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A rational synthesis of *trans*-2-(3-phenylprop-1-yl)cyclohexylamino-2-oxazoline enantiomers

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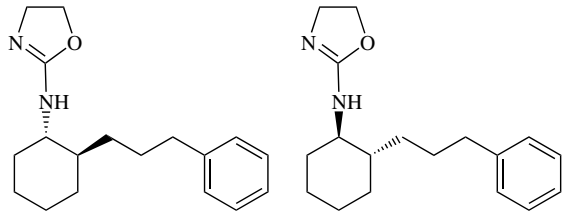
Abstract—A novel method has been developed for the synthesis of the optical antipodes of *trans*-2-(3-phenylprop-1-yl)cyclohexylamino-2-oxazoline **1** from racemic *cis*-octahydrocoumarin **4** instead of cyclohexene oxide **2**, because the synthesis of **1** from compound **2** was unsuccessful. Compound **4** was resolved with 1-phenylethylamine enantiomers. Although the preparation of this oxazoline from cyclohexene oxide is known, the resolution and the enantiomeric enrichment step have not been described.

1. Introduction

One of the most important methods for preparing a homochiral compound with a more sophisticated structure is asymmetric synthesis from homochiral starting materials.[1] The aim, both in industrial practices and in research, is to start from an appropriate enantiomer of the first chiral compound in the synthetic route. However, if only the racemic compound is available, we have to solve the problem of the separation of enantiomers.[1–5]

The synthesis of racemic *trans*-2-(3-phenylprop-1-yl)cyclohexylamino-2-oxazoline **1** has already been reported.[6] It was shown that 2-amino-2-oxazolines are the subtypes of selective α_2-adrenoreceptor agonists. The starting material for this process is cyclohexene oxide **2**, but the separation of a racemic product to its enantiomers failed, that is, if we like to prepare the enantiomers in this way, the resolution of racemic intermediates or racemic products should be addressed, because the separation of the isomers of the possible intermediates has yet to be carried out.

The efficient synthesis of the optical isomers of compound **1** [hereafter (*S*,*R*)-(+)- and (*R*,*S*)-(−)-oxazoline] is crucial for preparing 1,2-disubstituted cyclohexane derivatives based on the resolution of easily resolvable enantiomers (Fig. 1).



(1*S*,2*R*)-(+)-**1** (1*R*,2*S*)-(-)-**1**

Figure 1. The target enantiomers of *trans*-2-(3-phenylprop-1-yl)cyclohexylamino-2-oxazoline.

Therefore, we aimed to find a chiral starting material, which was suitable for building up the enantiomers of **1**. Among the possible compounds, ethyl 2-oxocyclohexanecarboxylate **3** and octahydrocoumarin **4** were investigated, but only compound **4** proved to be a suitable homochiral starting material (Fig. 2).

Octahydrocoumarin **4** is commercially available and the absolute configurations of a *cis*-octahydrocoumarin enantiomer is already known.[7] Therefore, the rational synthesis of the pure enantiomers of *trans*-2-(3-phenylprop-1-yl)cyclohexylamino-2-oxazoline (**1**) has been developed in our laboratory starting from the isomeric mixtures of compound **4**, as follows.

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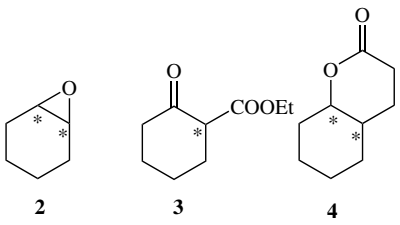


