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Calcium Pantothenate. Part 3.[1] Process for the Biologically Active Enantiomer of the Same via Selective Crystallization and Racemization

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Abstract:

Optically pure calcium (*R*)-pantothenate has been obtained from the racemic compound via direct fractional crystallization of the single enantiomer. Efficient racemization of the biologically inactive calcium (*S*)-pantothenate without its decomposition to pantolactone has been developed, resulting in a simple, complete, and efficient technology. The results elaborated in the laboratory have been then successfully applied in the industrial scale process.

Introduction

Calcium (*R*)-pantothenate ((*R*)-PTTCa) and (*R*)-panthenol are the most important commercial precursors of (*R*)-pantothenic acid, a compound possessing a vitamin activity, denoted also as vitamin B_5. The significance of calcium (*R*)-pantothenate as an ingredient of pharmaceutical and cosmetic compositions as well as food and feed supplements caused the methods of its production attract much attention since the first total synthesis by Stiller.[2] The most frequently used is the condensation of β-alanine calcium salt with (*R*)-pantolactone,[3] although the separation of the racemic pantothenic acid with chiral amines or by direct crystallization of its salts have also been described.[4,5] Lately, the importance of biosynthetical methods has also increased (Scheme 1).[6]

Among the methods shown in (Scheme 1), direct separation of enantiomers is an extraordinarily attractive alternative for industrial purposes. The fundamental requirement for such a process is the existence of conglomerates instead of the racemic crystals in the solid phase. Fortunately, PTTCa possesses this unique property. Particularly, its solvate containing four molecules of methanol and one of water crystallizes as a single enantiomer from the racemic solution when seeded with optically pure crystals. To date, the only drawback of the PTTCa resolution has been the lack in the literature of an efficient direct racemization method. According to the well-known procedures the PTTCa racemization rather may be made after its hydrolysis to pantolactone, which could be then racemized and reused in (*R*,*S*)-PTTCa synthesis.[7] Such a process, however, unreasonably elongates the whole technology. Fortunately, an effective procedure for direct PTTCa racemization has been developed in our laboratory and hence allowing to overcome the problem.

Considering these facts we have undertaken an attempt to develop an advantageous technology of calcium (*R*)-pantothenate via direct resolution of the racemate. Since the research has been carried out in co-operation with Grodzisk Pharmaceutical Works Polfa Ltd., the results obtained in the laboratory have been subsequently realized in industrial scale reactors (up to 3 m^3), with considerable scale-up factors (crystallization 1500, racemization 15000).

Results and Discussion

Crystalline calcium pantothenate forms a number of polymorphs and solvates, depending on the solvent and temperature applied for its crystallization.[5b,8] Although the processes described allow separation of the enantiomers of calcium pantothenate, they suffer from some drawbacks when thoroughly analyzed from the industrial point of view.[5] Since the PTTCa crystallizes as a methanol−water (4:1) solvate, the starting solution must contain some water, with the minimum level depending on the PTTCa concentration. For typical PTTCa concentration of 30%, the solution should contain at least 0.9% of water. The amount of water employed in the described processes was slightly over the minimum to achieve satisfactory yield of the product, since an increase of water content simultaneously increases the PTTCa solubility. We have found the process with such low water concentration to be, however,

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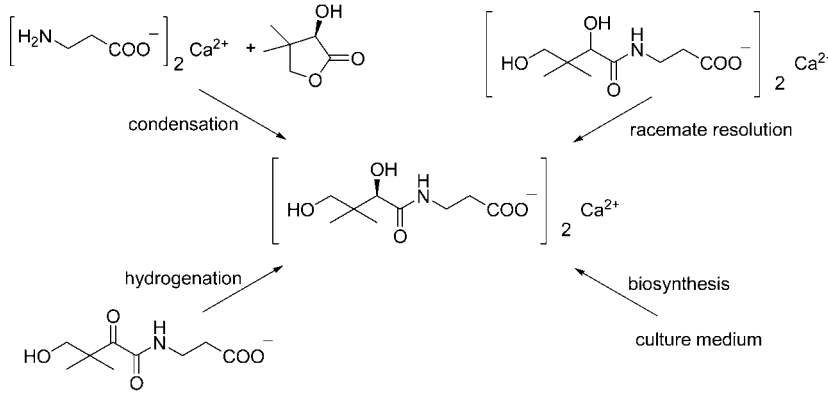
Scheme 1. **Methods of calcium (*R*)-pantothenate synthesis.**



