Hydrolytic and Reductive Action of Fermenting Yeast on a Keto Acetate: Synthesis of (+)-*endo*-Brevicomin

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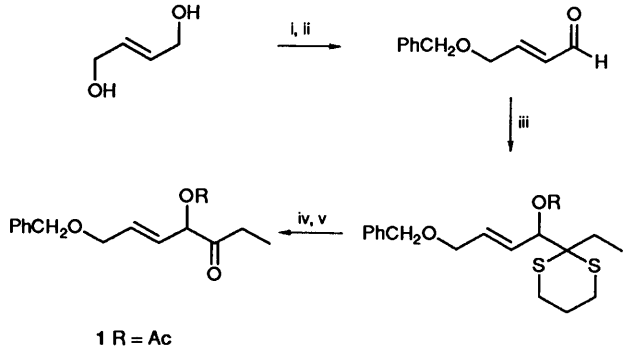
The keto acetate **1** in fermenting yeast gives the diol **2** with high enantiomeric excess. The product arises from hydrolysis–reduction and is transformed into (+)-*endo*-brevicomin. The hydroxy acetate from direct reduction of **1** is racemic.

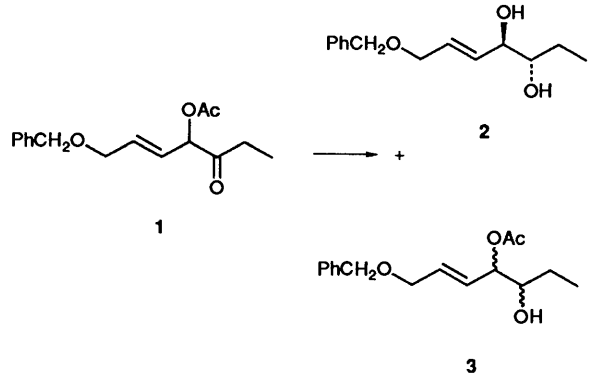
Baker's yeast (BY), used for a variety of selective transformations,[1] can effect enantio- and dia-stereoselective reduction of α-hydroxy-[2] and α-acetoxy-ketones[3] to give vicinal diols of varying optical purity. Here we describe our results for the reduction of racemic **1**, prepared in 20% overall yield (see Scheme 1).†‡ Although previous experience[4] suggested that an *anti* acetoxy alcohol with the stereochemistry depicted in **2** would be obtained from BY incubation of **1**, a *ca.* 2:1 mixture of the diol **2** and the acetoxy alcohol **3** was produced (see Scheme 2). The enantiomeric excess and diastereoisomeric composition of **2**/**3** was established by GLC analysis, on a chiral stationary phase, of mixtures of *exo*- and *endo*-brevicomin obtained from them (see Scheme 3).

Thus, **2**, protected as the dimethyl ketal **4**, was catalytically reduced to the saturated alcohol **5**, which in turn, was transformed into the bromide **6**. Alkylation of the other with lithium methyldithianyl gave **7**, from which by standard methodology the ketone **8** was obtained in 30% overall yield from **2**. Acid hydrolysis of the ketal **8**, afforded (+)-*endo*-brevicomin (96.5% ee) as proved by chiral capillary GLC.§ The compound was accompanied by 10% of the racemic *exo* stereoisomer (Fig. 1). The specific rotation of the above mixture is in good agreement with values reported in the literature.[5] This result allowed the assignment of the 3*S*,4*R* absolute configuration to the major component of the diol **2** from BY transformation of **1**. The hydroxy acetate **3** was then hydrolysed to the diol which, treated in a similar way to **2** and then converted into brevicomin of known analytical behaviour gave information about its optical purity and absolute configuration. That the synthetic sequence gave a 36:64 mixture of racemic *endo*- and *exo*-brevicomin indicates that **3** is similarly composed of an identical mixture of racemic *syn* and *anti* acetoxy alcohols. The results of the BY transformation of **1** appears then to be the consequence of a non stereoselective reduction of the carbonyl group to give **3** which is then hydrolysed in an enantioselective way to give optically enriched **2**. That this is not the case was proved by submitting to BY hydrolysis racemic **3** as a 7:3 mixture of *syn*/*anti* compounds: the diol thus obtained was a 3:7 *syn*/*anti* racemic mixture of (**rac2**), as proved by chiral HPLC analysis on the diol protected as the dimethyl ketal (**rac4**). While we have no explanation for the observed selectivity in the hydrolysis of **3**, we suggest as a mechanism for the overall reaction, that a slow hydrolysis occurs to give a labile intermediate hydroxy ketone from which, *via* a stereoselective reduction, the observed diols are obtained. At the same time reduction of the keto acetate **1** also takes place giving racemic **3**.



