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Stereochemistry of Baker's Yeast Mediated Reduction of α,β-Unsaturated δ-Lactones in the Goniothalamin Series.

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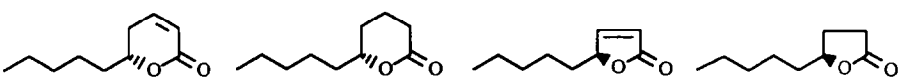
Key words: Baker's yeast, reduction, δ-lactones.

Abstract: Baker's yeast reduction of racemic α,β-unsaturated δ-lactones 5, 6 and 7 proceeds with kinetic preference for the (S) enantiomers. The procedure allows the obtainment of enantiomerically pure (+)-(R)-goniothalamin 5.

α,β-Unsaturated δ-lactones possessing a variety of biological functions occur widely in Nature.[1] Recently, in connection with studies on the conversion through natural methods of abundant natural products into rare aroma substances not accessible by extractive manipulation of plant materials,[2] there has been interest in the mode of the baker's yeast (b.y.) conversion of rather abundant (R)-2-decen-5-olide (*Massoia* lactone) **1** into **2**, present in butter fat and in a variety of fruits in minute amounts.[3,4]

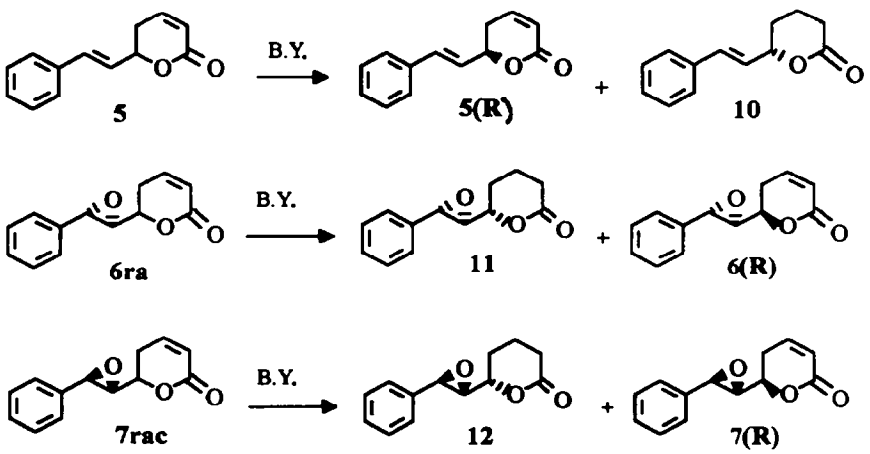
Deuterium labelling experiments showed that the saturation of the double bond of **1** in the transformation into **2** occurs through β-*re*-face *trans* formal addition of hydrogen atoms. The same is true in the b.y. conversion of (S)-2-nonen-4-olide **3** into **4**.[5] Using racemic **1** and **3** as substrates it has been shown that reduction takes place in the two series with kinetic preference for the (S) and (R) enantiomers, respectively. Moreover, the *ee* values of δ- and γ-lactones isolated at similar conversions appear higher in the former case. Experiments with a series of homologs of racemic **3** indicated that the *ee* values of the reduced lactones increase slightly with the length of the alkyl chain at position 4.



1 **2** **3** **4**

The above observations thus indicate a dependence of the stereochemical outcome of the b.y. reduction of unsaturated δ- and γ-lactones from rather subtle structural factors. In order to gain further information in this field we submitted to the action of b.y. racemic **5, 6 and 7** and we report here on the results obtained. (+)-(R)-**5**, Goniothalamin, showing CNS activity, and the corresponding embryotoxic epoxide **6**, occur in *Goniothalamus* species[1,6,7,8] and knowledges on the mode of their biotransformation could be of interest also in relationship with activity changes.

