

Short Communication
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Determination of Enantiomeric Excess and Degree of Hydrogenation in the Enantioselective Hydrogenation of Ketopantolactone

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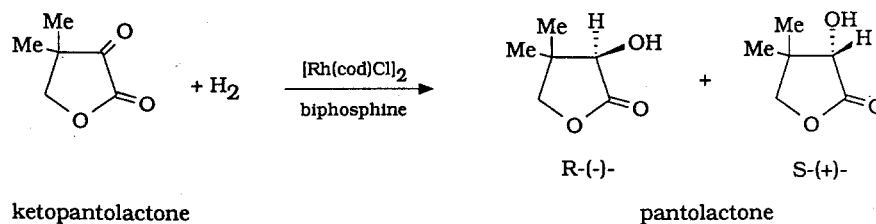
Summary. A new gas chromatographic method for the simultaneous determination of the degree of hydrogenation of ketopantolactone and the enantiomeric excess of pantolactone does not require any derivatisation.

Keywords. Ketopantolactone; Enantioselective hydrogenation; Catalysis with phosphines; Gaschromatography on Chirasil-*L*-Val.

Bestimmung von Enantiomerenüberschuß und Hydriergrad bei der enantioselektiven Hydrierung von Ketopantolacton (Kurze Mitt.)

Zusammenfassung. Zur Bestimmung des Hydriergrads von Ketopantolacton und des Enantiomerenüberschusses von Pantolacton wird ein neues gaschromatographisches Verfahren eingesetzt, das keine Derivatisierung erfordert.

In recent years the hydrogenation of ketopantolactone has become a standard reaction for the enantioselective reduction of carbonyl groups (Scheme 1). In this reaction in situ catalysts are used consisting of optically active chelate phosphines as cocatalysts and rhodium(I) complexes as procatalysts [2–19]. The aim is, as



Scheme 1

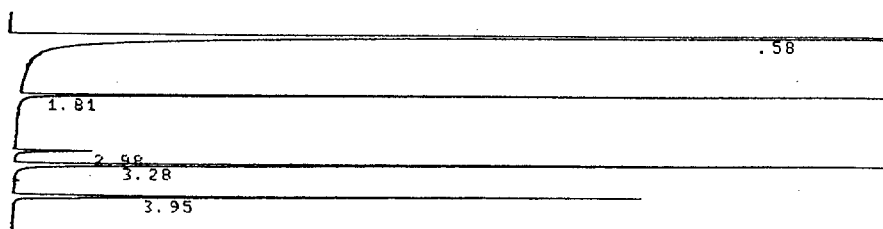


Fig. 1. Separation of ketopantolactone and *R,S*-pantolactone on a 25 m capillary Chirasil-*L*-Val column; column temperature 100°C, carrier gas 1.0 bar H₂, standard 2,6-dimethylnaphthalene. Retention times (min) and assignments: 0.58: CH₂Cl₂; 1.81: ketopantolactone; 2.98: *S*-(+)-pantolactone, 3.28: *R*-(-)-pantolactone (86.7% ee); 3.95: 2,6-dimethylnaphthalene

well as in other asymmetric reactions, to synthesise only one enantiomer, in this case *R*-(-)-pantolactone, involved in pantothenic acid (vitamin B 6) [15].

Early in the development of enantioselective catalysis, good results were achieved in the hydrogenation of ketopantolactone with up to 87% ee, using *BPPM* as a chiral cocatalyst [14–19]. The best result reported is 97% ee, obtained with *BCPM*, in which the C4-diphenylphosphine group of *BPPM* is replaced by a dicyclohexylphosphine group [7].

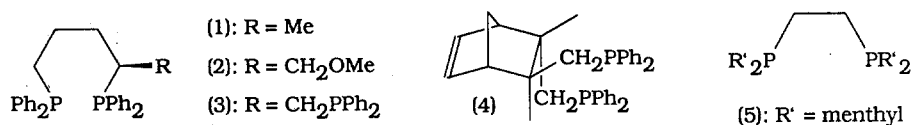
In this communication we present a gas chromatographic method which allows simultaneously the fast and accurate determination of the degree of hydrogenation of ketopantolactone and the enantiomeric excess of pantolactone. Up to now the enantiomeric excess has been determined by measuring the optical rotation which, however, can be inaccurate and susceptible to errors [3–19]. The use of opti-shift reagents has also been described [15]. In addition, *R,S*-pantolactone has been separated by gas chromatography after derivatisation as trifluoroacetate or urethane [20].

Based on the reported separation of the enantiomers of pantolactone using a Chirasil-*L*-Val column [21], we developed the following analytical method [22]. The reaction mixture of the hydrogenation of ketopantolactone is distilled to remove the volatile product from the catalyst. The distillate dissolved in CH₂Cl₂ can be immediately used for the gc analysis without any derivatisation. Unreacted starting material ketopantolactone and the enantiomers of the product pantolactone are base line separated on a commercial 25 m capillary Chirasil-*L*-Val column.

2,6-Dimethylnaphthalene proved to be suitable as an internal standard to correlate peak area and quantity of ketopantolactone and pantolactone. Figure 1 shows a gas chromatogram of a hydrogenation of ketopantolactone with [Rh(*cod*)Cl]₂/*BPPM* interrupted before completion. The deviation from 50 : 50 in the measurements of the racemate of pantolactone was 0.15% ee.

The new procedure was used to analyse the reaction mixtures in the enantioselective hydrogenation of ketopantolactone with the cocatalysts *BPPM* [23], *DIOP* [24], *BINAP* [25], and the chelate phosphines 1–5 [26, 27] shown in Scheme 2.

In a standard reaction the asymmetric hydrogenation was carried out with the substrate ketopantolactone (5 mmol), [Rh(*cod*)Cl]₂ (0.025 mmol) and phosphine (0.06 mmol) at 50°C in toluene (5 ml) using 50 bar hydrogen pressure. After 45 h the solvent was removed. The residue was distilled in a kugelrohr at 110°C/2 Torr and analysed as outlined above. The results are summarized in Table 1.



Scheme 2

Table 1. Asymmetric hydrogenation of ketopantolactone with [Rh(*cod*)Cl]₂/ligand. Chemical yields are between 90 and 95%

Ligand	Degree of hydrogenation	% ee	Conf.
<i>BPPM</i>	>99.0	86.7	<i>R</i>
<i>DIOP</i>	>99.0	53.2	<i>R</i>
<i>BINAP</i>	>99.0	41.2	<i>S</i>
1	>99.0	30.7	<i>R</i>
2	>99.0	35.8	<i>R</i>
3	>99.0	8.8	<i>R</i>
4	>99.0	57.0	<i>S</i>
5	>99.0	25.8	<i>R</i>

Similar to *DIOP* and *BINAP*, the chelate phosphines **1**, **2**, and **4** give rise to ee values in the middle range. The phosphines *BPPM*, *DIOP*, *BINAP*, **1**, **2**, and **4** form seven-membered chelate rings. The enantiomeric excess obtained with the tridentate ligand **3** is lower, probably because several chelate rings with different ring sizes are possible. Ligands forming five-membered rings usually induce only poor enantioselectivities associated with an incomplete hydrogenation. Atypically, ligand **5** gives good results both with respect to enantioselectivity and hydrogenation rate.

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