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CATALYTIC ASYMMETRIC SYNTHESES OF R(-)- AND S(+)-PANTOLACTONE[1)]

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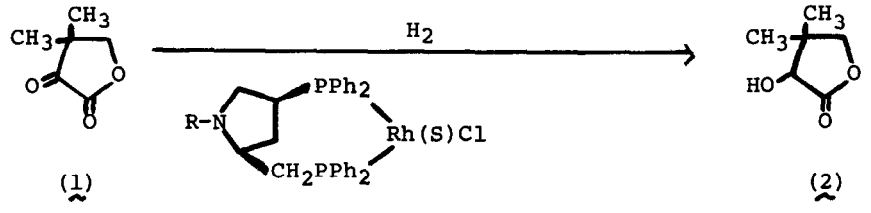
R(-)-Pantolactone(2) is an important intermediate in the syntheses of pantheine and Coenzyme A[2)]. The chiral synthesis of this simple α-hydroxylactone has been realized already via both chemical resolution[3)] and biochemical reactions [4)], as the key steps, but both methods usually included a troublesome isolation procedure due to its high solubility in water.

We wish to describe here a simple and efficient chiral synthesis of R(-)-pantolactone(2) by asymmetric hydrogenation of α-keto-β,β-dimethyl-γ-butyrolactone(1)[5)] as an application of the successful hydrogenation of the α-keto-esters catalyzed by BPPM-rhodium complex[6)], and also from our continued interest in the effects of the modified N-substituents of BPPM on the asymmetric hydrogenation of the conformationally fixed cyclic keto ester, since the modification of the N-substituent of BPPM gave rise to a dramatic effect on the optical yields of N-benzyloxycarbonylalanine and N-acetylsalsolidine in their asymmetric syntheses[7)].



(1) (3) (2)

3a, R= $COOC(CH_3)_3$ (BPPM)
3b, R= $COC(CH_3)_3$ (PPPM)
3c, R= H (PPM)

In a typical experiment, the asymmetric hydrogenation of 1 (5 mmole) was run in benzene (3 ml) under an initial hydrogen pressure of 50 atm at 50°C for 45 h in the presence of the rhodium catalyst which was synthesized in situ from PPPM (6×10^{-2}mmole) and [Rh(1,5-hexadiene)Cl]$_2$ (2.5×10^{-2}mmole). Then, the reaction mixture (100% conversion yield by vpc analysis) was simply distilled to give R-(-)-pantolactone, bp 103°C (6 mmHg), $[\alpha]_D^{20}$ -30.0°(c 3.79, H_2O)(59.2% optical yield) in a 93% isolated yield.

Similarly, the asymmetric hydrogenations of 1 with BPPM-, PPPM- or PPM-rhodium complex in benzene or ethanol as a solvent were carried out.

Table I. Asymmetric hydrogenation of α-keto-β,β-dimethyl-γ-butyrolactone[a)]

Chiral reagent (R)	Solvent	Time (h)	Conversion[b)] (%)	Opt.y.	(conf.[c)])
COOC(CH$_3$)$_3$(BPPM)	Benzene	45	100	54.6	(R)
COOC(CH$_3$)$_3$(BPPM)	Ethanol	95	100	32.1	(R)
COC(CH$_3$)$_3$ (PPPM)	Benzene	45	100	59.2	(R)
COC(CH$_3$)$_3$ (PPPM)	Ethanol	95	100	35.9	(R)
H (PPM)	Benzene	45	100	15.4	(S)
H (PPM)	Ethanol	95	100	8.5	(S)

a) All hydrogenations were carried out with 5 mmol of substrate, 0.025 mmol of [Rh(1,5-hexadiene)Cl]$_2$ and 0.06 mmol of bisphosphine in 3 ml of solvent at 50°C under an initial hydrogen pressure of 50 atm.
b) By vpc analysis.
c) Calculated on the basis of the reported value for optically pure R-2; $[\alpha]_D^{25}$ -50.7°(c 2.05, H_2O), ref. 3.

Table I shows clearly that BPPM- and PPPM-Rh complexes gave R(-)-pantolactone in benzene and ethanol, whereas PPM-Rh complex gave the S product in benzene and ethanol although the optical yield decreased. This fact may suggest that the N-substituents of PPM play an important role in affecting the optical yield of the product.

Further active investigations along this line are under way.

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