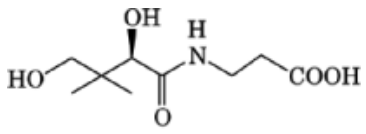
Kirk-Othmer Encyclopedia of Chemical Technology.

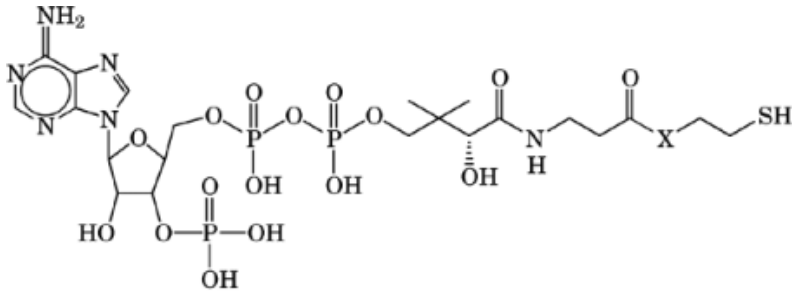
PANTOTHENIC ACID

(*R*)-Pantothenic acid [79-83-4] **(1)** is a member of the B-complex vitamins. It is a water-soluble vitamin and has been designated as vitamin B_5. It was discovered by Williams and co-workers in 1933 by extracting a growth factor for yeast from a wide range of biological tissues (1). Later the growth factor was identified as pantothenic acid **(1)**. Independently two groups, Woolley and co-workers (2) in 1939 and Jukes (3) between 1939 and 1941, identified the liver filtrate factor in rats and antidermatitis factor in chicks. These factors later proved to be identical with pantothenic acid. The total synthesis of (*R*)-pantothenic acid was achieved in 1940 by three groups: Stiller and co-workers (4), Reichstein and Grüssner (5), and Kuhn and Wieland (6).



(1)

After a full structural elucidation of coenzyme A in 1953 by Baddiley, it became evident that pantothenic acid is one of the components of coenzyme A **(2)** (7).



(2a, X = NH; coenzyme A)
(2b, X = S; thio analogue)

Biosynthesis of coenzyme A (CoA) in mammalian cells incorporates pantothenic acid. Coenzyme A, an acyl group carrier, is a cofactor for various enzymatic reactions and serves as either a hydrogen donor or an acceptor. Pantothenic acid is also a structural component of acyl carrier protein (ACP). ACP is an essential component of the fatty acid synthetase complex, and is therefore required for fatty acid synthesis. Free pantothenic acid is isolated from liver, and is a pale yellow, viscous, and hygroscopic oil.

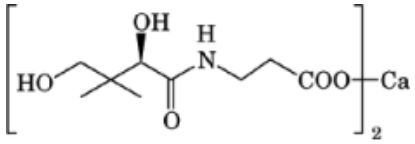
1. Occurrence, Source, and Bioavailability

Good food sources of pantothenic acid include yeast, chicken, beef, potatoes, oat cereal, vegetables, legumes, and whole grain. Pantothenic acid in foods and feedstuffs is fairly stable to ordinary means of cooking and storage, but appreciable losses have been reported as a result of canning and storage of some foods. Pantothenic acid is synthesized only by plants and microorganisms. Estimation of the dietary intake of pantothenic acid is difficult because the acid exists in the free form and is also incorporated in coenzyme A and fatty acid synthetase. Total pantothenic acid content present in the food is estimated after releasing the bound acid enzymatically (8, 9).

Relatively little is known about the bioavailability of pantothenic acid in human beings, and only approximately 50% of pantothenic acid present in the diet is actually absorbed (10). Liver, adrenal glands, kidneys, brain, and testes contain high concentrations of pantothenic acid. In healthy adults, the total amount of pantothenic acid present in whole blood is estimated to be 1 mg/L. A significant (2–7 mg/d) difference is observed among different age-group individuals with respect to pantothenic acid intake and urinary excretion, indicating differences in the rate of metabolism of pantothenic acid.

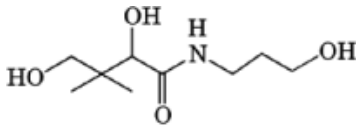
2. Physical and Chemical Properties

(*R*)-Pantothenic acid **(1)** contains two subunits, (*R*)-pantoic acid and β-alanine. The chemical abstract name is *N*-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)- β-alanine (11). Only (*R*)-pantothenic acid is biologically active. Pantothenic acid is unstable under alkaline or acidic conditions, but is stable under neutral conditions. Pantothenic acid is extremely hygroscopic, and there are stability problems associated with the sodium salt of pantothenic acid. The major commercial source of this vitamin is thus the stable calcium salt **(3)** (calcium pantothenate).



(3)

Panthenol **(4)** is the reduced form of pantothenic acid and is the pure form most commonly used. The alcohol is more easily absorbed and is converted into the acid *in vivo* (12). Both panthenol and pantyl ether are used in hair care products.