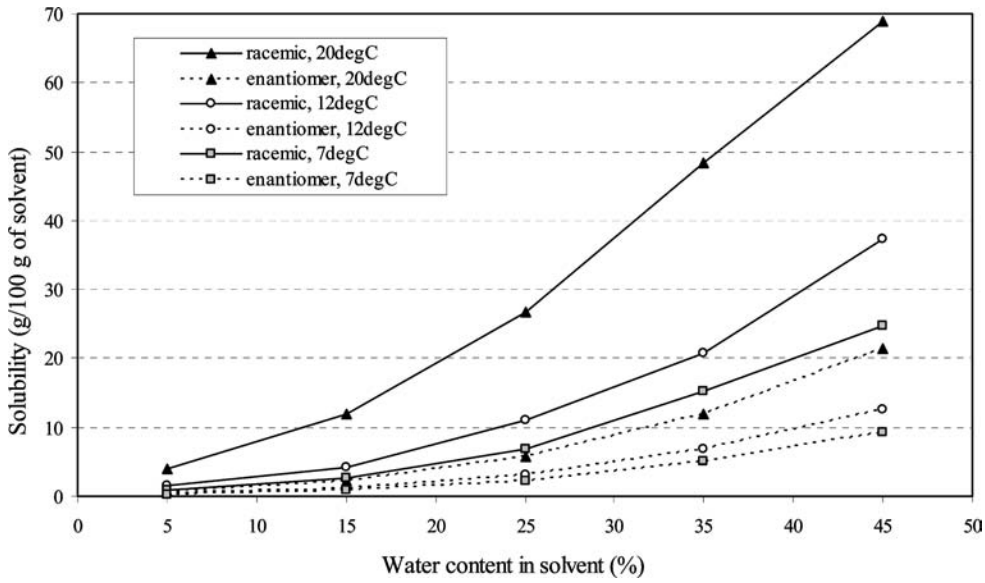


Figure 1. **Solubility of enantiomerically pure and racemic calcium pantothenate as a function of temperature and water content in the solvent.**

difficult to control because of at least two reasons. First, the crystallization rate is relatively high; thus, the optimal time, when the precipitate should be removed from the mother liquor is relatively short, since the second enantiomer begins to crystallize nearly immediately. It means that even a little delay in crystal separation can cause considerable deterioration of the product quality. Second, the initial solution is highly presaturated so spontaneous crystallization may occur, especially if there is a delay between the solution preparation and seeding with the proper crystal form. In case of low water concentration not only does the methanol−water solvate crystallize, but also an α-form of PTTCa may crystallize from the mother liquor.[9] The latter crystal form causes rapid crystallization with a significant thermal effect (increase of temperature by a few degrees has been observed). In both cases an optically inactive precipitate is a natural result.

As can be seen, even from a brief analysis as well as from our preliminary results an extraordinary accuracy is required to realize the literature process successfully, and even little disturbances in the conditions may cause failure in the quality of the product. Hence, we have examined a number of factors influencing the process to find the optimal conditions suitable for a large-scale procedure.

We have found the water content in the solution to be the most important factor determining the crystallization. Studies on the PTTCa solubility showed that high water content is more advantageous for the resolution process. The difference in solubility between optically pure and racemic PTTCa increases with an increase of water content in the solvent (Figure 1), thus offering a better yield of single enantiomer crystallization. Moreover, the general increase of solubility enables carrying out the process at a higher PTTCa concentration that results in higher total output of the product in a single step.

During our work we have found that optimal water content is between 20 and 30%. An increase in water level, when compared to the literature data (1−3%),[5] prevents the spontaneous crystallization of the α-form of PTTCa and enables application of ∼30% of a supersaturated PTTCa solution in methanol−water mixture as a starting material. Solutions of higher PTTCa concentration are difficult to operate because of their high viscosity. The starting solution may be easily prepared by dissolving the amorphous (*R*,*S*)-PTTCa in water, then adding

(9) The α form is the thermodynamically most stable form of PTTCa; it crystallizes as needles from methanol as well as other solvents. In contrary, PTTCa water−methanol solvate (PTTCa·4MeOH·H_2O) crystallizes as prisms. Those and other crystal forms of PTTCa have already been described in literature.[5b,8]

