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(14) Isomerization of vitamin D trienes under GC conditions is a common observation. GC of **3** (2 mm × 2 m glass column packed with 3% OV-101 on Chromosorb 30 100/120 mesh; nitrogen flow rate 30 mL/min; oven held isothermally at 260 °C) gave two peaks with retention times of 3.2 and 8.0 min. Interestingly, GC of either **5a** or **5b** gave the same trace as found for **3**. In all three traces, the ratio of peak heights of the 3.2 to the 8.0 min peak was about 2.5/1. GC–MS of **3** showed that both peaks were isomers of nominal parent mass 384. The early peak showed *m/e* (rel intensity) 384 (M^+, 18), 351 (36), 309 (41), 283 (35), 145 (35), 124 (32), 43 (100). The late peak gave 384 (M^+, 47), 369 (20), 271 (48), 253 (42), 199 (35), 81 (85), 43 (100).
(15) A minor component at t_R = 6.7 min was also found in this sample; its parent ion at *m/e* 110 and fragmentation pattern suggest that it is methylcyclohexenone, the dehydration product of **7b**.
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Effective Biomimetic Route to D(+)-Pantothenate Using Asymmetric Hydrogenation Catalyzed by a Chiral Rhodium Complex in the Key Step

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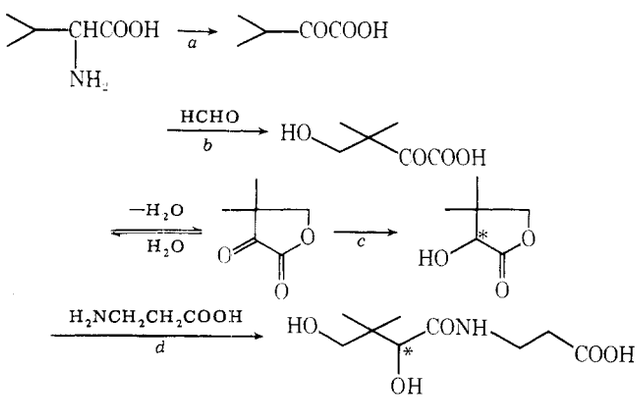
Asymmetric synthesis of D(+)-pantothenate from ketopantoyl lactone following a biomimetic route using asymmetric hydrogenation in the key step is described. The asymmetric hydrogenation of ketopantoyl lactone was effectively catalyzed by a rhodium complex with BPPM as chiral ligand to afford D(−)-pantoyl lactone with 86.7% optical purity under optimum conditions. This was further recrystallized to give the pure lactone in good yield. The pure D(−)-pantoyl lactone thus obtained was converted to ethyl D(+)-pantothenate by reacting with β-alanine ethyl ester.

Pantothenic acid is a member of the B complex vitamins and is an important constituent of Coenzyme A. Pantothenic acid is converted to pantetheine, which further reacts with adenosine triphosphate (ATP) to form Coenzyme A. The biosynthesis of pantothenic acid from valine has been postulated to involve[1,2] (a) the oxidative deamination of valine to α-ketoisovaleric acid, (b) the hydroxymethylation of this acid to form ketopantoyl lactone, (c) the asymmetric reduction of ketopantoyl lactone to pantoyl lactone, and (d) the coupling of pantoyl lactone with β-alanine to give pantothenic acid

Scheme I



[a] Transaminase. [b] Ketopantoaldolase. [c] Reductase. [d] Pantothenate synthetase.

(Scheme I). Among these processes, step c is the most significant since only D(+)-pantothenic acid derived from D(−)-pantoyl lactone has biological activity.[3] Although the biological synthesis of D(+)-pantothenic acid has been reported using microbial reduction of ketopantoyl lactone to pantoyl lactone,[4] no attempts have been made on the chemical asymmetric synthesis of this substance following the biosynthetic route. We have found that a rhodium complex with a chiral pyrrolidinodiphosphine, (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM),[5] displays a high chiral recognition ability comparable to that of microorganisms, and thus the chiral rhodium complex can be considered as a functional biomimetic model of the ketopantoyl lactone reductase. We wish to present here an effective biomimetic route to D(+)-pantothenic acid using a catalytic asymmetric hydrogenation in the key step as an application of the successful hydrogenation of α-keto esters catalyzed by neutral rhodium complexes with phosphine ligands.[6]

One of the key compounds in the biosynthetic route is ketopantoyl lactone since the asymmetric reduction of this compound is the characteristic process in biological systems. This eliminates the need for the optical resolution of racemic pantoyl lactone as employed in the commercial synthesis of D(+)-pantothenic acid derivatives.[7] As the formation of ketopantoyl lactone is not restricted to enzymatic process but a simple aldol condensation, we started the asymmetric synthesis from ketopantoyl lactone.