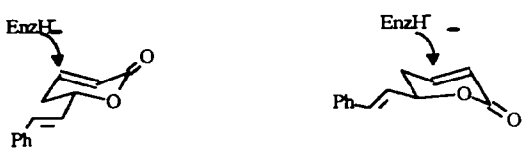
Accordingly, racemic **5**, **6** and **7** were prepared from **8**, obtained, in turn, from cinnamaldehyde and propargylmagnesium bromide, through unexceptional steps (see experimental part). Incubation with fermenting b.y. of racemic **5-7** indicated that the only noticeable operation taking place is the rather rapid saturation of the carbonyl activated double bond (Scheme 1).



Scheme 1

The steric outcome of the reduction was determined, at 50% *ca.* conversion, through HPLC analysis on a Chiracel OD column (Daicel) and comparison with authentic samples of (S)-**10**,[9] and of the epoxides **11** and **12**. The latter were prepared from **10** by 3-chloroperbenzoic acid treatment.[7] Examination of the product distribution in the b.y. treatment of racemic **5**, **6** and **7** thus shows in all instances the preferential reduction of the (5S) enantiomers. Moreover, at similar conversions the distribution of the four species appears quite similar in the three instances (see table in the experimental part).

This would suggest that the bulkiness of the substituents in the side chain at position 5 of the unsaturated lactone framework and the relative stereochemistry of the substituents are influential on the mode of the double bond saturation. If the mechanism of the formal saturation of the double bond of **5-7** is identical to the one invoked to occur in **1** and **3**[4,5] (*i.e.*: formal hydride delivery in beta position from the upper *re*-face of the molecule) it seems reasonable from the models of Scheme 2 that, only in terms of formal interactions, the enantiomer easier to reduce should be the (S) one.



(S) (R)

Scheme 2

Purification by column chromatography and crystallization (hexane, petroleum ether) of the survived material obtained in the incubation of racemic **5** allowed to obtain (+)-(R)-goniothalamin **5** (R), $[\alpha]^{D}_{20}$ + 134 (c 1, MeOH), in good agreement with the lit.[6,8] values reported for the product of natural origin, 0.99 *ee* by HPLC.

These results, seen together, thus show the synthetic utility of b.y. transformations of non conventional substrates in organic synthesis.[10]

EXPERIMENTAL

General procedure. ^{1}H NMR spectra were recorded with a Bruker AC-250 or a Bruker CXP-300 instrument in the FT mode or with a Varian EM-390 with tetramethylsilane as internal standard. Optical rotations were measured in a 1 dm cell of 1 mL capacity by using a Jasco DIP-181 polarimeter. Silica gel 60 F254 plates (Merck) were used for analytical TLC, 270-400 mesh silica gel (Merck) for flash chromatography or 70-230 mesh silica gel (Merck) for chromatography. HPLC analysis were performed on a Merck Hitachi L-6200 with a Chiracel OD (Daicel) column and a UV (254 nm) detector using a Merck Hitachi D-2500 integrator. HPLC analyses conditions: eluent *n*-hexane/*i*PrOH 96/4 for **5**, 8/2 for **6** and **7** , flow 0.6 mL/min.

(E)-6-phenyl-5-ene-4-hydroxy-1-hexine 8. 13.63 g (0.568 mol) of Mg were covered with anhydrous THF (dried over $LiAlH_4$) and a mixture of 45 g (0.378 mol) of propargylbromide and 50 g (0.378 mol) of cinnamic aldehyde were added dropwise at a rate so to keep a gentle boiling. At the end of the addition the reaction mixture was left under stirring for 2 h at 25 °C. The reaction mixture was quenched by sequential addition of ethyl acetate, a saturated solution of ammonium chloride and water. The organic layer was separated, dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (n-Hexane/AcOEt=70/30) to give 38.8 g (0.227 mol) (60% yield) of oily **8**. (Found: C, 83.22; H, 7.59. $C_{12}H_{13}O$, requires C, 83.20; H, 7.56); ^{1}H NMR ($CDCl_3/D_2O$, 250 MHz) δ: 2.09 (1H, t), 2.50-2.59 (2H, m), 4.47 (1H, q), 6.27 (1H, dd), 6.67 (1H, d), 7.19-7.45 (5H, m).

