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PREPARATION OF HOMOCHIRAL CHROMAN-4-OLS AND THIOCHROMAN-4-OLS BY MICROBIAL BIOTRANSFORMATION

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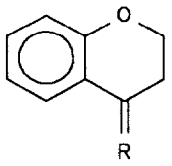
Abstract: Reduction of the carbonyl groups of chromanone and thiochromanone by Mortierella isabellina ATCC 42613 proceeds to give the (S) alcohols in high yield and enantiomeric excess. Benzylic hydroxylation of chroman by this fungus provides (R)-chroman-4-ol, and the (R) enantiomer of thiochroman-4-ol is obtained by bioconversion of thiochromanone or (±)-thiochroman-4-ol by Helminthosporium species NRRL 4671.

As part of our programme of studies into the enzymic benzylic hydroxylation reaction[1-4], we have recently had occasion to investigate methods for the preparation of single enantiomers of chroman-4-ol and thiochroman-4-ol, and report herein procedures for microbial bioconversions which result in the isolation of both enantiomers of these materials in homochiral form. The bioconversions which we have performed are summarized in the accompanying Table. Of the 4 chiral compounds which we have prepared only one has been previously described. (S)-chroman-4-ol (**6**) has been reported as the product of a microbiological reduction of chromanone, but no experimental details or analytical data were presented.[5] The compounds described herein have value as model compounds and as chiral intermediates for natural products which contain the 2,3-benzotetrahydropyran-4-ol moiety.

Reduction of the ketones **2** and **4** by M. isabellina proceeded according to Prelog's rule[6] to give the (-) alcohols, **6** and **9**, respectively, in high enantiomeric purity. In both cases, the crude biotransformation products gave material of ≥98% ee on crystallization. The absolute stereochemistry of (-)**6** has been shown to be (S) by ruthenium tetraoxide oxidation of its acetate **7** to 2-acetoxysuccinic acid of known configuration[5]: a sample of acetate **7** produced from our sample of **6** proved have a negative rotation, thus establishing the absolute stereochemistry of the M. isabellina reduction product as (S). The thiochroman-4-ol **9** generated by reduction of **4** by M. isabellina is

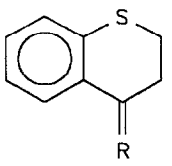
provisionally assigned the (S) configuration on the basis of consistency with Prelog's rule for microbial carbonyl reduction, now established to be valid for M. isabellina with chromanone (see above) and α-tetralone[1], and the observed sign of rotation.

Reduction of the ketones **2** and **4** by H. species is complicated by the fact that the corresponding alcohols are not configurationally stable in the presence of this fungus. Incubations with H. species of racemic chroman-4-ol (**5** + **6**) and thiochroman-4-ol (**8** + **9**) were performed (see Table) which demonstrate a stereopreference for oxidation of the (S) alcohols in both series. For the oxidation of chroman-4-ol this preference is not significant, (S)-thiochroman-4-ol is oxidized stereospecifically to the ketone, leaving unreacted (R) alcohol in high enantiomeric purity. This phenomenon is undoubtedly responsible for the formation of (R)-**8** in low yield from bioconversion of thiochromanone by H. species, during which reversible reduction/oxidation must occur.



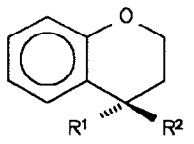
1, R = H_2

2, R = O



3, R = H_2

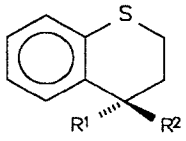
4, R = O



5, R^1 = H, R^2 = OH (R)

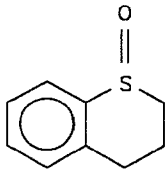
6, R^1 = OH, R^2 = H (S)

7, R^1 = OAc, R^2 = H (S)



8, R^1 = H, R^2 = OH (R)

9, R^1 = OH, R^2 = H (S)



10

Benzylic hydroxylation of chroman (**1**) by M. isabellina proceeded stereospecifically to give the (R) alcohol **5** in low yield. Nevertheless, this bioconversion provides a direct method for the preparation of **5** in a simple procedure. Thiochroman (**3**) gave only sulfoxide **10** when subjected to bioconversion by either of the fungi used in this study[7], but as described above either enantiomer of thiochroman-4-ol can be readily prepared by alternative bioconversion procedures.