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Table I. Asymmetric Hydrogenation of Ketopantoyl Lactone to D(−)-Pantoyl Lactone Catalyzed by the BPPM–Rhodium(I) Complex

Solvent	Initial H_2 pressure, atm	Conditions[a]	Conversion[b] %	$[\alpha]^{25}_D$,[c] deg	Optical purity,[d] % ee
Benzene	50	10 °C, 48 h	95.4	−23.4	46.2
Benzene	50	20 °C, 48 h	99.2	−43.4	85.5
Benzene	50	30 °C, 48 h	100.0	−44.0	86.7
Benzene	50	50 °C, 24 h	100.0	−43.0	84.8
THF[e]	50	0 °C, 70 h	46.1	−13.4	26.4
THF[e]	50	15 °C, 48 h	69.7	−41.9	82.6
THF[e]	50	30 °C, 48 h	99.5	−40.9	80.7
Chlorobenzene	50	50 °C, 48 h	94.5	−32.2	63.5
Toluene	50	50 °C, 48 h	99.6	−39.4	77.7

[a] A 0.99–1.06 mol % amount of the catalyst was employed; [BPPM]/[Rh] = 1.12–1.17. [b] Determined by GLC analysis. As the reaction does not involve any side reactions at all, this value corresponds to the chemical yield. [c] Measured in water; c = 2.010–2.098. [d] Optical purity was calculated on the basis of the maximum rotation of the pure enantiomer, $[\alpha]^{25}_{D\ max}$ −50.7° (c 2.05, H_2O) (ref 3). [e] THF = tetrahydrofuran.

The asymmetric hydrogenation of ketopantoyl lactone was carried out by means of a homogeneous rhodium complex having BPPM as the chiral ligand. This gave D(−)-pantoyl lactone with an optical purity of 86.7% in almost quantitative yield under optimum conditions.[8] The results obtained in the asymmetric hydrogenation under a variety of conditions are summarized in Table I. The corresponding asymmetric hydrogenation using (−)-DIOP[9] as the chiral ligand in tetrahydrofuran at 20 °C resulted in only a 35% enantiomeric excess.

As Table I shows, (i) the optical yield is affected by the solvent employed, with benzene affording the best results as far as we have examined, and (ii) a remarkable effect of the reaction temperature on the optical yield is observed. It is of interest that the extent of asymmetric induction decreases precipitously at temperatures below ca. 10 °C. This phenomenon could be caused by either (i) a change in the rate-determining step or (ii) an exchange of one mechanism for another, provided the reaction proceeds via two parallel mechanisms. A configurational change of the chiral ligand in the coordination sphere of the rhodium complex could be also suggested.

As to the direction of asymmetric induction, R configuration is found to be extremely favored, thus leading to the formation of the naturally occurring D(−)-pantoyl lactone which has been shown to have the R configuration.[3b] Thus, the direction of asymmetric induction realized in the present reaction is the same as that observed in the asymmetric hydrogenation of pyruvates using either (−)-DIOP or BPPM as the chiral ligand.[6]

The pantoyl lactone thus obtained was easily purified to give the pure D isomer by recrystallization from n-hexane–benzene. Accordingly, a pure sample of D(−)-pantoyl lactone was obtained in at least 70% yield from ketopantoyl lactone. The pure sample of D(−)-pantoyl lactone was converted in 77% yield to the ethyl ester of D(+)-pantothenic acid by reacting with β-alanine ethyl ester. The transformations of ethyl D(+)-pantothenate to D(+)-pantothenic acid and to pantetheine are known processes.[3,10] Synthesis of calcium pantothenate from D(−)-pantoyl lactone, β-alanine, and calcium metal or ions has been established.[7]

As the optical yield attained in a microbial reduction of ketopantoyl lactone using baker's yeast has been reported to be ca. 72%,[4] our chiral rhodium catalyst is shown to be superior to baker's yeast in this reaction. Although Lanzilotta et al. recently have found that specific strains of an ascomycete, *Byssochlamys fulva*, can achieve exceedingly high optical yield production of the D isomer,[4] the isolation procedure from aqueous media, i.e., extraction, recovery of raw materials, and purification, is very troublesome because of the high solubility of the product in water. Thus, the present reaction has some advantages from a synthetic point of view; i.e., (i) conversion of the reaction is virtually 100%, and (ii) the isolation of the product is quite simple and convenient since the reaction is carried out in small amounts of nonaqueous media.