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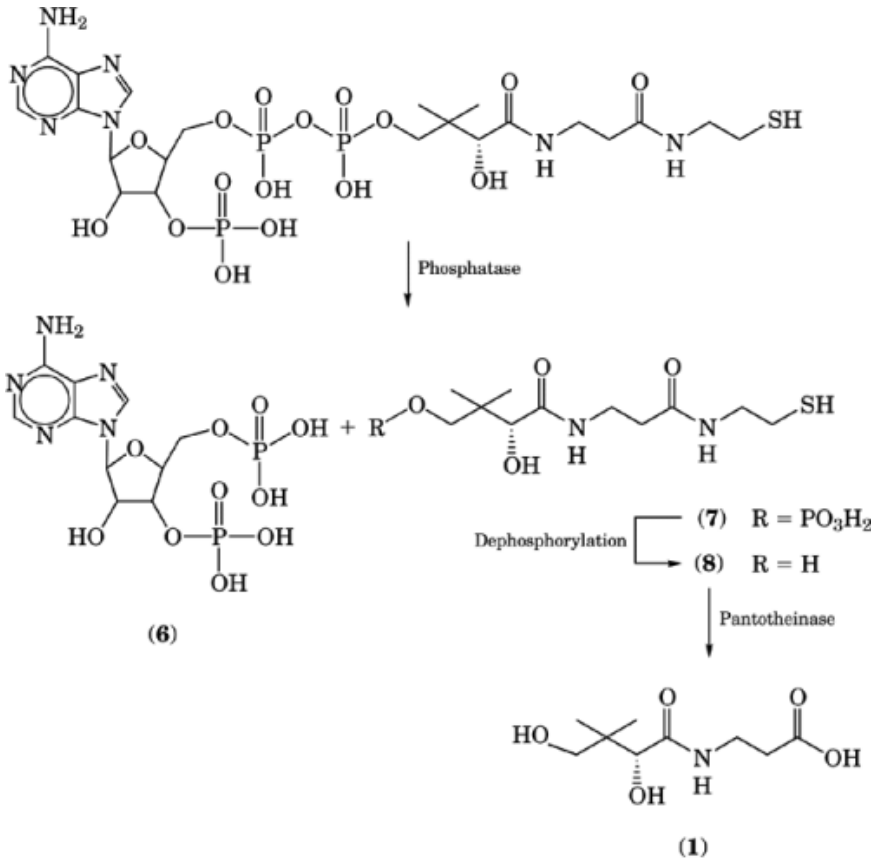
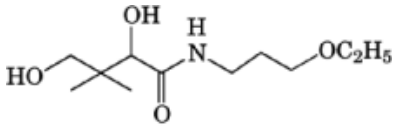


Fig. 1. Enzymatic hydrolysis of coenzyme A **(2)**.



(5)

The biologically active *R*- or *d*-pantothenic acid can be obtained upon hydrolysis of coenzyme A with a combination of two enzymes, alkaline phosphatase and pantotheinase (13) (Fig. 1). The phosphatase catalyzes the selective cleavage of the phosphate bond in coenzyme A to afford adenosin-3′5′-diphosphate 1 and 4-phosphopantetheine 1. The latter substance is dephosphorylated enzymatically to yield pantetheine 1, which is rapidly converted by pantotheinase to pantothenic acid **(1)**. Table 1 lists some physical properties of pantothenic acid and its derivatives.

Table 1. Physical Properties of Pantothenic Acid and Derivatives

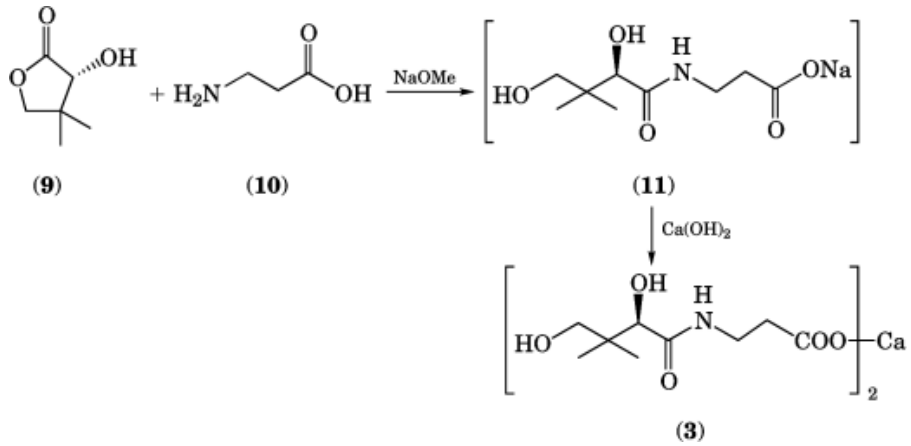
Compound	CAS Registry Number	$\alpha^{20}{}_D{}^a$	bp/mp, °C	Molecular formula	Molecular weight
(*R*)-pantothenic acid	[79 – 83 – 4]			$C_9H_{17}NO_5$	219.24
(*S*)-pantothenic acid	[37138 – 77 – 5]			$C_9H_{17}NO_5$	219.24
(*R*)-pantothenic acid calcium salt	[137 – 08 – 6]	+28.2°	195°C	$(C_9H_{16}NO_5)_2Ca$	476.5
(*R*)-pantothenic acid sodium salt	[876 – 81 – 2]	+27.7°	171–178°C	$C_9H_{16}NO_5Na$	241.2
(*R*)-panthenol	[81 – 13 – 0]	+29.5°	120°C[b]	$C_9H_{19}NO_4$	205.25
(*S*)-panthenol	[74561 – 18 – 5]	−29.5°	120°C[b]	$C_9H_{19}NO_4$	205.25
(*R,S*)-panthenol	[16485 – 10 – 2]	0	66–69°C	$C_9H_{19}NO_4$	205.25
(*R,S*)-ethylpanthenol	[667 – 84 – 5]	0	210°C	$C_{11}H_{23}NO_4$	233.1
(*R*)-ethylpanthenol	[667 – 83 – 4]			$C_{11}H_{23}NO_4$	233.1

[a] $C = 5$ in H_2O for all values other than 0.
[b] At 0.02 mm Hg.