Table: Production of chiral chromanol and thiochromanol by bioconversion

Substrate	biocatalyst	product	config.	yield(%)	e.e.(%)
1	M. isabellina	**5**	R	10	≥98
	H. species	**5**	R	2	54
2	M. isabellina	**6**	S	75	≥98
	H. species	**6**	S	35	≥98
3	M. isabellina	**10**		77	
	H. species	**10**		54	
4	M. isabellina	**9**	S	82	≥98
	H. species	**8**	R	20	≥98
5+6	M. isabellina	**5+6**	-	100	0
	H. species	**5**	R	84	4
		2	-	16	-
8+9	M. isabellina	**8+9**	-	100	0
	H. species	**8**	R	50	≥98
		4	-	50	-

Experimental: apparatus and general methods were identical with those previously described.[1] Mortierella isabellina ATCC 42613 (identical with NRRL 1757) and Helminthosporium species NRRL 4671 were maintained on malt agar slopes, and biotransformations performed on a 1g scale as described elsewhere[1], with the following alterations: the initial growth of fungus was allowed to proceed at 27°C for 16-18h in stationary 1L flasks prior to agitation of the growth flasks for a further 72h; and substrates were then biotransformed for 72h at concentrations of 0.33mg/mL (a solution of 1g in 30mL of 95% ethanol added to 3L of transformation medium) in 15 1L flasks stoppered with foam plugs. Product isolation was carried out as described[1], and the tabulated data refer to isolated, purified and chromatographically homogeneous materials. Products were identified by comparison of spectral data (listed below) with that obtained for authentic samples of racemic material.

Chroman-4-ol: from chromanone/M. isabellina. Crude material mp 65-73°C, $[\alpha]_D$ -56.4°, ee 84% (^{1}H nmr/Eu(thfc)$_3$), crystallization from acetone/hexane gave material of mp 73-75°C, ^{1}H n.m.r. δ 2.03 (2H, m), 4.27 (2H, m), 4.75 (1H, br.s), and 6.60-7.26 (4H, m) ppm, m.s. (EI) M/z

150(100), 131(20), 121(59), 105(15), 94(8), 77(19), 65(15), 55(19), 51(14), $[\alpha]_D$ -67.45° (c = 0.5, EtOH), ee ≥98% From chroman/M. isabellina, identical with the above except $[\alpha]_D$ +67.03° (c = 0.5, EtOH). Thiochroman-4-ol: from thiochromanone/M. isabellina. Crude material mp 70-73°C, $[\alpha]_D$ -108° (c = 2.0, EtOH), ee 88%. Crystallization from chloroform/pentane (twice) gave material of mp 77-79°C, $[\alpha]_D$ -129°, ^1H n.m.r. δ 1.9-2.1 (1H, m), 2.22-2.39 (1H, m), 2.73-2.88 (1H, m), 3.21-3.42 (1H, m), 4.60-4.64 (1H, m), and 6.94-7.21 (4H, m) ppm, m.s. (EI) M/z 166(25), 148(58), 147(100). From thiochromanone/H. species, $[\alpha]_D$ +129° (c = 1.3, EtOH), ee = ≥98% (^1H nmr/Eu(thfc)$_3$). From (±)-thiochromanol/H. species, crude material mp 76-78°C, $[\alpha]_D$ +120°, raised to mp 77-79°C, $[\alpha]_D$ +129° on crystallization as described above.
(S)-Chroman-4-ol acetate: from crude (S)-chroman-4-ol/acetic anhydride/pyridine/18h, oil, ^1H n.m.r. δ 2.08 (3H, s, CH_3), 2.0-2.3 (2H, m, CH_2), 4.15-4.35 (2H, m, OCH_2), 5.94 (1H, t, CHOAc), 6.8-7.0 and 7.2-7.45 (each 2H, m, aromatic H's) ppm, ir ν_{max} 1733 cm^{-1}, MS (EI) M/z(%) 192(44), 150(26), 105(28) relative to 131(100), $[\alpha]_D$ -178.1° (c = 2, $CHCl_3$), ee (^1H nmr/Eu(thfc)$_3$) 85%. (Lit.[5] $[\alpha]_D$ -209° (c = 2.2, $CHCl_3$)).

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