1 R = Ac

Scheme 1 *Reagents:* i, NaH–$PhCH_2Br$; ii, pyridinium chlorochromate; iii, ethyldithianyllithium; iv, AC_2O–py; v, BF_3–HgO



Scheme 2

Experimental

Fermentation of Compound **1**.—In a 20 dm^3 open jar containing D-glucose (700 g) and commercially available baker's yeast (1 kg) in tap water (12 dm^3) at 38 °C, **1** (10 g, 36 mmol) in EtOH (20 cm^3) was added. The fermentation mixture was vigorously stirred for 18 h and then extracted with ethyl acetate to give 10.5 g of material. Chromatography gave the following products: **1** (6.8 g, 25 mmol, 69%), $[\alpha]_D^{20}$ +9.6° ($CHCl_3$, *c* 1); **2** (1.6 g, 7 mmol, 20%), $[\alpha]_D^{20}$ +1° ($CHCl_3$, *c* 1); and **7** (1.1 g, mmol, 11%), $[\alpha]_D^{20}$ −1.7° ($CHCl_3$, *c* 1).

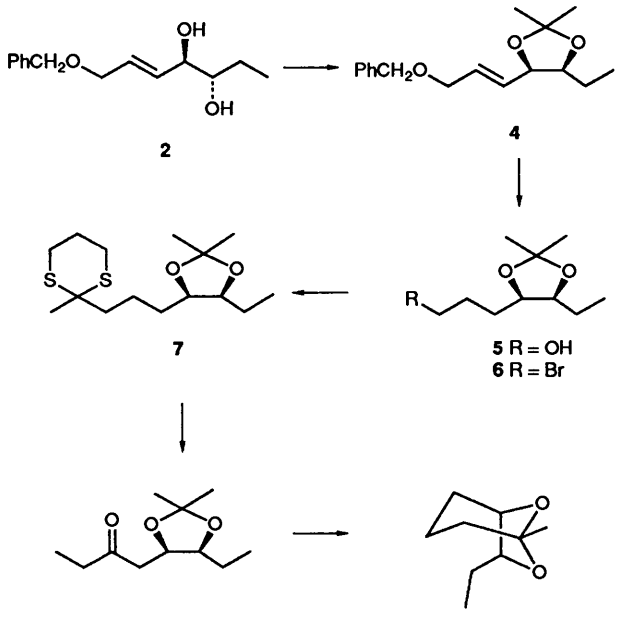
Preparation of (+)-endo-*Brevicomin*.—To **2** (5 g, 0.021 mol)

† ^1H NMR data for compounds **1**, **2**, **3**, **4**, **6**, **7** are available as supplementary publication [Sup. No. 56830 (2 pp.)].¶

¶ See 'Instruction for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1, for details of the Scheme.

‡ All new compounds exhibited correct analytical data.

§ Having established the chemical identity of **9** from NMR and MS spectra and absolute configuration from its rotation sign, optical purity was established by chiral GLC (Fig. 1). The elution order of stereoisomers resulted identical with the one reported by other authors (ref. 6).



