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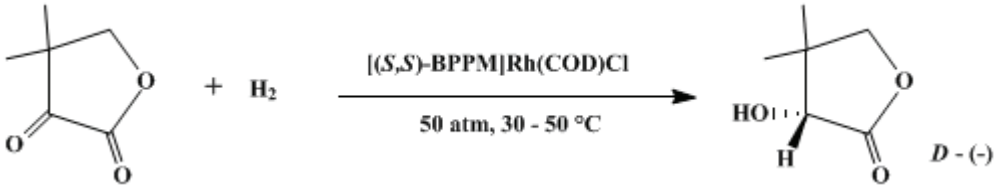
ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE: D-(−)-PANTOYL LACTONE

[2(3*H*)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-]



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Checked by Larry K. Truesdale, Stanley D. Hutchings, and Gabriel Saucy.

1. Procedure

A. *Preparation of catalyst solution*. A 250-mL, round-bottomed flask fitted with a septum and magnetic stirring bar is charged with 486.9–488.2 mg (Note 1) (0.985–0.990 × 10^{-3} mol) of chloro(1,5-cyclooctadiene)rhodium(I) dimer (Note 2) and, under argon (Note 3), with 1.20 g (2.15 × 10^{-3} ml) of (2*S*, 4*S*)-*N*-*tert*-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (*S,S*)-BPPM (Note 4). The sealed flask is charged by cannula, under argon, with 150 mL of degassed benzene (Note 5) and stirred under argon for 15 min at room temperature. The catalyst is transferred by cannula, under argon, into the autoclave (see below).

B. *Asymmetric hydrogenation*. A stainless steel stirred autoclave with a total volume of 500 mL is charged with 25.6 g (0.2 mol) of ketopantoyl lactone (Note 6),(Note 7),(Note 8),(Note 9). The autoclave is flushed with argon and the catalyst solution (see above) is added by cannula, under argon. The autoclave is sealed and hydrogenation is carried out at 40°C, 750-psig hydrogen and 950–1050 rpm for 48 hr (Note 10). Care should be taken to flush all the lines before connecting to the autoclave. After the autoclave is cooled to room temperature, it is vented and opened. The reaction mixture is then transferred to a 500-mL, round-bottomed flask and most of the solvent is removed by rotary evaporator. Distillation (Note 11) of this reddish solid affords 24–25.6 g (92–98%) (Note 1) of D-(−)-pantoyl lactone: bp 90–110°C (4 cm); $[\alpha]_D^{25}$ −39.3° to −42.4° (*c* 2, H_2O) (Note 12) (78 to 84% e.e.) (Note 1) and (Note 10).

The pantoyl lactone thus obtained (25.41 g), $[\alpha]_D^{25}$ −40.8° (80.5% e.e.) (Note 13) is refluxed with 75 mL benzene and 290 mL of UV-grade hexanes. The cloudy solution is stirred briskly overnight as solids form. Filtration of the solids and drying for 3 hr at 0.25 mm, 30°C in a vacuum oven affords 21.51 g of product; $[\alpha]_D^{25}$ −47.7° (94.27% e.e.). This material is again refluxed and crystallized (Note 14) from 30 mL of benzene and 116 mL of UV-grade hexanes to afford 19.97 g (77%) of product; $[\alpha]_D^{25}$ −49.87° (98.5% e.e.). Anal. calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.34; H, 7.57 (Note 15).

2. Notes

1. The reaction was done four times at this scale. The range represents the high and low amounts of catalyst precursor used over the four reactions.
2. Chloro(1,5-cyclooctadiene)rhodium (I) dimer is commercially available from Strem Chemicals, Inc., Newburyport, MA.
3. The addition and measurement of (*S,S*)-BPPM is most conveniently done in a dry box or glove bag under argon. A Schlenk tube apparatus can be used if these are not available.
4. (2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (*S,S*)-BPPM,[2,3] is commercially available from E. Merck, Darmstadt, West Germany and Kanto Chemical Company, Tokyo, Japan.