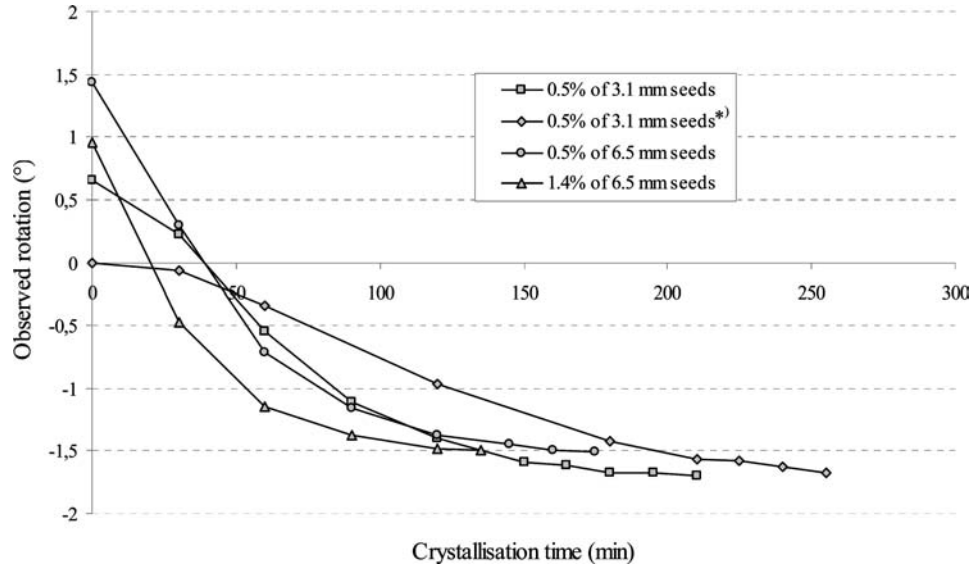


Figure 2. **Observed rotation of PTTCa mother liquor versus time for various amounts and sizes of seeds. All experiments were run at 8 °C, with the starting solution containing 30% of PTTCa and 25% of water. (*Starting from racemic PTTCa.)**

the desired amount of methanol, maintaining at 35−40 °C for ∼15 min. However, before seeding with a single enantiomer solvate, the solution must be filtered to remove traces of the PTTCa α-form that always remains as a fine suspension. Relinquishment of this filtration results in uncontrolled crystallization of the PTTCa α-form during cooling or standing, whereas the filtered solutions could be stored for at least 18 h at room temperature.

The thus prepared solution can be then seeded with a single enantiomer solvate to start the crystallization. The crystallization rate depends mainly on four factors: temperature, seeding particle distribution, the amount of the PTTCa in the starting solution, and the enantiomeric excess of the PTTCa. The process has been easily monitored by measuring the optical activity (observed rotation) of the mother solution. We have found that optimally it should be carried out at 8 °C, while the crystallization is completed in ∼3 h. Increasing the temperature up to 12 °C causes the process to be twice as long. Decreasing the temperature obviously increases the crystallization rate, thus curtailing the process. Such an alternation makes, however, no advantage since spontaneous crystallization of the second enantiomer occurs rapidly, thus decreasing the optical purity of the crystals. To complete the crystallization within 3 h, 0.5% of well-ground solvate has been typically used as seed crystals (amount calculated on PTTCa in solution, 6.5 μm average size). The amount of seed crystals can be even decreased to 0.1% with no change in the crystallization rate, if the solvate micronized in a jetmill (3.1 μm average size) has been used. The optical activity of the starting solution also influences the crystallization rate. The higher the optical activity of the solution, the higher the crystallization rate at the beginning; however, the conditions applied enable completion of the process in ∼3 h even, when starting from the racemic solution (Figure 2).

The optimal conditions, i.e. crystallization temperature 8 °C, PTTCa and water content in solution 28−31% and 23−26%, respectively, and 3 μm seeding (0.1% calculated on PTTCa) has been therefore applied in the industrial scale process. Thirteen batches for (*R*)- and 12 batches for (*S*)-PTTCa have been run, giving (*R*)- and (*S*)-enantiomers alternatively (26−33% yield of crystallization in a single step). The (*S*)-PTTCa has been racemized in 5 batches in the recycling loop (83−93% yield of racemization in a single step) (Scheme 2). Product amounts and optical rotation received from some batches is shown in Table 1. The consumption of raw material was 1.2 kg (*R*,*S*)-PTTCa for 1 kg (*R*)-PTTCa, the overall yield 83%, quality in compliance with the European Pharmacopoeia (Ph. Eur.) and the United States Pharmacopoeia (USP).