Scheme 3

in dry benzene (100 cm^3), dimethoxypropane (4.4 g, 0.042 mol) and *p*-TsOH (0.1 g) were added in one portion. The solution was heated at reflux for 4 h, with water removal, cooled and washed with 10% aqueous $NaHCO_3$. Removal of the solvent and purification through a short silica gel column gave pure **4** (5.2 g, 19 mmol, 90%), $[\alpha]_D^{20}$ +1.9° ($CHCl_3$, *c* 1). Compound **4** (5 g, 18 mmol) was diluted with EtOH (50 cm^3) and 10% Pd on charcoal (0.5 g) was added. The mixture was stirred in an atmosphere of H_2 at 25 °C for 4 h. The solution was filtered, evaporated to dryness and the crude extract obtained was directly used for the subsequent reaction. The alcohol obtained **5** (2.6 g, 14 mmol) and triphenylphosphine (14 mmol) were diluted with dry CH_2Cl_2, and *N*-bromosuccinimide (14 mmol) was added portionwise so as to keep the reaction temperature <20 °C. After 30 min the reaction was completed (TLC). After work-up and purification by silica gel chromatography the bromide **6** was obtained (2.5 g, 0.01 mol, 75%, oil): $[\alpha]_D^{20}$ +13.5° ($CHCl_3$, *c* 1). To a solution of methyldithiane (1.1 g, 8.2 mmol) in anhydrous THF (20 cm^3), BuLi in hexane (10.4 mol dm^{-3}; 0.8 cm^3) was added dropwise at −70 °C. The mixture was left at −30 °C for 8 h and then cooled to −70 °C; **6** (2 g, 8 mmol) in dry THF (10 cm^3) was then added in 30 min. The mixture was stirred overnight at −20 °C, treated with water and extracted to give, after purification, compound **7** (1.7 g, 6.1 mmol, 78%) as an oil, $[\alpha]_D^{20}$ +10° ($CHCl_3$, *c* 1). To **7** (1.7 g, 5 mmol) dissolved in a mixture of THF (30 cm^3) and water (10 cm^3), HgO (2.2 g, 10 mmol) and BF_3·OEt_2 (1.2 cm^3, 10 mmol) were added. The mixture was stirred for 2 h and then an equal volume of diethyl ether was added; the mixture was then filtered and washed with a 7% aqueous $NaHCO_3$. Evaporation of the solvent gave crude **8** (0.75 g, 3.5 mmol, 70% oil), $[\alpha]_D^{20}$ +4.5° ($CHCl_3$, *c* 1). The crude extract was diluted with acetone (2 cm^3) and an aqueous solution of oxalic acid (10%, 5 cm^3) was added at 25 °C. The mixture was stirred for 4 h, extracted with pentane and the organic part washed with aqueous $NaHCO_3$. It was then evaporated at atmospheric pressure to give crude (+)-*endo*-brevicomin **9** (90% purity by GLC). GC/EI.MS (SE 54 capillary column): *m/z* (%) 156 M^+ (6.5), 114 (65), 113 (22), 99 (26), 98 (100), 86 (52), 71 (53) and 68 (54); $[\alpha]_D^{20}$ +49° (Et_2O, *c* 1) [lit.,[5] +74.6° (Et_2O, *c* 1)]; δ_H(250 MHz, $CDCl_3$) 1.00 (3 H, CH_3, t), 1.44 (3 H, CH_3, s), 1.43–2.0 (8 H, 4 CH_2, m), 4.00 (1 H, CH, dt) and 4.21 (1 H, CH, br); δ_C(250 MHz, $CDCl_3$) 10.96, 17.51, 21.88, 23.61, 25.01, 34.42, 76.51, 81.62 and 106.96.

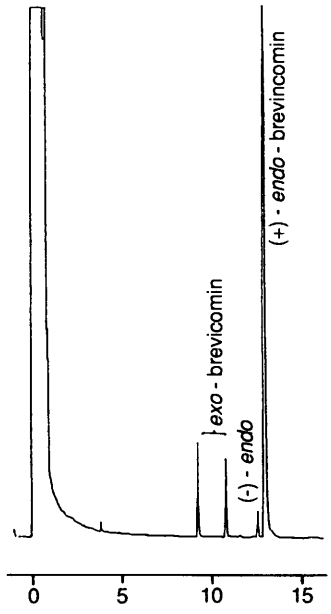


Fig. 1 Fused silica capillary column MEGADEX 1 30 m × 0.25 i.d. OV-1701 coated with 0.25 μm of Permethyl-β-cyclodextrin, H_2 0.8 bar 75 °C 1 min, 20 °C/min, 90 °C 2 min, 1 °C/min; R_t 9.56 (*exo*), 11.07 (*exo*), 12.82 (−)-*endo* and 13.36 (+)-*endo*

Chiral GLC of mixtures of brevicomin. Fused silica capillary column megadex 1 (MEGA), 30 m × 0.25 i.d.; OV-1701 coated with 0.25 μm of permethyl-β-cyclodextrin. H_2, 0.8 bar, 75 °C 1 min, 20 °C/min, 90 °C 2 min, 1 °C/min, R_t 9.56 (*exo*), 11.07 (*exo*), 12.82 [(−)-*endo*] and 13.16 [(+)-*endo*].

Chiral HPLC analysis on (**rac4**). Chiracel OD (DIACEL). Hexane 98, Pr^iOH 2, 0.6 cm^3/min, 254 nm, R_t *anti* 11.62 and 13.58; *syn* 12.64 and 18.61.

Acknowledgements

The authors thank Dr. M. Galli (MEGA) for supplying the Megadex column, Mrs. R. Bernardi for GLC analysis and Dr. A. Mele for GC-MS of brevicomin, and C.N.R. Piano Finalizzato Chimica Fine II for financial support.

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Paper 1/01682B
Received 11*th April* 1991
Accepted 11*th April* 1991