47. Optical Resolution of (*RS*)-Pantolactone through Amide Formation

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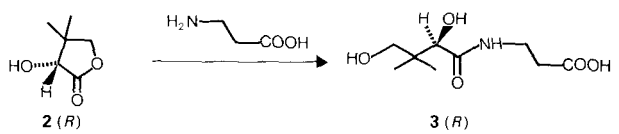
The optical resolution of (*RS*)-pantolactone (**1**) is carried out through formation of diastereoisomeric amides. These are separated by a single hot washing with CH_2Cl_2 or $CHCl_3$. The used asymmetric amine, (1*R*)-3-*endo*-aminoborneol (**4**), is readily accessible and can be recovered almost quantitatively after resolution.

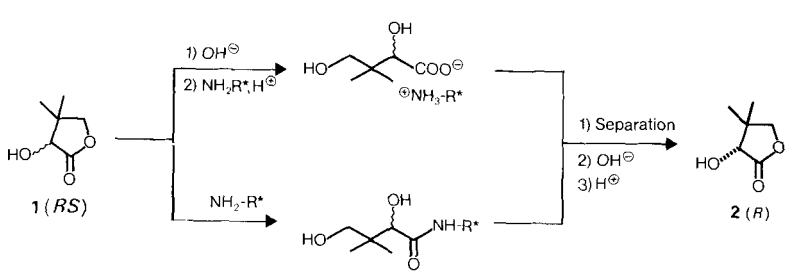
(+)-D-Pantothenic acid (**3**), a vitamin belonging to the B group, is obtained by condensation of β-alanine (or of its salts) with (−)-(*R*)-2-hydroxy-3,3-dimethyl-γ-butyrolactone (**2**), also named (*R*)-pantolactone *(Scheme 1)*.

Scheme 1

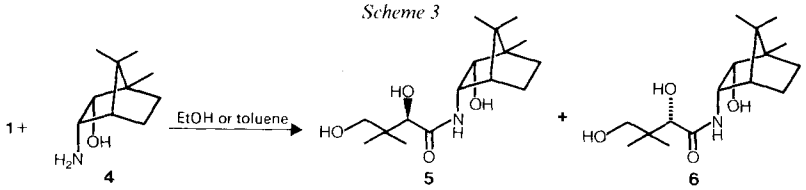


The required (*R*)-pantolactone (**2**) has been obtained either by asymmetric synthesis [1], by bioconversion [2], or by optical resolution of the racemic mixture **1**. Optical resolution is widely applied using the classic formation of diastereoisomeric salts obtained from **1** and optically active amines [3] [4] *(Scheme 2)*, the so called dehydroabietylamine being a reagent of choice [4]. From the same asymmetric amines and **1**, the diastereoisomeric amides can also be formed. Two examples are known in the literature, the separation with (−)-α-phenylethylamine [5] and with the earlier cited dehydroabietylamine [6] *(Scheme 2)*.

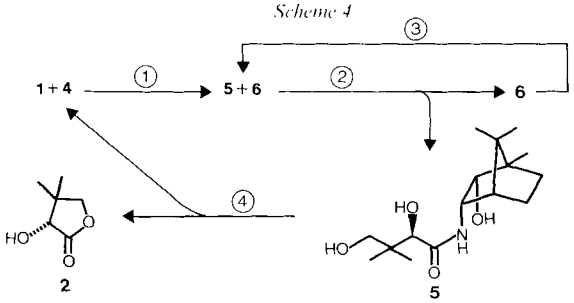
Scheme 2



Scheme 3



Scheme 4



① Formation of the epimeric amides **5** and **6** starting from lactone **1** and amine **4**.
② Separation of the two amides through washing.
③ Epimerisation of the undesired amide **6**.
④ Cleavage of the desired amide **5** into lactone **2** and amine **4**.

We wish to describe here a very effective optical resolution of (*RS*)-pantolactone (**1**) using (1*R*)-3-*endo*-aminoborneol (**4**) as asymmetric amine to form the two diastereoisomeric amides *(Scheme 3)*. This hydroxy-amine is technically readily accessible from natural D-camphor [7]; it shows a high stability and can be recycled almost quantitatively after the resolution.

This resolution is described in *Scheme 4;* it undergoes four steps.