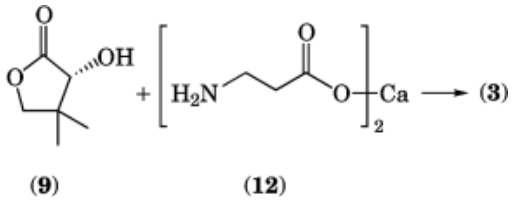
3. Synthesis

Currently (ca 1997) pantothenic acid is produced mainly by chemical methods. Initial efforts in this area are summarized in Reference 14. Several groups are actively involved in developing syntheses of pantothenic acid or its precursor, (*R*)-pantolactone **(9)** by microbial methods.

(*R*)-Calcium pantothenate **(3)** is prepared by condensing (*R*)-pantolactone **(9)** with β-alanine **(10)** in the presence of base, followed by treatment of the sodium salt **(11)** with calcium hydroxide.

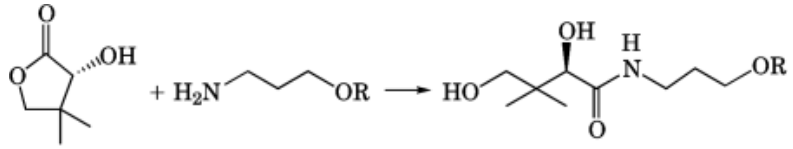


An alternative procedure for the preparation of (*R*)-calcium pantothenate **(3)** is to condense (*R*)-pantolactone **(9)** with the preformed calcium salt **(12)** of β-alanine (15).



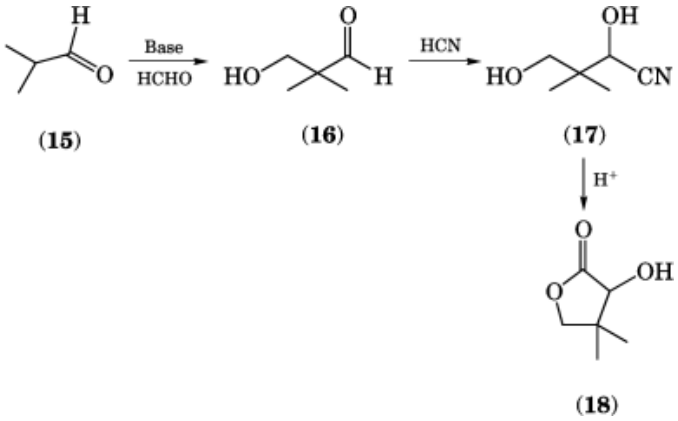
(9) (12) (3)

Similarly, panthenol **(4)** and pantyl ether **(5)** are prepared by condensing 3-aminopropanol **(13)** and 3-ethoxypropylamine **(14)** with (*R*)-pantolactone (16, 17).



(9) (13, R = H) (14, R = C_2H_5) (4, R = H) (5, R = C_2H_5)

Racemic pantolactone is prepared easily by reacting isobutyraldehyde **(15)** with formaldehyde in the presence of a base to yield the intermediate hydroxyaldehyde **(16)**. Hydrogen cyanide addition affords the hydroxy cyanohydrin **(17)**. Acid-catalyzed hydrolysis and cyclization of the cyanohydrin **(17)** gives (*R,S*)-pantolactone **(18)** in 90% yield (18).

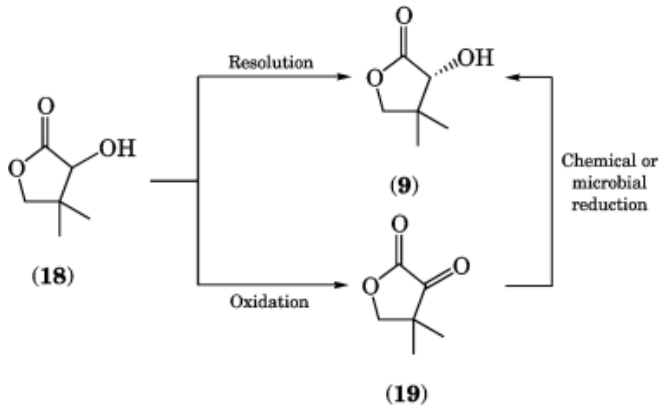


(15) (16) (17) (18)

(*R*)-Pantolactone **(9)** is prepared in either of two ways: by resolution of the (*R,S*)-pantolactone mixture **(18)**, or by stereoselective reduction of ketopantolactone **(19)** by chemical or microbial methods (19).

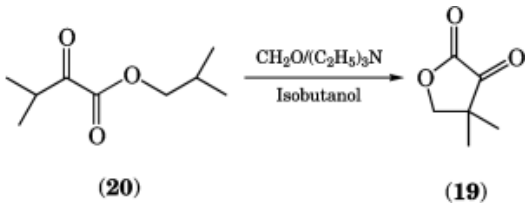
Table 2. Asymmetric Hydrogenation of Ketopantolactone (19)

Catalyst/Chiral ligand	Isolated yield %	ee %	Reference
[Rh(bppm)(1,5-hexadiene)Cl]	93	56	37
[Rh(bppm)(COD)Cl]	93	86.7	38
dimethyl-(*R*)-malate	40	>99	39
di-(μ-carboxylato)bis(aminophosphine-phosphinite) dirhodium complexes	100	91	36