Special care should be taken only with the preparation and handling of starting solution and seeding. Since the succeeding batches are run without cleaning of the reactors, the filtration off the PTTCa α-form is extremely important to ensure proper mixture behavior during the crystallization. The solvate crystals used as seeding must be stored wet at low temperature, i.e. under 5 °C. At higher temperatures slow-phase metamorphosis occurs, resulting in the appearance of the α-form.[9]

The direct racemization of the biologically inactive (*S*)-PTTCa is critical for the economic effectiveness of the whole process. Although such a process has already been described in the literature,[10] we have found the conditions presented difficult to repeat. In particular, we have never succeeded in (*S*)-PTTCa racemization with calcium methoxide in boiling methanol.

Application of sodium methoxide indeed allows to racemize (*S*)-PTTCa under the reflux of methanol as described, due to the difference in solubility between respective pantothenates but not due to the different basic properties of calcium and sodium methoxides. Contrary to sodium pantothenate, calcium pantothenate is only slightly soluble in methanol so that at reflux the racemization observed is negligible. The application of sodium methoxide is unfortunately inconvenient for technological purposes, since sodium must be removed before (*R*,*S*)-PTTCa crystallization.

(10) Okuda, N.; Kuniyoshi, I.; Kamada, M.; Nakagawa, K. (Daiichi Seiyaku Co., Ltd.). FR Patent 1,524,617, 1968; *Chem. Abstr.* **1969**, *70*, 58291g (for corresponding Japanese patent).

Scheme 2. **Block diagram of the technological process**

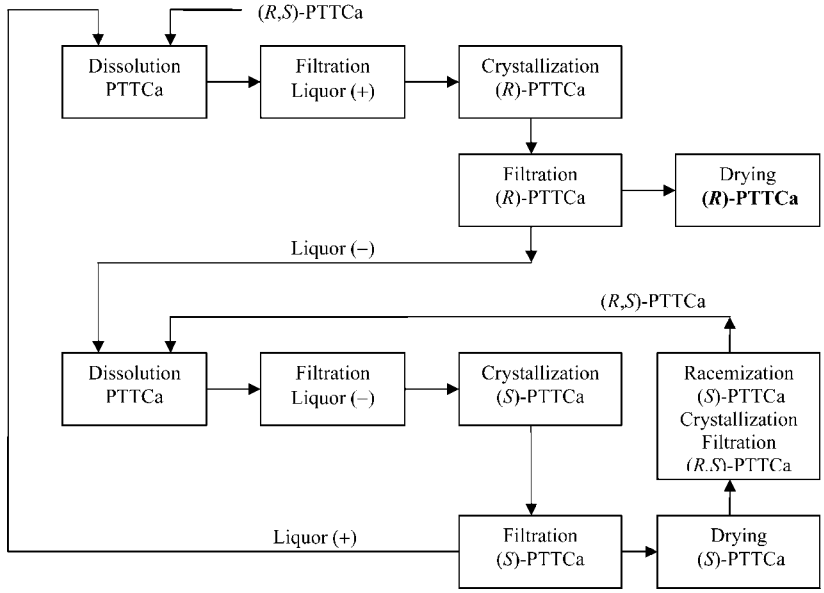


Table 1. **Product amounts and specific rotation obtained from some batches of the industrial process**

	R)-PTTCa		*S*)-PTTCa		*R*,*S*)-PTTCA	
batch no.	(kg)	$[\alpha]_D$ (deg)/ee (%)	(kg)	$[\alpha]_D$ (deg)	(kg)	$[\alpha]_D$ (deg)
		Fractional Crystallization of (*R*,*S*)-PTTCa (690−765 kg per batch)				
1	198	+26.5/99.6	195	−25.8		
2	212	+25.8/97.0	203	−23.8		
12	195	+26.8/100	227	−23.4		
13	228	+26.0/97.7	−			
		Racemization of (*S*)-PTTCa (300 kg per batch)				
1					258	−0.5
3					248	−1.2
5					254	−0.7

After solving some technological problems we have found the conditions for the quantitative racemization of (*S*)-PTTCa directly with calcium methoxide as a base. Calorimetric curve for (*S*)-PTTCa suspension in methanolic calcium methoxide exhibits an endothermic peak at 80−100 °C, certainly being a result of the simultaneous dissolving/racemization process (Figure 3).