5. The submitters claim that tetrahydrofuran can also be used giving D-(−)-pantoyl lactone with 83.3–84.8% e.e. This was not checked.
6. (a) Ketopantoyl lactone is readily prepared by the oxidation of *d,l*-pantoyl lactone (Note 8) with bromine as follows.[4] Into a 500-mL, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, condenser, and thermometer is charged 13.0 g (0.1 mol) of *d,l*-pantoyl lactone (Note 7) and 150 mL of carbon tetrachloride. The mixture is stirred and heated to reflux. Bromine (16.5 g, 0.103 mol) in 100 mL of carbon tetrachloride is slowly added from the dropping funnel over 3 hr. After 8 hr, generation of hydrogen bromide subsides and the red color of bromine almost disappears, indicating completion of the reaction. Dry air is bubbled through the solution to remove the remaining hydrogen bromide and the small quantity of bromine. The solvent is removed with a rotary evaporator and further evacuated with a vacuum pump to afford 12.8 g (100%) (Note 9) of almost pure ketopantoyl lactone. One recrystallization from 150 mL of carbon tetrachloride (heat to reflux and then cool to −10°C) affords 11.6–12.2 g (90–95%) of pure ketopantoyl lactone, mp 66–67.5°C. (b) An alternative procedure preferred by the checkers to prepare highly pure ketopantoyl lactone follows. A 5-L, round-bottomed flask equipped with a mechanical stirrer, condenser, thermometer, and dropping funnel is charged with 700 g of $Ca(OCl)_2$ (analyzed as 20% active chlorine) and 1.5 L of acetonitrile dried overnight over Linde 4A molecular sieves. *d,l*-Pantoyl lactone (165 g) (Note 7) is dissolved in 500 mL of dried acetonitrile. The $Ca(OCl)_2$ slurry is stirred while ~1/7 of the pantoyl lactone solution is added. The temperature of the exothermic reaction is controlled with an ice bath to below 35°C. The remainder of the pantoyl lactone solution is added in ~75-mL aliquots over 25–30 min while taking care to control the temperature. The ice bath is removed and stirring is continued. After 3.5 hr, GLC analysis indicates 94% product. The reaction mixture is filtered and the solids are rinsed with acetonitrile. The crude product is dried on a rotary evaporator and further evacuated overnight to yield 105.6 g. The material is dissolved in methylene chloride, dried over Na_2SO_4, filtered through Celite, and concentrated under reduced pressure. The crude product (94.1 g) is then purified by refluxing and stirring overnight with 500 mL of ethyl ether. The slurry is allowed to stand at 5°C. The solids are filtered, washed with cold ether, and dried in a vacuum oven at room temperature for 6 hr to afford 80.8 g (86% recovery) of pure ketopantoyl lactone. Ketopantoyl lactone has also been reported to be easily prepared by the oxidation of *d,l*-pantoyl lactone with alkaline metal hypochlorite[5] or by reaction of sodium dimethylpyruvate with formaldehyde in the presence of potassium carbonate.[6]
7. *d,l*-Pantoyl lactone is very hygroscopic. Care must be taken during this oxidation that dry starting material is used and that water does not contaminate the reaction; the yield will fall drastically probably because of hydrolysis.
8. *d,l*-Pantoyl lactone is commercially available from Sigma Chemical Company, St. Louis, MO 63178.
9. GLC analysis indicates 97–98% yield. A simple GLC system to determine the relative completion of the reaction is a 3-ft × 1/8-in column packed with 10% Carbowax 20 M on Anakrom Q 90/100. With this column a program of 150 to 210°C at 8°/min and a 7-min hold gives baseline separation of ketopantoyl lactone at 2.75–3.2 min and pantoyl lactone at 3.7–3.95 min. The flow rate of the carrier gas is 20 mL/min.
10. When ketopantoyl lactone prepared by method 6b was used, the reaction was complete in 2 hr.
11. A bulb-to-bulb distillation using a Kugelrohr apparatus is most convenient.
12. The reported maximum rotation, $[\alpha]_D^{25}$, max, for pure D-(−)-pantoyl lactone is −50.7° (*c* 2.05, H_2O).[7 8]
13. The enantiomeric excess and the speed of reduction are both greatly influenced by impurities that are not detectable by GLC. Digestion in ether seems to remove these impurities better than recrystallization from CCl_4.
14. This recrystallization is very temperature-sensitive; for example, this purification was done at ambient temperature (28–30°C). The first recrystallization removes 3.7 g of *d,l*-pantoyl lactone and 0.2 g of D-(−)-pantoyl lactone. When the recrystallization was done at 5°C, twice as much solvent served to remove only 4.2 g of *d,l*-pantoyl lactone and none of the D-isomer.
15. The procedure described is a scaled-up version (20 ×) of the original submission worked out by the checkers.

3. Discussion

D-(−)-Pantoyl lactone is a key intermediate for the synthesis of pantothenic acid, which is a member

of the vitamin B complex and is an important constituent of Coenzyme A. Although D-(−)-pantoyl lactone has been obtained by classical optical resolution using quinine, ephedrine, and other chiral amines, catalytic asymmetric synthesis appears to be more effective from a practical point of view.[9] [10] One problem of the present approach was the availability of ketopantoyl lactone, but the recent method developed by Hoffmann–La Roche,[6] consisting in the condensation of sodium dimethylpyruvate with formaldehyde, may open a commercial route to ketopantoyl lactone. Thus, asymmetric reduction of ketopantoyl lactone now becomes an important route to D-(−)-pantoyl lactone. Asymmetric reduction of ketopantoyl lactone can also be achieved with micro-organisms. For example, microbial reduction of ketopantoyl lactone using baker's yeast was reported to give ca. 72% e.e.,[11] and the specific strain of an ascomycete, *Byssochlamys fulva*, was reported to give D-(−)-pantoyl lactone with 95–100% e.e.[11] However, the isolation procedure from aqueous media in these microbial reductions—specifically: extraction, recovery of raw materials, and purification—is very troublesome because of the high solubility of the product in water. Consequently, the present method has considerable advantages from a synthetic point of view; for instance, (a) the yield of the reaction is virtually 100% and (b) isolation of the product is simple and convenient since the reaction is carried out in small amounts of nonaqueous media.

The present method has been successfully applied[12] to the asymmetric reduction of various α-keto carboxylates and α-keto lactones.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

H_2O

hexanes

chloro(1,5-cyclooctadiene)rhodium(I) dimer

(2S, 4S)-N-tert-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (S,S)-BPPM

Chloro(1,5-cyclooctadiene)rhodium (I) dimer
(S,S)-BPPM

(2S,4S)-N-tert-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (S,S)-BPPM

D-(−)-pantoyl lactone

$Ca(OCl)_2$

potassium carbonate (584-08-7)

Benzene (71-43-2)

ether,
ethyl ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

formaldehyde (50-00-0)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Na_2SO_4 (7757-82-6)

carbon tetrachloride,
CCl_3 (56-23-5)

chlorine (7782-50-5)

methylene chloride (75-09-2)

Tetrahydrofuran (109-99-9)

argon (7440-37-1)

Ephedrine (90-82-4)

sodium dimethylpyruvate (3715-29-5)

pantothenic acid

quinine (130-95-0)

ketopantoyl lactone (13031-04-4)

pantoyl lactone,
d,l-pantoyl lactone,
2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl- (79-50-5)