Chemical resolution of pantoic acid, readily available from (*R,S*)-pantolactone **(18)**, is the most efficient method currently being practiced on an industrial scale. A wide variety of chiral resolving agents are being used, such as (+)-2-aminomethylpinane by BASF (20), 2-benzylamino-1-phenylethanol by Fuji (21), chiral aminoalcohols by Alps and Sumitomo (22, 23), (1*R*)-3-endo-aminoborneol by Hoffmann-La Roche (24), and 1-ethylbenzylamine by Daicel (25). Other approaches include optical resolution by inclusion crystallization (26) and spontaneous resolution of (*R,S*)-pantolactone by seeding (27). (*R,S*)-Pantolactone can be resolved directly using chiral phase chromatography (28), or after derivatization using optically active acids or isocyanates (29). The sodium salt of pantoic acid is enantioselectively protonated in the presence of (1*S*)-(+)-10-camphorsulfonic acid and then undergoes spontaneous cyclization to (*R*)-pantolactone **(9)** (30).

Ketopantolactone **(19)** is conveniently prepared by oxidation of (*R,S*)-pantolactone **(18)**. Various oxidizing agents have been patented for the oxidation of pantolactone, such as MnO_2 (31), DMSO–Ac_2O (32), and hypohalites (33). An improved yield of ketopantolactone **(19)** via electrolytic oxidation of pantolactone with an aqueous solution containing an alkali metal salt was reported (34). Ketopantolactone **(19)** has been prepared in good yield via cyclocondensation of the 2-keto-3-methylbutyrate **(20)** with formaldehyde (35).

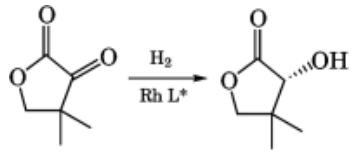


Asymmetric hydrogenation of ketopantolactone **(19)** in the presence of chiral dirhodium complexes gave (*R*)-pantolactone **(9)** in high yield and excellent selectivity (36) (Table 2).

Table 3. Microbial Reduction of Ketopantoate (21) to (*R*)-Pantoate (22)

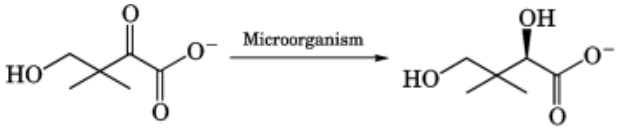
Microorganism	% Conver-sion yield	% ee	Final product concentration, m*M*	PN[a]	Reference
Rhodotorula erythropolis	90.5	94.4	140		40
Agrobacterium sp. S-242	90	>98	910	120	41
Nocardia asteroides/*Agrobacterium radiobacter*	89	82.8	620	130	42
Candida macedonienis-AK4 4588	97.2	98	80		43
Proteus vulgaris	98.5	>97	460	740	44

[a]Productivity number (PN) = product in mmol/dry wt of cells in kg *x* time, h.



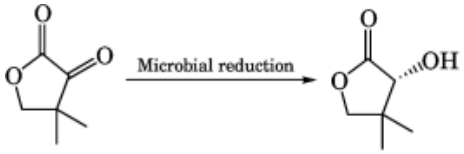
(19) **(9)**

The microbial reduction of ketopantoate **(21)** to (*R*)-pantoate **(22)** has been investigated, employing one or two microorganisms (40–44). Reduction with *Proteus vulgaris* gave (*R*)-pantoate **(22)** in high (460 mmol) concentration, excellent selectivity (97% ee), and 98.5% yield with acceptable productivity numbers. Productivity number (PN) is derived by dividing the concentration in mmol of product formed by the dry weight in kg of the cells, multiplied by the time in hours required for the conversion. Higher PN is favored for production (44) (Table 3).



(21) **(22)**

Reduction of ketopantolactone **(19)** to (*R*)-pantolactone **(9)** also was evaluated using microbes (45–52) (Table 4).



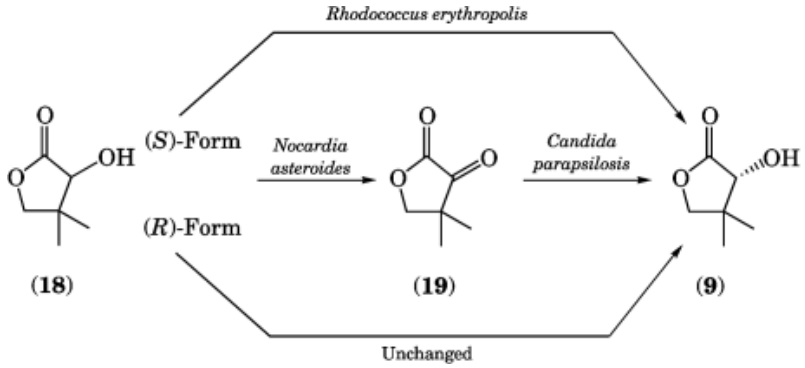
(19) **(9)**

These microbial methods have afforded excellent ee values and yields (40–52). However, owing to low, ie, 30–130, productivity numbers these processes have not yet been commercialized.

In a novel approach, enantiomerically enriched (*R*)-pantolactone **(9)** is obtained in a enzymatic two-step process starting from racemic pantolactone.

