, with the hydride delivered to the re-face. This study shows that Baker's yeast reduction of chroman-4-ones **1a-10a** offers a new route to optically active (*S*)-chroman-4-ols **1c-10c**.

Experimental Section

Baker's yeast, Eagle brand, India was used. Specific rotations were recorded on JASCO J-20 polarimeter. and CD spectra on JASCO J-20 spectropolarimeter. Chiral HPLC was done on Shimadzu LC 6A with Chiracel OD column (250×5 mm), using *n*-hexane: isopropanol (98:2). ^{1}H (200 MHz) and ^{13}C NMR (50.3) MHz) were recorded on Varian Gemini 200 NMR spectrometer.

The chiral HPLC of (±) racemic chroman-4-ols **1b-10b** as well as the Baker's yeast reduction products **1c-10c** was recorded on Chiracel O.D. column (25×0.46 cm, Diacel, Japan) under following conditions: flow 0.5 mL/min using 2% isopropanol in *n*-hexane as the eluent. The retention times (min) were (±) **1b** 23.4 and 26.9, (±) **2b** 13.0 and 14.1, (±) **3b** 18.0 and 20.3, (±) **4b** 10.6 and 13.5, (±) **5b**, 13.5 and 16.9, (±) **6b** 22.0 and 27.6, (±) **7b** 16.3 and 18.4, (±) **8b** 13.2 and 16.1, (±) **9b** 13.0 and 14.5, (±) **10b** 17.2 and 18.3; (±) **11b** 17.7 and 20.2; (-) **1c** 23.6 and 27.0, (-) **2c** 13.1 and 14.7, (-) **3c** 18 and 20.4, (-)**4c** 10.7 and 13.9, (-) **5c** 13.9 and 17.1, (-)**6c** 22.1 and 27.6, (-) **7c** 16.4 and 18.7, (-) **8c** 13.8 and 15.2, (-) **9c** 13.1 and 14.6, (-) **10c** 17.4 and 18.4; (-) **11c** 17.9 and 20.6.

Chroman-4-ones **1a-10a** are already known[9]. **1b-10b** were obtained by $NaBH_4$ reduction of chroman-4-ones **1a-10a**[8]. (±) Chroman-4-ols (**1b, 2b, 3b, 6b, 8b, 9b, 10b**) are already known[8]. Baker's yeast beads immobilised in calcium alginate are prepared as per reported method[7,10].

General procedure for the Baker's yeast mediated synthesis of (*S*)-chroman-4-ols. Baker's

yeast (10 g) immobilised in calcium alginate to give beads, was kept in 20% glucose solution for 48 hr The beads were filtered, washed with water and transferred to a flask containing 0.05 *M* citrate buffer (300 mL) with *p*H 4.5-5.0. Chroman-4-ones **1a-10a** (0.3 mol) dissolved in ethanol (5 ml) were added slowly during 24 hr The reaction mixture was gently stirred at RT for 48-168 hr The *p*H of the reaction mixture was maintained by addition of 3 *N* NH_3. The progress of the reaction was monitored by TLC by comparison with racemic chroman-4-ols. When there is no further increase in the concentration of the product, the supernatant solution decanted and extracted with ethyl acetate (200 ml), dried and chromatographed on silica gel. Chroman-4-ols **1c-10c** were obtained in 30-40% yield.

1b: IR: 3375 cm^{-1}; ^1H 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, 8), 7.20 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$): δ 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).

2b: IR: 3352 cm^{-1};. ^1H NMR ($CDCl_3$): δ 4.18 (m, 2H, OCH_2), 2.00 (m, 2H, CH_2), 4.65 (bs, 1H, H-4), 1.90 (bs, 1H, OH), 7.20 (d, J = 2 Hz, 1H, H-5), 7.08 (dd, J = 10 Hz, 2 Hz, 1H, H-7), 6.70 (d, J = 10 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$): δ 62.1 (C-2), 30.3 (C-3), 63.0 (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).

3b: IR: 3348 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.15 (m, 2H, OCH_2), 1.98 (m, 2H, CH_2), 4.60 (t, J=2Hz, 1H, H-4), 2.40 (bs, 1H, OH), 7.02 (d, J=2Hz, 1H, H-5), 6.95 (dd, J=10 Hz, 2 Hz, 1H, H-7) 6.60 (d, J=10 Hz, 1H, H-8), 2.26 (bs, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 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).

4b: IR: 3334 cm^{-1}; ^1H 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 Hz, 2Hz, 1H, H-6), 6.74 (dd, J=10 Hz, 2 Hz, 1H, H-7), 7.00 (m, 1H, H-8) 2.20 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 62.0 (C-2), 31.0 (C-3), 63.2 (C-4), 123.8 (C-4a), 126.3 (C-5), 127.3 (C-6), 131.0 (C-7), 120.0 (C-8) 153.0 (C-8a), 16.0 (CH_3).

5b: R: 3299 cm^{-1}; ^1H 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, 1H, H- 5) 6.64 (m, 1H, H-6) 6.64 (m, 1H, H-7), 2.28(s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 61.6 (C-2), 30.9 (C-3), 62.9 (C-4), 123.8 (C-4a), 129.1 (C-5), 129.9 (C-6), 130.1 (C-7), 116.7 (C-8) 152.2 (C-8a), 20.4 (CH_3).

6a: IR: 3336 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.28 (m, 2H, OCH_2), 2.05 (m, 2H, CH_2,), 4.75 (bs,1H, H-4), 1.95 (bs, 1H, OH), 7.20 (d, J=10 Hz, 1H, H-5), 6.52 (dd, J=10 Hz, 2 Hz, 1H, H-6), 6.38 (d, J=2 Hz, 1H, H-8), 3.80 (s, 3H, OCH_3); ^{13} C NMR ($CDCl_3$): δ 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).

7b: IR: 3375 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.38 (m, 2H, OCH_2), 2.10 (m, 2H, CH_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 ($CDCl_3$): δ 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).

8b: IR: 3389 cm^{-1}; ^1H 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 Hz, 2 Hz, 1H, H-7), 6.72 (d, J=10 Hz, 1H, H-8). ^{13} C NMR ($CDCl_3$): δ 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 (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).

9b: IR: 3297 cm^{-1}; ^1H 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, H-5), 6.80 (m, 1H, H-6), 6.80 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$): δ 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 (95), 165 (35), 155 (100), 149 (95), 131 (10), 103 (5), 91 (10), 75 (20), 63 (15) and 51 (20).

10b: IR: 3364 cm^{-1}; ^1H 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 Hz, 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 ($CDCl_3$): δ 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).

11b: IR: 3274 cm^{-1}; ^{1}HNMR ($CDCl_3$): 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-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).

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