Formation of the Diastereoisomeric Amides 5 and 6. – The (*RS*)-pantolactone (**1**) and (1*R*)-3-*endo*-aminoborneol (**4**) are refluxed in an organic solvent, EtOH and toluene being preferred, to give the amides **5**/**6** *(Scheme 3)*. The reaction actually is an equilibrium which one shifts by the use of a 30% excess of amine **4**. Thus, a yield of 95–97% of **5**/**6** can be obtained. On working up, 33–35% of unreacted **4** is recovered as hydrochloride.

Higher reaction temperatures (autoclave) lead to shorter reaction times but do not permit to reduce the excess of amine **4**, because of a negative influence on the equilibrium. The best results are obtained when the reaction mixture is allowed to stand at room temperature for 12 h after 90 min heating in toluene. Under these conditions, the yield of **5**/**6** rises up to 98–99%. The crude material **5**/**6** (white powder) contains no detectable impurity and can directly be used in the next step. Its $[\alpha]_D$ of +73.5 to +75° (*c* = EtOH) is in agreement with a 1:1 mixture (see below).

Separation of 5/6. – In order to find the best separation conditions, the physical properties and solubilities of the pure amides **5** and **6** obtained from **2** and (*S*)-pantolactone, respectively, were determined *(Table)*. The most polar solvents give unfavourable solubility ratios for **5** and **6**, but CH_2Cl_2, $CHCl_3$, and dioxane should be suitable for a separation. Indeed, a short and hot washing of pulverized **5**/**6** with CH_2Cl_2

Table. *Properties of the Amides* **5** *and* **6**

	M.p.	$[\alpha]_D^{20}$	Approximative solubility, in g/l at r.t.							
		(EtOH)	CH_2Cl_2	AcOEt	MeOH	EtOH	MeCN	Acetone	Dioxane	$CHCl_3$
5 (*R*)	180–181°	+125°	0.75	3.3	43	47	2.5	13	10	2.2
6 (*S*)	172–173°	+ 22.5°	9	25	125	130	14.5	115	120	40
Solubility ratio			12	7.6	2.9	2.8	5.8	8.8	12	18.8

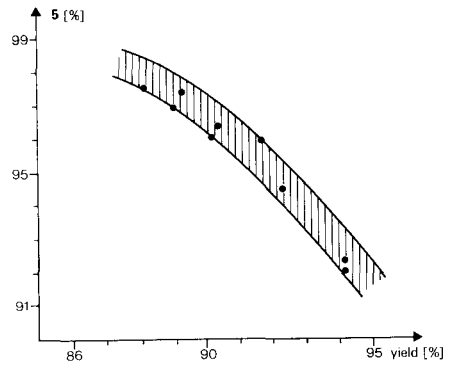


Fig. 1. *Separation of* **5**/**6**

leads to an effective separation of the two amides. The results are described in *Fig. 1*. One obtains, for example[1]), 89.5% of a 97.5:2.5 mixture **5**/**6** or 91.9% of a 96:4 mixture **5**/**6**, *etc. Fig. 1* also demonstrates a good reproduction of this separation for a laboratory procedure.

It is somewhat critical to evaluate the appropriate volume of CH_2Cl_2 to be used for a requested purity as it is dependent on the speed of the cooling and on the filtration temperature. As an example, a 100- to 190-ml volume of solvent is required for 10 g of **5**/**6**. This volume can be reduced by filtration at higher temperatures. $CHCl_3$ and dioxane, in spite of better solubility ratios, give worse results.

The purity of amide **5** is determined by its $[\alpha]_D$ *(Fig. 2)* on its m.p. *(Fig. 3)*.

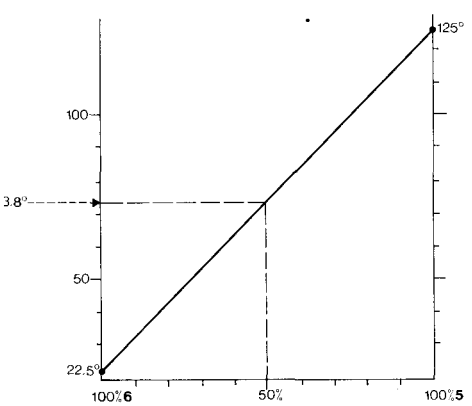


Fig. 2. *Specific rotation* $[\alpha]_D$ *(in °) of the* **5**/**6** *mixture.* $c = 2$, EtOH.