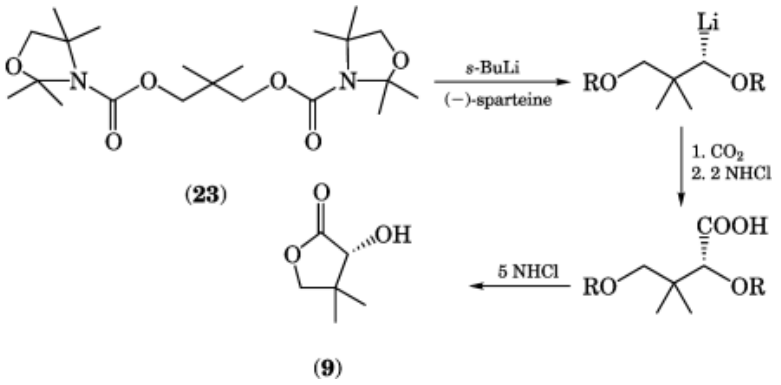
Table 4. Microbial Reduction of Ketopantolactone (19) to (*R*)-Pantolactone (9)

Microorganism	% Conver-sion yield	% ee	Final product concentration, m*M*	PN	Reference
Saccharomyces cerevisiae	>90	>98	40	30	45
Byssochamys fulva	>90	>96			46
Nocardiaasteroides/candida parapsilosis	>90	>98	390	130	47
Candida parapsilosis	>90	94–98	700		48
Rhodotorulaminuta	80.3	99.7	380		49
Saccharomyces cerevisiae	39	93	20		50
Zygosaccharo-myces	96.8	90			51
Baker's yeast/β-cyclodextrin	39	93			52



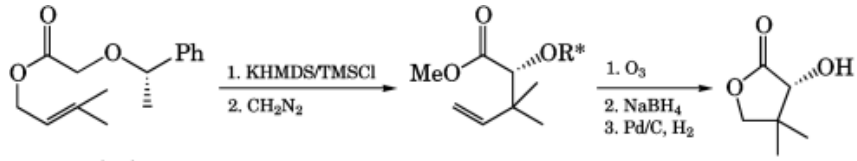
In a first step, *Nocardia asteroides* selectively oxidizes only (*S*)-pantolactone to ketopantolactone **(19)**, whereas the (*R*)-pantolactone remains unaffected (47). The accumulated ketopantolactone is stereospecifically reduced to (*R*)-pantolactone in a second step with *Candida parapsilosis* (product concentration 72 g/L, 90% molar yield and 100% ee) (48). Racemic pantolactone can also be converted to (*R*)-pantolactone by one single microbe, ie, *Rhodococcus erythropolis*, by enantioselective oxidation to (*S*)-pantolactone and subsequent stereospecific reduction in 90% yield and 94% ee (product concentration 18 g/L) (40).

Although not of industrial importance, several asymmetric syntheses of (*R*)-pantolactone **(9)** have been developed. Stereoselective abstraction of the *si*-proton of the achiral 1,3-propanediol derivative **(23)** by *sec*-butylithium–(-)-sparteine, followed by carboxylation and hydrolysis, results in (*R*)-pantolactone in 80% yield and 95% ee (53).



(23) (9)

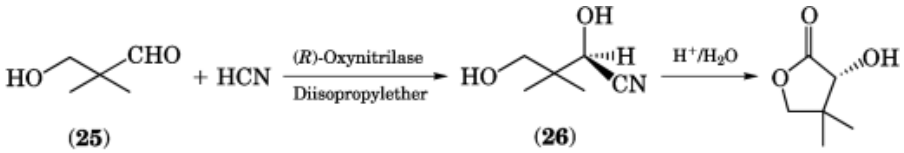
(*R*)-Pantolactone is also prepared in a sequence involving Claisen rearrangement of the chiral glycolate **(24)**, although with poor enantioselectivity (54).



(24) (9)

By employing Sharpless epoxidation as a key step, a multistep chemical synthesis of (*R*)-pantolactone has also been reported (55).

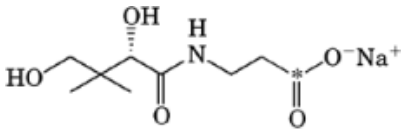
Enantioselective addition of hydrogen cyanide to hydroxypivaldehyde **(25)**, catalyzed by (*R*)-oxynitrilase, afforded (*R*)-cyanohydrin **(26)** in good optical yield. Acid-catalyzed hydrolysis followed by cyclization resulted in (*R*)-pantolactone in 98% ee and 95% yield after one recrystallization (56).



(25) (26) (9)

4. Labeled Compounds

Various labeled degradation products of pantothenic acid and coenzyme A are known. Both (1-^{14}C)-sodium pantothenate **(27)** and (*R*)-(1-^{14}C)-panthenol are

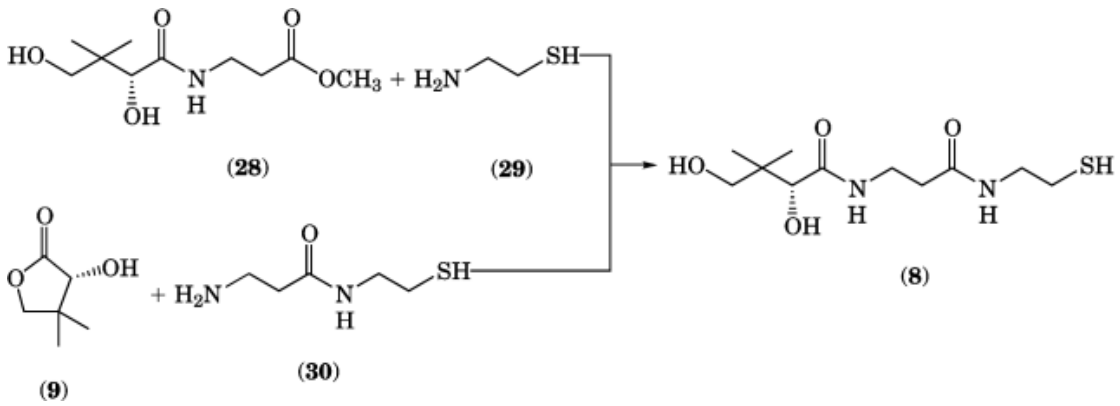


(27)

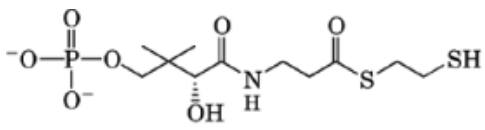
known and are commercially available from New England Nuclear Corporation (NEN, Boston, Mass.). The syntheses of ^{14}C-phosphopantotheine (57) and ^{14}C-labeled coenzyme A (58) have also been reported.