(E)-7-phenyl-6-ene-5-hydroxy-2-heptinoic acid 9. Keeping the temperature below -40 °C, 7.48 g (0.116 mol) of BuLi were added dropwise to a solution of 10 g (0.058 mol) of **8** in 150 mL of dry THF. At the end of the addition the mixture was left under stirring for 1 hr at the same temperature. The reaction mixture is added to a suspension of solid CO_2 in dry THF and left until the temperature rose to 25 °C. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and the organic layer was washed with a solution of 10% NaOH. Acidification of the water phase and extraction with ethyl acetate gave after evaporation under reduced pressure 11 g (0.051 mol) (87.5% yield) of crude oily **9**. ^{1}H NMR ($CDCl_3/D_2O$, 250 MHz) δ: 2.60-2.68 (2H, m), 4.52 (1H, q), 6.20 (1H, dd), 6.63 (1H, d), 7.20-7.43 (5H,m).

Lactone 5. 7 g (0.032 mol) of crude **9** are dissolved in 100 mL of AcOEt and 700 mg of Lindlar catalyst are added in one portion. The reaction mixture was left under H_2 atmosphere until 90% of theoretical amount of H_2 was absorbed. The catalyst was filtred off and the organic residue evaporated in vacuo so as to obtain 7 g of an oil which was purified on SiO_2 gel column chromatography (*n*-Hexane/AcOEt=6/4) to give 5 g (0.023 mol) (71.4% yield) of yellow pale crystals of **5**, m.p. 83 °C. All spectroscopical data coincide with those reported .[6,8]

Epoxides 6, 7. 1.1 eq of 70% MPBA were added to a solution of 1 g (4.6 mmol) of racemic **5** dissolved in 25 mL of CH_2Cl_2. The reaction mixture was heated at reflux for 8 h. The excess of peracid was destroyed with an aqueous solution of sodium bisulfite and the resulting acid was separated by extraction with

$NaHCO_3$. The aqueous phase was separated, extracted with CH_2Cl_2 and the combined organic layer was dried over Na_2SO_4 and evaporated in vacuo to give the crude mixture of **6** and **7**. The two diastereoisomers were separated by SiO_2 column chromatography (*n*-Hexane/AcOEt=6/4) so as to obtain 220 mg (0.9 mmol) of **6** as white crystals m.p. 92 °C and 580 mg (2.5mmol) of **7** as white crystals m.p. 112 °C. All spectroscopical data coincide with those reported.[6,7]

Yeast Reduction. A suspension of 50 g of baker's yeast and 12.5 g of D-glucose in 0.5 l of tap water was stirred at 36 °C. A solution of unsaturated lactones **5** or **6** or **7** (2.3 mmol) in 5 mL of DMSO was then added. The mixture was stirred for 6 h, and the aqueous phase was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure gave the crude products for HPLC analysis (Chiracel OD,Hexane/*i*PrOH, flow 0.6 mL/min), the retention times are reported below. Pure **5(R)** was obtained through flash column chromatography (*n*-Hexane/AcOEt=7:3) of the crude extract.

Table. Enantiomeric excess of the products of b.y. treatment of racemic **5**, **6** and **7**, determined through HPLC, (Chiracel OD, Hexane/*i*PrOH, flow 0.6 mL/min.).

substrate	enantiomeric excess in the b.y. reduction	eluent ratio	retention time (min)	
			R	S
5(R)	0.99	96 : 4	68.11	74.00
6(R)	0.96	80 : 20	25.04	37.34
7(R)	0.84	80 : 20	28.70	48.51
10(S)	0.77	96 : 4	60.54	84.88
11(S)	0.58	80 : 20	23.28	28.42
12(S)	0.52	80 : 20	25.60	32.86

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