Effective racemization can therefore be carried out in substantially anhydrous conditions, at above 90 °C, which means that the reaction proceeds under elevated pressure. The necessity of water absence is obvious since it causes calcium methoxide decomposition and irreversible hydrolysis of PTTCa in basic as well as acidic conditions (Scheme 3). Elevated temperature also causes partial decomposition of PTTCa even in the absence of water, but in this case the process is reversible; thus, cooling down the mixture and maintaining it at room temperature allows recovery of the compound in high yield.

We have found that to perform the reaction quantitatively and to recover ∼90% of the starting material the reaction conditions should be as follows. The water content in methanol has to be not higher than 0.04%; exceeding this value up to 0.5% increased the PTTCa decomposition by 10−15% (Figure 4). Therefore, to keep the water level reasonable in the reaction mixture, the (*S*)-PTTCa used has to contain not more than 0.3% of water. However, the water content in the product from the optical resolution process was always not lower than 2.9% since it has been a solvate containing four molecules of methanol and one molecule of water. Therefore, the starting material for racemization must be dried to attain the amorphous, water-free compound.

Another problem has been the behavior of the reaction mixture during the first part of racemization. The dried (*S*)-PTTCa used for racemization has been an amorphous form that readily dissolved in methanol before the reaction. However, during heating up, the α-form of (*S*)-PTTCa crystallized rapidly from the solution, causing problems with stirring and heat transfer. A powerful stirrer had to be used to ensure that all the suspension was stirred to avoid local overheating near to the reactor's surface. This is important, since the decomposition of PTTCa has been found to be irreversible in the temperature range around 120 °C, even in the absence of water. The reason for such a phenomenon has been the further decomposition of β-alanine calcium salt to form ammonia and the respective acrylate, which polymerized in the reaction conditions. As a result, a considerable increase of the reaction mixture viscosity as well as a decrease in β-alanine concentration have been observed. Excessive elongation of the reaction time caused the problems mentioned to appear even at 110 °C. Therefore, the time of heating the reaction mixture should be curtailed to the minimum, the temperature of the heating medium should be near to but not exceeding 90 °C, and the mixing has to be effective enough to prevent local overheating. At around 90 °C the reaction mixture has become homogeneous again due to racemization that has started at this temperature, transforming the slightly soluble (*S*)-PTTCa into much better soluble racemic PTTCa (Figure 3). Typically, the time of heating the suspension to 90 °C has been in the range of 30−60 min, and the racemization at 110 °C has been carried out for further 1.5 h. The racemized PTTCa with the 84−90% yield has been recycled to the resolution loop.