Further studies on achieving high stereoselectivity using a variety of chiral ligands are actively under way.

Experimental Section

Measurements. Melting points and boiling points are uncorrected. The infrared spectra were measured on a Hitachi EPI-G3 spectrophotometer using samples as neat liquid or in KBr disks. The nuclear magnetic resonance spectra were obtained using a Varian XL-100, HA-100, or T-60 spectrometer with Me_4Si as an internal standard. Analytical gas chromatography (GLC) was carried out on a Shimadzu GC-3BF using a column packed with 3% PEG-20M.

Materials. [Rh(cycloocta-1,5-diene)Cl]$_2$ was prepared from rhodium trichloride trihydrate and cycloocta-1,5-diene.[11] BPPM was prepared from L-4-hydroxyplorine in accordance with a previously reported method.[5] Ketopantoyl lactone was prepared by the oxidation of DL-pantoyl lactone with N-bromosuccinimide in 85% yield by a modified method of Broquet and Bedin.[12] The shift reagent for NMR measurements, tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III) [Eu(facam)$_3$], was commercially available from Willow Brook Laboratories, Inc.

Preparation of the Catalyst Solution. The optically active catalyst was prepared in situ by the reaction of [Rh(cycloocta-1,5-diene)Cl]$_2$ with the chiral diphosphine in a degassed solvent at ambient temperature. In a typical experiment, 24.4 mg (4.95×10^{-5} mol) of [Rh(cycloocta-1,5-diene)Cl]$_2$ and 60.0 mg (1.08×10^{-4} mol) of BPPM were dissolved in 8 mL of benzene under an argon atmosphere and stirred for 15 min. Similarly, the (−)-DIOP–rhodium catalyst was prepared from 24.4 mg (4.95×10^{-5} mol) of [Rh(cycloocta-1,5-diene)Cl]$_2$ and 53.8 mg (1.08×10^{-4} mol) of (−)-DIOP in 8 mL of benzene.

Asymmetric Hydrogenation of Ketopantoyl Lactone. In a typical run, 1.28 g (10.0 mmol) of ketopantoyl lactone was added to 8 mL of a degassed benzene solution of BPPM–rhodium complex (1.08×10^{-2} mmol, 1.08 mol%) in a autoclave under argon. After the argon atmosphere was displaced by hydrogen, the hydrogenation was carried out under an initial hydrogen pressure of 50 atm at 30 °C for 48 h with stirring. The GLC analysis of the reaction mixture revealed that the conversion of the reaction was 100%. The solvent was evaporated, and the residue was distilled under reduced pressure to afford 1.21 g (93%) of pantoyl lactone: bp 92 °C (4 mmHg); $[\alpha]^{25}_D$ −44.0° (c 2.010, H_2O). An NMR (100 MHz) measurement using Eu(facam)$_3$ showed that the purity of the enantiomer thus obtained was 86% enantiomeric excess.

The pantoyl lactone (1.21 g) thus obtained was recrystallized from n-hexane–benzene (3:1) to afford 854 mg (70.6%) of pure D(−)-pantoyl lactone, $[\alpha]^{25}_D$ −50.8 ± 0.1° (c 2.055, H_2O).

When the conversion of the reaction was lower than 99%, the reaction mixture was submitted to column chromatography on silica. Then, pantoyl lactone was separated from unreacted ketopantoyl lactone and used for the measurement of optical rotation.

Synthesis of Ethyl D(+)-Pantothenate. Ethyl D(+)-pantothenate was synthesized by a modified method of Güssner et al.[13] Pure

D(−)-pantoyl lactone (2.60 g, 20 mmol), obtained in the above reaction, was mixed with freshly distilled β-alanine ethyl ester (2.80 g, 24 mmol) in 20 mL of benzene and heated under reflux for 6 h. After the solvent was evaporated, the residue was submitted to column chromatography on silica. The unreacted pantoyl lactone was recovered (0.52 g, 20%) from the *n*-hexane–benzene eluate, and ethyl D(+)-pantothenate (3.80 g, 77%) was obtained from the ether eluate. Ethyl D(+)-pantothenate: colorless liquid; $[\alpha]^{18}_D$ +42.20° (*c* 2.18, absolute EtOH). Anal. Calcd for $C_{11}H_{21}O_5N$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.39; H, 8.69; N, 5.47.