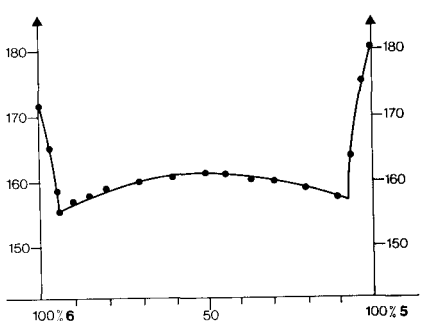
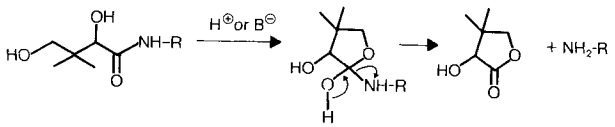


Fig. 3. *Melting-point diagram of the* **5**/**6** *mixture*

[1]) Yields refer to the quantity of amide **5** in the crude mixture **5**/**6**.

Cleavage Amide 5 to Lactone 2 and Amine 4. – It is known that amides of pantolactone (for example pantothenic acid and derivatives) are very sensitive to acidic or basic conditions. This is probably due to the primary OH end group which promotes an intramolecular hydrolysis *(Scheme 5)*. Therefore, the cleavage of amide **5** is carried out under acidic (5% HCl, $EtOH/H_2O$, 75°) or basic conditions (1.3 equiv. of NaOH,

Scheme 5

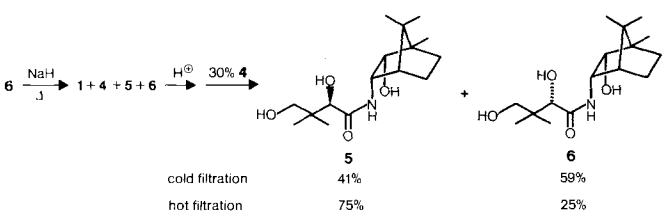


$EtOH/H_2O$, r.t.). In both cases, (*R*)-pantolactone (**2**) is isolated, after distillation, in at least 95% yield, and **4** is recovered as chlorohydrate in a nearly quantitative yield. No racemisation is observed; starting from pure amide **5**, the (*R*)-lactone **2** is obtained in a chemically and optically pure form (96–98% yield).

Epimerisation of Amide 6. – Amide **6** can be cleaved analogically to the (*S*)-pantolactone and the latter can be racemised by well-known methods. This method is somewhat tedious.

Better results are obtained on treatment of the amide **6** with a catalytic amount of a base (for example NaH). This leads to epimerisation of **6** as well as to cleavage of the resulting **5**/**6** yielding a mixture **1**/**4**/**5**/**6**. Recycling of this mixture, after neutralisation of the base and addition of the required 30% excess of amine **4**, gives, after cold filtration (see *Exper. Part*), **5**/**6** in ratio of 41:59. The unfavourable ratio **5**/**6** can be improved to 75:25 by a hot filtration. The epimerisation of **6** can also be combined with a new batch of amides obtained from **1**, leading to a 45:55 mixture **5**/**6** *Scheme 6* (see also *Exper. Part*), also suitable for the separation.

Scheme 6



We wish to thank Dr. *W. Arnold*, Dr. *L. Chopard* and Mr. *W. Meister* for the interpretations of spectroscopic data and Dr. *A. Dirscherl* for the determination of the microanalyses. The skilful technical assistance of Mr. *T. Mühlebach* is gratefully acknowledged.

Experimental Part

General. The reactions are monitored by TLC (SiO_2 plates, AcOEt; development: 0.2% $KMnO_4$ soln. and subsequent heating). The obtained products still contain some H_2O (0.5–1%) after drying; the reported data (weights, yields, rotations, and analyses) are corrected and refer to dry compounds. M.p. are determined in capillary tubes (*Büchi* apparatus, *Tottoli* type).