5. Derivatives and Analogues

Methyl and diacetyl derivatives of pantothenic acid are prepared via methylation and acetylation of pantothenic acid (59). Pantethein 1 is one of the biochemical degradation products derived from coenzyme A. Synthetically, it can be prepared in several different ways, starting from either methyl pantothenate **(28)** or (*R*)-pantolactone. Pantethein 1 is prepared either by condensing cysteamine **(29)** with methyl pantothenate **(28)** (60) or by coupling (*R*)-pantolactone **(9)** with 3-amino-*N*-(2-mercaptoethyl)propanamide **(30)** (61). Phosphopantetheine analogue **(31)** was prepared starting from (*R*)-pantothenic acid. Enzymatic condensation of this compound with adenosin-3,5-diphosphate 1 gave CoA analogue **(2b)** (62).



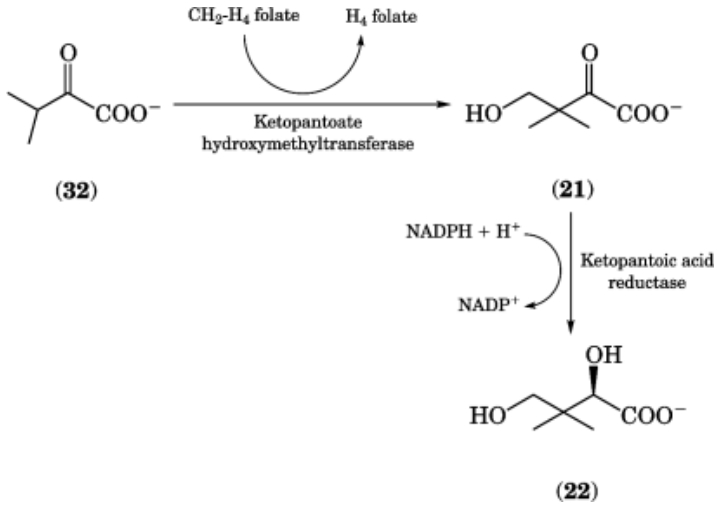
(28) **(29)** **(8)** **(9)** **(30)**



(31)

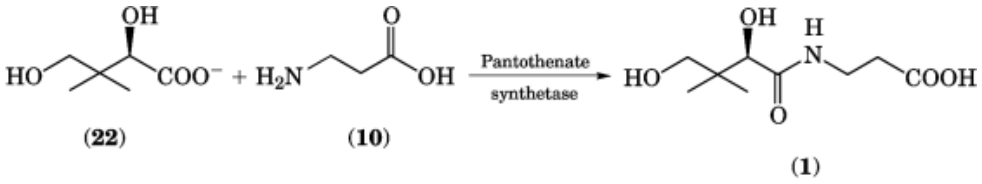
6. Biosynthesis

The metabolically active form of pantothenic acid is coenzyme A. Pantothenic acid is produced only by microorganisms, starting from (*R*)-pantoate **(22)** and β-alanine. (*R*)-Pantoate is synthesized by a set of enzymatic reactions, as follows (63, 64):



The conversion of α-ketoisovalerate **(32)** to ketopantoate **(21)** is catalyzed by ketopantonate hydroxymethyltransferase and a cofactor tetrahydrofolate (65). Further reduction of ketopantoate **(21)** to (*R*)-pantoate **(22)** is catalyzed by ketopantoic acid reductase (66).