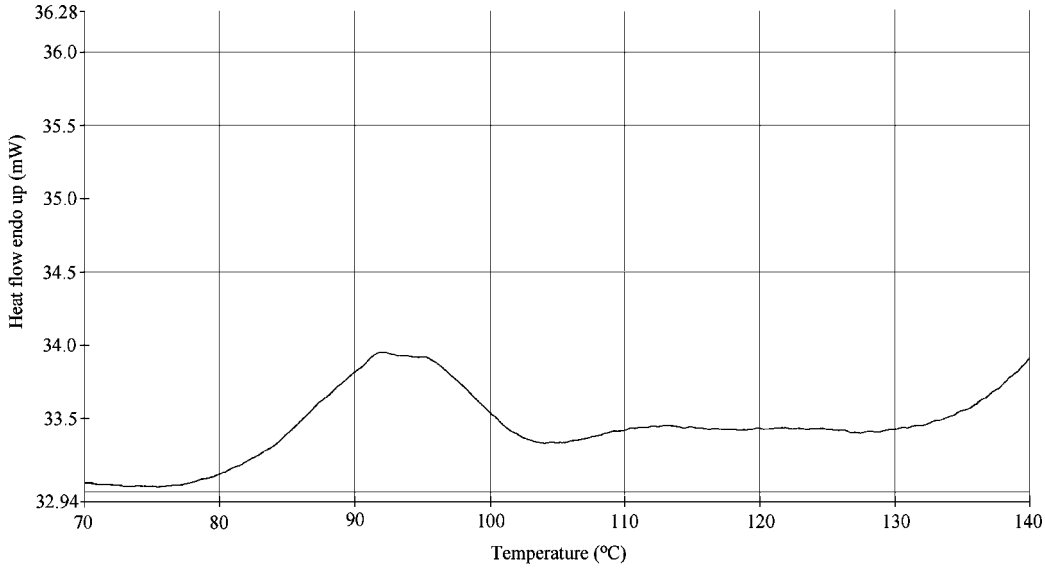
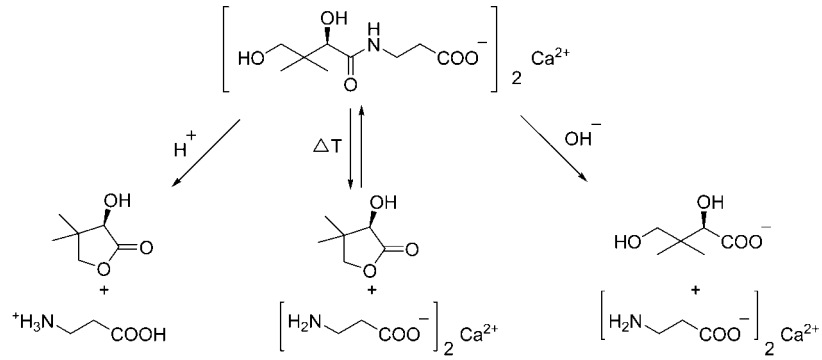


Figure 3. **Calorimetric curve for (*S*)-PTTCa suspension in methanolic calcium methoxide. Unsubtracted heat flow endo up (mW): Steps: (1) hold for 1:0 min at 25.00 °C, (2) heat from 25.00 to 150.00 at 10.00 °C/min.**

Scheme 3. **Reversible and irreversible decomposition of PTTCa under various conditions**



Conclusions

The complete technology of (*R*)-PTTCa including racemate resolution via selective crystallization of a single enantiomer and direct racemization of biologically inactive (*S*)-enantiomer in the recycling loop has been elaborated. A self-controlling resolution process consisted of the alternate crystallization of (*R*)- and (*S*)-enantiomers, in a methanol−water solvent system with high content of the later. The (*S*)-PTTCa racemization process was catalyzed by calcium methoxide in dry methanol at elevated temperature under pressure. The complete technology has been successfully scaled up in 3 m^3 reactors with an overall yield 83% of (*R*)-PTTCa (based on (*R*,*S*)-PTTCa used) and quality in compliance with Ph. Eur. and USP.

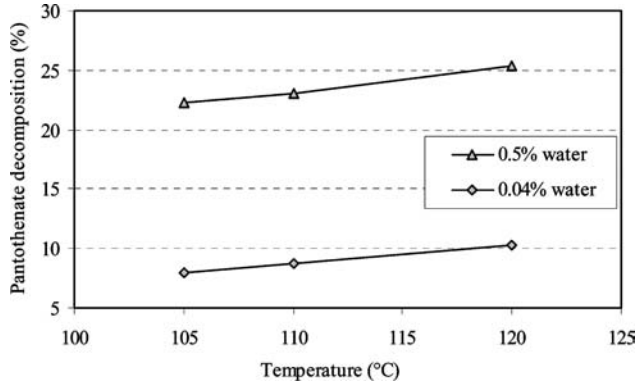


Figure 4. **Decomposition of PTTCa during racemization as a function of temperature and the water content in methanol used for reaction.**

Experimental Section

Commercially available solvents and reagents were used without further purification. Calcium (*R*,*S*)-pantothenate was supplied by Grodzisk Pharmaceutical Works Polfa Ltd. Water and calcium content were determined by Karl Fisher method and complexometric titration, respectively. Optical rotation was measured on an Optical Activity Ltd. automatic polarimeter. Determination of the crystals particle size distribution was performed with Malvern Instruments Ltd. automatic particle fraction analyzer. Calorimetric analysis has been carried out with Perkin-Elmer PYRIS 1 calorimeter.