1. *(R)-2,4-Dihydroxy-*N*-[(1R)-2-*endo*-hydroxy-3-*endo*-bornyl]-3,3-dimethylbutyramide* (**5**). At 78°, (*R*)-pantolactone (**2**; 65.05 g, 0.5 mol) and (1*R*)-3-*endo*-aminoborneol (**4**; 110 g, 0.65 mol) are reacted for 3 h in 300 ml of abs. EtOH. To the cooled mixture, 300 ml of H_2O are added followed by conc. HCl (16–20 ml; pH *ca.* 1.8–2). EtOH is evaporated and H_2O added several times to the mixture. At the end, the volume amounts to 600–700 ml. The white powder is filtered, washed with 150 ml of H_2O, and dried at 80°/15 Torr and then at 80°/high vacuum to constant weight: 144 g (96.2%) of **5**, m.p. 179–180°. $[\alpha]_D^{20} = +124.1°$ (*c* = 2, EtOH). An anal. pure sample is obtained by crystallisation from EtOH/H_2O, m.p. 180–181°. $[\alpha]_D^{20} = +125°$ (*c* = 2, EtOH). IR (KBr): 3432, 3400, 1625, 1538. ^{1}H-NMR ((D$_6$)DMSO): 7.5 (*d*, *J* = 5, 1 H); 5.57 (*d*, *J* = 5.5, 1 H); 5.27 (*d*, *J* = 5, 1 H); 4.6 (*t*, *J* = 5.5, 1 H); 4.2–3.8 (*m*, 3 H); 3.5–3.1 (*m*, 2 H); 2–1.1 (*m*, 5 H); 0.95–0.72 (*m*, 15 H). MS: 299 (M^+). Anal. calc. for $C_{16}H_{29}NO_4$ (299.41): C 64.18, H 9.76, N 4.68; found: C 63.82, H 9.85, N 4.68.

2. *(S)-2,4-Dihydroxy-*N*-[(1R)-2-*endo*-hydroxy-3-*endo*-bornyl]-3,3-dimethylbutyramide* (**6**). Starting from (*S*)-pantolactone and **4**, **6** is obtained in almost quantitative yield under exactly the same conditions as described in *Exper. 1*. M.p. 172–173° (from EtOH/H_2O). $[\alpha]_D^{20} = +22.5°$ (*c* = 2, EtOH). IR (KBr): 3392, 1640, 1528. ^{1}H-NMR ((D$_6$)DMSO): 7.75 (*d*, *J* = 5.5, 1 H); 5.62 (*d*, *J* = 6, 1 H); 5.29 (*d*, *J* = 4.5, 1 H); 4.55 (*t*, *J* = 5.5, 1 H); 4.2–3.75 (*m*, 3 H); 3.53–3.1 (*m*, 2 H); 2–1.1 (*m*, 5 H); 1–0.75 (*m*, 15 H). MS: 299 (M^+). Anal. calc. for $C_{16}H_{29}NO_4$ (299.41): C 64.18, H 9.76, N 4.68; found: C 64.05, H 9.93, N 4.59.

3. *Mixture* **5**/**6** *in EtOH.* Starting from (*RS*)-pantolactone (**1**) and **4**, **5**/**6** is obtained as above (see *Exper. 1*). Yield 94–96%. M.p. 162–163°. $[\alpha]_D^{20} = +73.8$ to $+74.3°$, corresponding exactly to a 1:1 mixture of **5**/**6**. Anal. calc. for $C_{16}H_{29}NO_4$ (299.41): C 64.18, H 9.76, N 4.68; found: C 64.15, H 9.92, N 4.63.

4. *Recovering the Excess of* **4**. In all cases, the excess of **4** can be recovered as here described for the synthesis of **5**: The acidic aq. phase (obtained after filtration of **5**) is made basic (pH 11.5) by addition of a 28% NaOH soln. and extracted with CH_2Cl_2 (3 × 150 ml). The combined org. phase is dried (Na_2SO_4) and evaporated. The obtained oil is dissolved in 150 ml of Et_2O and **4**·HCl precipitated by addition of 2M HCl in Et_2O (*ca.* 90 ml). Filtration and drying (50°, high vacuum) yield 33.2 g of **4**·HCl, *i.e.* the full amount of the excess of **4** plus the non-reacted one. M.p. > 250°. $[\alpha]_D^{20} = +35.9°$ (*c* = 2, MeOH). Anal. calc. for $C_{10}H_{20}ClNO$ (205.73): C 58.38, H 9.80, Cl 17.23, N 6.81; found: C 57.94, H 9.69, Cl 16.92, N 6.88.

5. *Mixture* **5**/**6** *in Toluene.* At 110°, **1** (13 g, 0.1 mol) and **4** (22 g, 0.13 mol) are reacted for 1.5 h in 70 ml of toluene. The solvent is evaporated, the obtained paste triturated in 150 ml of H_2O with vigorous agitation, and the mixture made acidic (pH 1.5–2) by the addition of conc. HCl (5–10 ml). The product is filtered, washed with 60 ml of H_2O, and dried at 80°/15 Torr, then at 80°/high vacuum, to constant weight: 28.6 g (95.7%) of **5**/**6**, m.p. 162–163°. $[\alpha]_D^{20} = +73.9°$ (*c* = 2, EtOH), corresponding exactly to a 1:1 mixture of **5**/**6**. Anal. calc. for $C_{16}H_{29}NO_4$ (299.41): C 64.18, H 9.76, N 4.68; found: C 64.15, H 9.92, N 4.63.