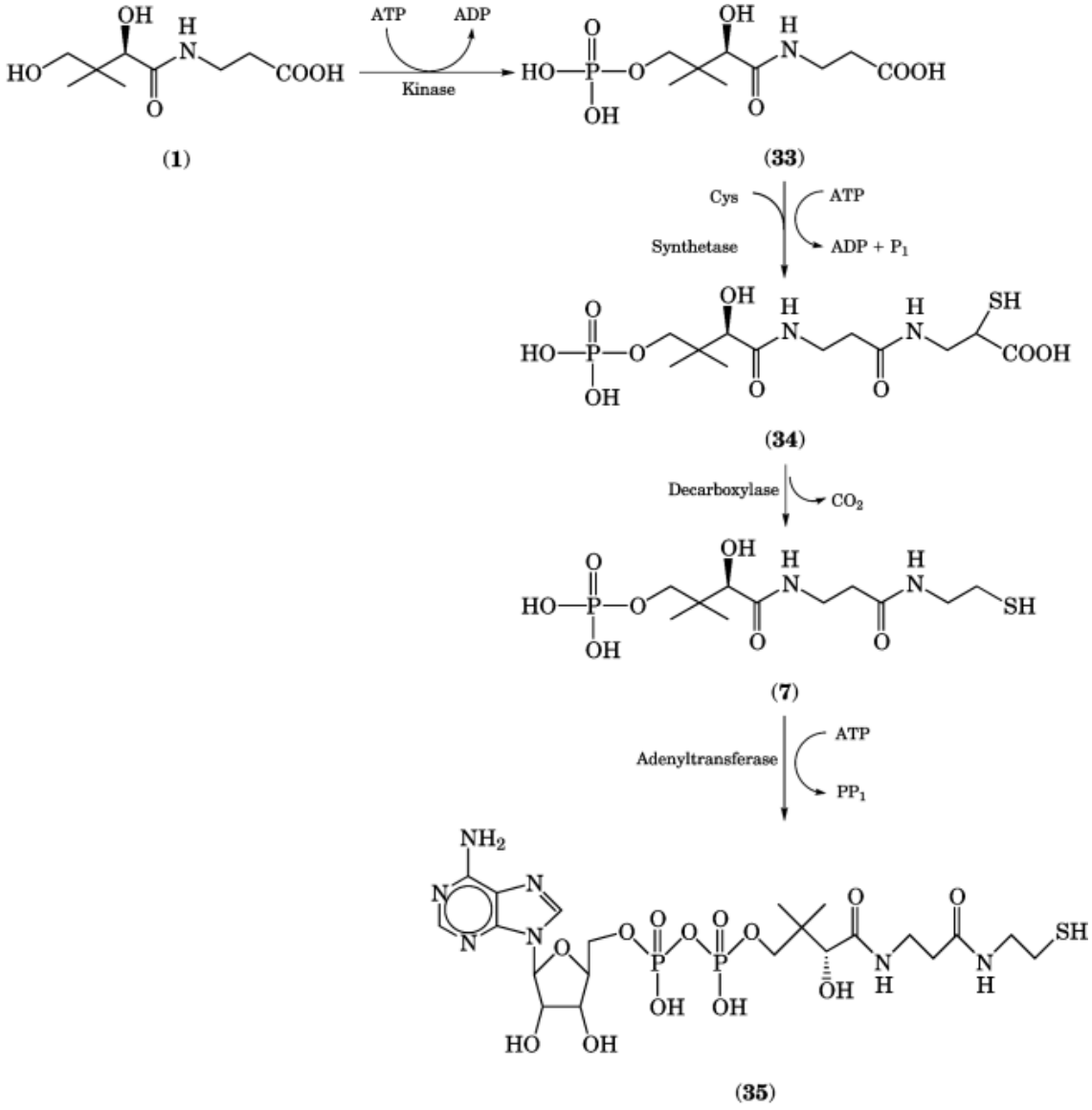
Aspartic acid decarboxylase catalyzes the decarboxylation of asparatic acid to yield β-alanine **(10)**, a precursor for the biosynthesis of pantothenic acid (67). Finally, (*R*)-pantothenic acid is obtained by coupling β-alanine **(10)** with (*R*)-pantoate **(22)** in the presence of pantothenate synthetase:



Various pathways have been proposed for the conversion of pantothenic acid to coenzyme A (68, 69). The currently accepted pathway involves the following sequence; pantothenate to 4-phosphopantothenic acid **(33)**, 4-phosphopantothenyl cysteine **(34)**, 4-phosphopantetheine 1, dephosphocoenzyme A **(35)**, and coenzyme A **(2)**. Phosphorylation of pantothenic acid to 4-phosphopantothenic acid is catalyzed by pantothenic kinase in the rate-limiting step in the overall synthesis of coenzyme A (70).

7. Analytical Methods

Chemical, physical, animal, microbiological, and biochemical assays have been used to determine pantothenic acid. Pantothenic acid in foods is found in both the free form and as the vitamin moiety of coenzyme A and phosphopantetheine.



For most assays, the incorporated pantothenic acid has to be liberated enzymatically. Usually, a combination of pantotheinase and alkaline phosphatase is used to liberate the bound pantothenic acid. The official method for pantothenic acid of the Association of Official Analytical Chemists (AOAC) is the microbiological assay that uses *L. Plantarium (ATCC 8014)* as the test organism (71). Samples are extracted at 121°C at pH

5.6–5.7, proteins are precipitated at pH 4.5, and the resulting clear extracts are adjusted to pH 6.8 prior to assay. This procedure is only suitable to determine calcium pantothenate or other free forms of pantothenic acid.

A radioimmunoassay method has been developed by Wyse and co-workers (72). It is a sensitive method for the determination of small amounts of pantothenic acid in biological fluids. The assay is based on the binding of an enzyme specific for pantothenic acid. Hemolyzed blood samples are subjected to a double-enzyme treatment with 5 IU of bovine intestinal alkaline phosphatase and 0.1 IU of pantetheinase. After hydrolysis, the clear supernatant extract is analyzed for pantothenate by a radioimmunoassay method. In the case of pharmaceutical preparations, vitamin concentrations are determined by using spectrophotometric and fluorometric methods (73). For spectrophotometric methods, detection is done at 358 nm and for fluorescence, excitation is done at 350 nm and collection at 450 nm. Food pantothenate assays involve hydrolysis of the food by 25% hydrochloric acid in a 95–100°C water bath, extraction of the pantoyl lactone into dichloromethane and analysis by gas chromatography with flame ionization detection (74). Chiral polysiloxane fused silicon capillary columns (XE-60-L-Val-(*S*)- or (*R*)-α-phenylethylamide) have been developed for separation of the (*R*)- and (*S*)-pantothenic acid mixture (75). Recently, clinical separation and simultaneous determination of (*R*)- and (*S*)-pantothenic acids in rat plasma using gc–ms has been described (76). Deproteinization of the plasma samples is done by eluting the plasma sample through an anion-exchange resin using 1 *M* sodium chloride solution. Pantothenic acid is extracted quantitatively with ethyl acetate after acidifying the basic aqueous solution. After esterification of the carboxylic group, each derivative is identified using gs–ms.