The previously reported maximum rotation of this compound by Güssner et al. was $[\alpha]^{15}_D$ +36.8° (*c* 4.68, absolute EtOH). This lower value could be due to a partial racemization during distillation at high temperature.

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Registry No.—Ethyl D(+)-pantothenate, 10527-68-1; BPPM, 61478-28-2; $[Rh(cycloocta\text{-}1,5\text{-}diene)Cl]_2$, 12092-47-6; ketopantoyl lactone, 13031-04-4; D(−)-pantoyl lactone, 599-04-2; BPPM–rhodium(I) complex, 66787-44-8; ethyl β-alaninate, 924-73-2.

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Synthesis of Pomiferin, Auriculasin, and Related Compounds

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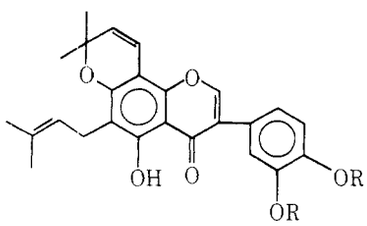
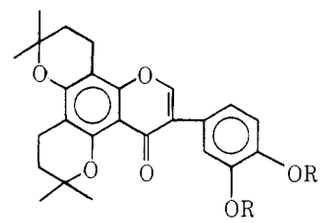
Nuclear prenylation of 3′,4′-di-*O*-methylorobol (**4**) with prenyl bromide under alkaline conditions has yielded its 7-*O*-prenyl (**8**), 6-*C*-prenyl (**12**), and 6,8-di-*C*,*C*-prenyl (**9**) derivatives. Acetylation, partial methylation, and cyclization with formic acid of **12** and **9** separately and their NMR spectra established their structures. Cyclodehydrogenation of **9** with DDQ gave di-*O*-methyl derivatives (**6** and **18**) of pomiferin and auriculasin, respectively. Pomiferin (**1**) and auriculasin (**5**) themselves were synthesized by nuclear prenylation of orobol (**19**), giving the 6-*C*-prenyl (**21**) and the 6,8-di-*C*,*C*-prenyl (**20**) derivatives. Cyclodehydrogenation of 6,8-di-*C*,*C*-prenylorobol (**20**) afforded both the isomers (**1** and **5**). Cyclodehydrogenations of **21** and **12** yielded 6″,6″-dimethylpyrano[2″,3″:7,6]orobol (**22**) and its dimethyl ether (**16**), respectively.

Pomiferin was isolated from the fruit of the osaje orange tree, *Maclura pomifera* Raf., along with osajin (Dr. D. Dreyer, Western Regional Research Laboratory, Berkeley, states that both osajin and pomiferin are present in almost equal amounts in the fruit), and assigned the structure of 5,3′4′-trihydroxy-6-*C*-prenyl-6″,6″-dimethylpyrano[2″,3″:7,8]isoflavone (**1**) by Wolfrom et al.[1,2] using mostly the chemical

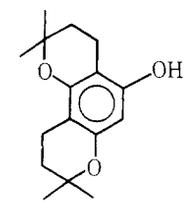


1, R = H (pomiferin)
6, R = Me

methods of degradation and color reactions. The only synthetic evidence given so far has been the synthesis of its derivative, dihydroisopomiferin (**2**), formed in two stages. Wolfrom et al.[2] synthesized dihydroisopomiferin (**2**) from bis(dihydropyrano)phloroglucinol (**3**) by Hoesch reaction with 3,4-dimethoxybenzyl cyanide, followed successively by isoflavone condensation with ethyl formate in the presence of sodium and demethylation with HI, whereas Raizada et al.[3]



2, R = H (dihydroisopomiferin)
11, R = Me



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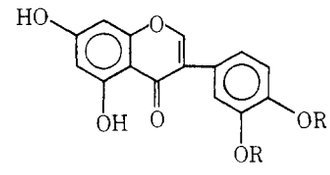
synthesized **2** from 3′,4′-di-*O*-methylorobol (**4**) by reacting it with prenyl bromide in the presence of zinc chloride and benzene. Auriculasin recently isolated from *Milletia auriculata* (Leguminosae) has been assigned the isomeric structure **5** by Minhaj et al.[4] on the basis of its special data and those on its trimethyl ether and triacetate. We now report the synthesis



4, R = Me
19, R = H

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