The excess of **4** can be recovered exactly as described in *Exper. 4*.

6. *Separation of* **5**/**6**. The mixture **5**/**6** obtained in *Exper. 3* or *5* (10 g, 0.0167 mol of each epimer) is refluxed in 120 ml of CH_2Cl_2 for 20 min. The mixture is cooled under stirring to 25–27°, filtered, and dried (80°/high vacuum, 2 h): 4.42 g (88.4%) of product, m.p. 175–179°. $[\alpha]_D^{20} = +122.5°$ (*c* = 2, EtOH), corresponding to a 97.6:2.4 ratio of **5**/**6**.

7. *Acidic Cleavage of* **5**. At 75°, **5** (20 g, 0.0669 mol; $[\alpha]_D^{20} = +122°$, corresponding to a 97:3 ratio of **5**/**6**) and 18 g of conc. HCl (*ca.* 0.2 mol) are reacted in 120 ml of EtOH/H_2O 1:1 for 2.5 h. The EtOH is evaporated and the aq. phase extracted with CH_2Cl_2 for 8 h. After drying (Na_2SO_4) and evaporation, 9.62 g of crude product are obtained. Distillation (bulb to bulb, 80–90°/0.1 Torr) yields 8.31 g (96%) of **2**, m.p. 90–91°. $[\alpha]_D^{20} = -49°$ (*c* = 2, H_2O) corresponding to a 97:3 ratio of the two enantiomeric lactones. All other data are identical to those of an authentic sample.

The amine **4** is recovered from the acidic aqueous phase as described in *Exper. 4*: 13.5 g (98% recovery) of **4**·HCl.

8. *Basic Cleavage of* **5**. At 30°, **5** (10 g, 0.0334 mol: m.p. 181°, $[\alpha]_D^{20} = +125°$, pure compound) is dissolved in 90 ml of EtOH/H_2O 5:4. A soln. of 1.54 g of NaOH (15% excess) in 10 ml of H_2O is then added. The mixture is heated

at 40° for 1 h. EtOH is evaporated and H_2O added in order to maintain the volume. The pH of the soln. is adjusted to 11.5 and the amine extracted with CH_2Cl_2 (3 × 40 ml). The aq. phase is made acidic (pH 1.5–2) by addition of conc. HCl (6–8 ml) and the product extracted with CH_2Cl_2 for 8 h. After drying (Na_2SO_4) and evaporation, a bulb-to-bulb distillation of the crude material (90°/0.1 Torr) yields 4.21 g (96.8%), of **2** m.p. 91–92°. $[\alpha]_D^{20} = +50.9°$ ($c = 2$, H_2O), optically pure.

The amine **4** is recovered by precipitation of **4**·HCl as described in *Exper. 4:* 6.65 g (96.8% recovery) of **4**·HCl.

9. *Epimerisation and Recycling of* **6**. For 1 h, 29.94 g (0.1 mol) of **6** (containing some **5**) and 131 mg (55% in oil, 0.003 mol) of NaH are refluxed in 150 ml of toluene. After neutralization of the base with 570 mg (min. 0.003 mol) of TsOH·H_2O, 13 g (0.1 mol) of **2** and 27.07 g (0.16 mol, 30% excess) of **4** are added to the mixture, which is then refluxed for 90 min. The solvent is evaporated, the obtained paste triturated in 350 ml of H_2O with vigorous agitation, and the mixture made acidic (pH 1.5–2) by the addition of conc. HCl (12–24 ml). The product is filtered, washed with 100 ml of H_2O, and dried at 80°/15 Torr, then at 80°/high vacuum, to constant weight: 56.9 g (95.1%) of **5/6**, m.p. 161–163°. $[\alpha]_D^{20} = +68.7°$ ($c = 2$, EtOH), corresponding to a 45:55 ratio of **5/6**. Anal. calc. for $C_{16}H_{29}NO_4$ (299.41): C 64.18, H 9.76, N 4.68; found: C 64.25, H 10.02, N 4.71.

The excess of **4** is recovered from the acidic aq. phase as described in *Exper. 4:* 14 g (97% recovery) of **4**·HCl.

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