8. Deficiency

A deficiency of pantothenic acid in humans has not been detected because it is widely available in food (77). In the case of prisoners of war in the 1940s, a burning feet syndrome, which was attributed to pantothenic acid deficiency as a result of severe malnutrition, was observed (78). Pantothenic acid deficiency in humans is induced experimentally by feeding a diet deficient in pantothenic acid along with a pantothenic acid antagonist such as ω-methylpantothenic acid. This results in clinical malaise, fatigue, headache, sleep disturbance, nausea, vomiting, and cardiovascular instability. Impaired responses to insulin, histamine, and ACTH (stress hormone) have also been observed. A wide variety of abnormalities such as retarded growth, impaired fertility, gastrointestinal lesions, and adrenal necroses are reported when rats are fed a pantothenic acid-deficient diet (79, 80). Chicks on a pantothenic acid-deficient diet develop lesions at the corners of the mouth, swollen eyelids, hemorrhagic cracks on the feet, and listlessness (81).

9. Absorption

Pantothenic acid occurs in most foods and feedstuffs as CoA and acyl-carrier protein. The utilization of the vitamin depends upon the hydrolytic digestion of these protein complexes to release the free vitamin. Coenzyme A is hydrolyzed in the intestinal lumen before absorption into the cell by a sodium ion-dependent, passive mechanism (82, 83). High concentrations of pantothenic acid are found in the heart and kidney, compared to other organs such as the intestine and liver (84). Pantothenic acid utilization in the formation of acetyl CoA is impaired in alcoholics because the ethanol metabolite acetaldehyde inhibits the conversion (85). Erythrocytes, which carry most of the vitamin in the blood, carry it predominantly in the form of CoA. Blood and urinary levels of pantothenic acid are lower for oral contraceptive users than for nonusers (86, 87). Absorption is also inhibited in the presence of known antagonists, such as ω-methylpantothenic acid, and to some extent with (*S*)-pantothenic acid. Another factor which influences vitamin absorption is a high fat diet. This condition significantly lowers the utilization of pantothenic acid in the formation of coenzyme A in the liver because of

changes in lipid metabolism (88). On the other hand, high levels of protein in the diet may promote better utilization of this vitamin in the synthesis of coenzyme A (89).

10. Nutritional Requirements

Pantothenic acid is widely distributed in food and because of the lack of conclusive evidence regarding quantitative needs, a recommended dietary allowance (RDA) for pantothenic acid has not been established. In 1989, the Food and Nutrition Board of the United States National Research Council suggested a safe intake of 4–7 mg/d for adults. The provisional allowance for infants is 2–3 mg daily (90).

11. Functions

The most important functions of pantothenic acid are its incorporation in coenzyme A and acyl carrier protein (ACP). Both CoA and ACP/4-phosphopantetheine function metabolically as carriers of acyl groups. Coenzyme A forms high-energy thioester bonds with carboxylic acids. The most important coenzyme is acetyl CoA. Acetic acid is produced during the metabolism of fatty acids, amino acids, or carbohydrates. The active acetate group of acetyl CoA can enter the Krebs cycle and is used in the synthesis of fatty acids or cholesterol. ACP is a component of the fatty acid synthase multienzyme complex. This complex catalyzes several reactions of fatty acid synthesis (condensation and reduction). The nature of the fatty acid synthase complex varies considerably among different species (91).

12. Toxicity

Pantothenic acid toxicity has not been reported in humans. Massive doses (10 g/d) in humans have produced mild intestinal distress and diarrhea. Acute toxicity was observed in case of mice and rats by using calcium pantothenate at fairly large doses (92).

13. Uses

The bulk of the industrial supply of the calcium salt of (*R*)-pantothenic acid is used in food and feed enrichment. Food enrichment includes breakfast cereals, beverages, dietetic, and baby foods. Animal feed is fortified with calcium-(*R*)-pantothenate which functions as a growth factor.

Panthenol is used in skin care products. When applied topically to alleviate itching, it helps to keep the skin moist and supple, stimulates cell growth, and accelerates wound healing by increasing the fibroblast content of scar tissue (93, 94). It is also used as a moisturizer and conditioner in hair care products. It is believed to protect hair against chemical and mechanical damage caused by perming, coloring, and shampooing (95).

14. Economic Aspects

The major producers of the calcium salt of pantothenic acid and panthenol are Hoffmann-La Roche, Daiichi, BASF, and Alps. Racemic panthenol is used mainly in hair care products, whereas (*R*)-panthenol is exclusively used in top-of-the-line, more expensive skin and hair care products. The current (ca 1997) price of

(*R,S*)-panthenol varies between $12 and $18 per kg, that of D-panthenol varies between $30 and $45 per kg, and that of D-calcium pantothenate (Calpan) varies between $22 and $30 per kg.

15. Future Prospects

Despite the progress made in the stereoselective synthesis of (*R*)-pantothenic acid since the mid-1980s, the commercial chemical synthesis still involves resolution of racemic pantolactone. Recent (ca 1997) synthetic efforts have been directed toward developing a method for enantioselective synthesis of (*R*)-pantolactone by either chemical or microbial reduction of ketopantolactone. Microbial reduction of ketopantolactone is a promising area for future research.

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