Separation of Calcium Pantothenate into Optical Isomers: Laboratory Procedure. *1. Starting Cycle.* Water (232.0 g) and methanol (350.0 g) were added to 300.0 g (0.629 mol) of racemic PTTCa. The mixture was then maintained at 35 °C until PTTCa dissolved (∼15 min). The insoluble material was separated by pressure filtration, washed twice with 40 cm^3 (31.6 g) of methanol, and the washes were combined with the mother liquor. The solution obtained (982 g, water content 24.0%, PTTCa content 29.7%) was transferred to a 2 dm^3 reactor, cooled to 8 °C with stirring (Bola-Stirrer shafts with one rigid

paddle, 300 rpm), and seeded with 1.5 g (0.003 mol) of calcium (*R*)-pantothenate solvate suspended in 3 g of methanol. Samples were taken out and crystallization of (*R*)-PTTCa was monitored by measurement of the observed rotation of the mother liquor. After 175 min (when α_0 reached −1.51°) the precipitate was filtered off, washed twice with 40 cm^3 (31.6 g) of cold methanol, and dried at room temperature under reduced pressure (20 hPa). Obtained was 81.7 g of pure calcium (*R*)-pantothenate, having $\alpha_D = +27.0°$. The washes were concentrated and combined with the mother liquor to give 833 g of PTTCa solution (water content 25.6%, PTTCa content 25.1%, $\alpha_0 = -1.42°$).

2. Repeatable Cycle. (*R*,*S*)-PTTCa (89.0 g, 0.187 mol) was added to the mother liquor from the previous cycle. The suspension was then maintained at 35 °C until PTTCa was dissolved (∼15 min) and purified by pressure filtration as described above. The solution obtained (986 g, water content 26.09%, PTTCa content 30.2%, $\alpha_0 = -1.22°$) was transferred to a 2 dm^3 reactor, cooled to 8 °C with stirring, and seeded with 2.4 g (0.005 mol) of calcium (*S*)-pantothenate solvate suspended in 4.8 g of methanol. Samples were taken out as in the starting cycle, and crystallization of (*S*)-PTTCa was monitored by measurement of the observed rotation of the mother liquor until the α_0 reached +1.5°. The precipitate was then filtered off, washed twice with 40 cm^3 (31.6 g) of cold methanol, and dried at room temperature under reduced pressure (20 hPa). Pure calcium (*S*)-pantothenate (80.4 g), having $\alpha_D = -26.5°$, was obtained. The washes were concentrated and combined with the mother liquor to give 843 g of PTTCa solution (water content 26.1%, PTTCa content 25.8%, $\alpha_0 = +1.36°$). The dissolving−crystallization cycles were then repeated by alternate seeding with each of the enantiomers, resulting in calcium (*R*)-pantothenate in every odd cycle, and calcium (*S*)-pantothenate in every even cycle. Subsequent analyses of α_0, water, and Ca content are necessary for the proper amount of (*R*,*S*)-PTTCa, methanol, and water being added in every cycle, thus keeping the monitored values within the safe range.

Separation of Calcium Pantothenate into Optical Isomers: Technical Scale Procedure. Fifteen kg (31.5 mol) of calcium (*R*)-pantothenate and 750 kg (1577 mol) of calcium (*R,S*)-pantothenate along with methanol and water (1040 and 540 kg, respectively) were placed in a 3 m^3 reactor and heated up to 35 °C for ∼15 min to dissolve the solid. The insoluble material was immediately separated by pressure filtration with 2.5 kg of diatomite, washed with 40 dm^3 of water, and the washes were combined with the mother liquor. The solution obtained (∼2385 kg, water content ∼24%, PTTCa content 30.3%) was transferred to a 3 m^3 reactor, cooled to 8 °C, and seeded with 0.8 kg (1.68 mol) of calcium (*R*)-pantothenate solvate suspended in 1.6 kg of methanol. Samples were taken out, and crystallization of (*R*)-PTTCa was monitored by measurement of the mother liquor observed rotation. When the α_0 reached −1.5° the precipitate was filtered off in a centrifuge, washed with 50 dm^3 (39.5 kg) of methanol, and dried in a fluidized drier to give ∼200 kg of calcium (*R*)-pantothenate ($\alpha_D = +26.5°$). The washes were combined with the mother liquor to give 2050 kg of PTTCa solution to which 200 kg of (*R,S*)-PTTCa was added. The mixture was maintained at 35 °C for 15 min to dissolve the solid, then the PTTCa and water content were adjusted to 31% and 24% respectively. While still warm, the solution was pressure filtrated as previously described, transferred to the reactor, cooled to 8 °C, and seeded with 0.8 kg (1.68 mol) of calcium (*S*)-pantothenate solvate suspended in 1.6 kg of methanol. Samples were taken out, and crystallization of (*S*)-PTTCa was monitored by measurement of the mother liquor observed rotation. When the α_0 reached +1.5° the precipitate was filtered off in a centrifuge (without washing) and dried in a fluidized drier to give 200 kg of calcium (*S*)-pantothenate ($\alpha_D = -24°$). The dissolving−crystallization cycles were then repeated by alternate seeding with each of the enantiomers, resulting in calcium (*R*)-pantothenate in every odd cycle and calcium (*S*)-pantothenate in every even cycle. Subsequent analyses of α_0, water, and Ca content are necessary for the proper amount of (*R*,*S*)-PTTCa, methanol, and water being added in every cycle, thus keeping the monitored values within the safe range.

Racemization of Calcium (*S*)-Pantothenate: Laboratory Procedure. Due to the necessity of keeping the water and carbon dioxide concentration under the allowable level all reactions and operations must be carried out in the atmosphere or under the flush of an inert gas. Dry methanol (70 g) and calcium (0.330 g, 0.008 mol) were stirred with gentle heating until the hydrogen emission ceased and then refluxed for a while to make the calcium methoxide formation complete. The solution was cooled to room temperature and transferred to a 200 cm^3 pressure reactor (stainless steel with Bola-magnetic stirring bars, dumbbell-shape) containing dry, amorphous calcium (*S*)-pantothenate (35.3 g, 0.074 mol) and (*R*,*S*)-pantolactone (1.54 g, 0.003 mol). (Amorphous PTTCa can be obtained from the methanol−water solvate by heating it to 110 °C under 2.5 kPa for 1.5−2 h.) The reactor was closed and immediately placed in an oil bath heated previously to 110 °C. After the temperature and pressure in the reactor reached 105−108 °C and 0.30−0.32 MPa, respectively, the solution was mixed at these conditions for further 1.5 h. The reactor was then cooled to room temperature, and the transparent or slightly cloudy solution was transferred to a round-bottomed flask and stirred overnight. Water was added to the mixture to a final concentration of 3.5%, the pH was adjusted to 8−9 with acetic acid, and the solution was stirred with activated carbon for 20 min. The insoluble material was filtered off, and the clear solution was transferred to the reactor, cooled to 3 °C, and seeded with 0.24 g (0.0005 mol) of the (*R*,*S*)-PTTCa. Crystallization was then carried out at −13 °C for at least 12 h, the precipitate was filtered off and dried at 20−80 °C for 8 h under reduced pressure (20 hPa). Calcium (*R*,*S*)-pantothenate (41.3 g) that could be used as the starting material for the selective enantiomer crystallization was obtained.

Racemization of Calcium (*S*)-Pantothenate: Technical Scale Procedure. As in the laboratory procedure, all reactions and operations must be carried out in the atmosphere or under the flush of an inert gas due to the necessity of keeping the water and carbon dioxide concentration under the allowable level. Dry methanol (632 kg, 800 dm^3) and 3.6 kg (90 mol) of calcium were placed in a 3 m^3 reactor with jacket (heating with steam 140 °C) and refluxed for 0.5 h. After cooling the calcium

methoxide suspension to 20 °C, 300 kg (630 mol) of (*S*)-PTTCa was added to the reactor, and the mixture was quickly heated to 105−108 °C (heating with steam 180 °C). The racemization was carried out at 105−108 °C and pressure of 0.30−0.32 MPa for 1.5 h. The solution of racemic PTTCa was then cooled to 20 °C and maintained at this temperature for 20 h. Water was added to the mixture to a final concentration of 3.5%, the pH was adjusted to 8−9 with acetic acid, and the solution was stirred with activated carbon for 20 min. The mixture was filtered through a pad of diatomite, and the clear solution was transferred to another reactor, cooled to 3 °C, seeded with 1.4 kg of the (*R*,*S*)-PTTCa, and crystallized at −13 °C for 12 h. The precipitate was filtered off and dried in a fluidized drier to give 237 kg of amorphous calcium (*R*,*S*)-pantothenate that was further used as a starting material for the selective enantiomer crystallization.

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