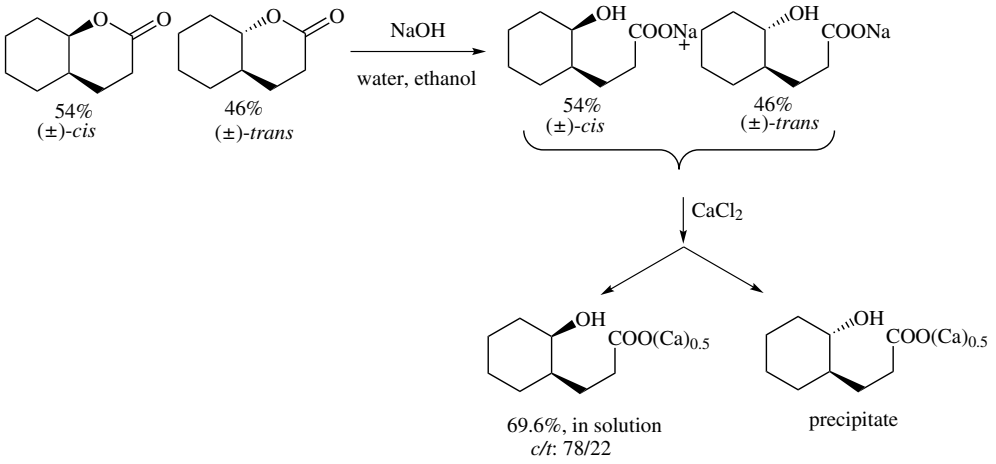
Figure 2. Compounds considered as starting materials for the synthesis of product **1**.

2. Results and discussion

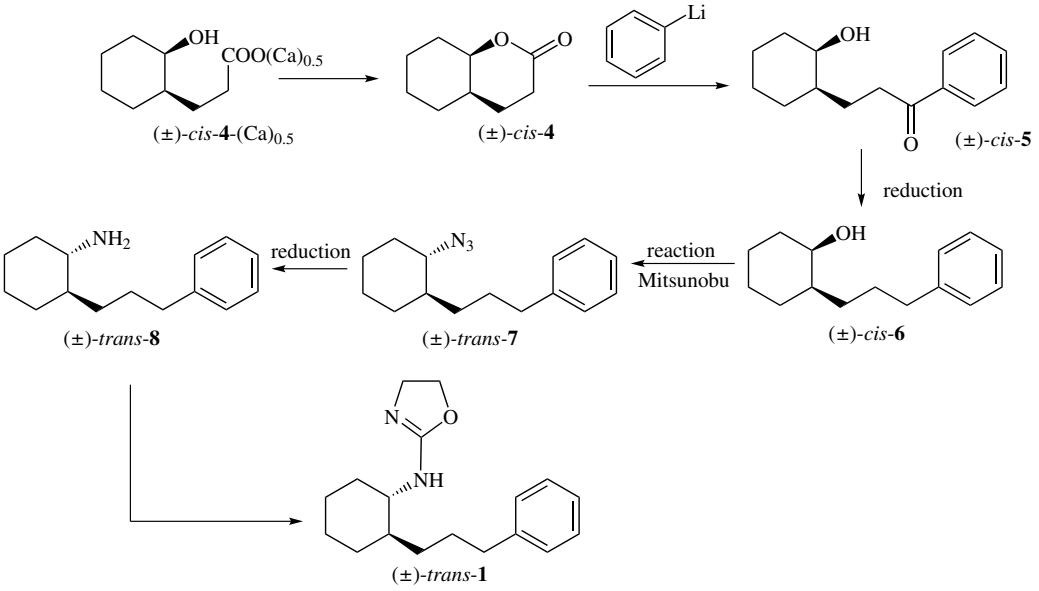
The racemic mixture of *cis*/*trans*-octahydrocoumarin (*cis*/*trans*-**4**) was separated to *cis* and *trans* fractions based on the different solubilities of their Ca-salts (Scheme 1). The commercially available *cis*/*trans*-**4** mixture (*cis*/*trans* = 54/46) was converted into the sodium salt with aqueous NaOH, then it was reacted with $CaCl_2$ in ethanolic solution. The less soluble Ca-salt enriched in the *trans*-isomer was precipitated and from the mother liquor the *cis*-lactone was separated with 78% purity and 60% yield calculated to the amount of the mixture.

According to our new method, from *cis*-**4**, racemic *trans*-**1** compound was obtained in good yield (Scheme 2).

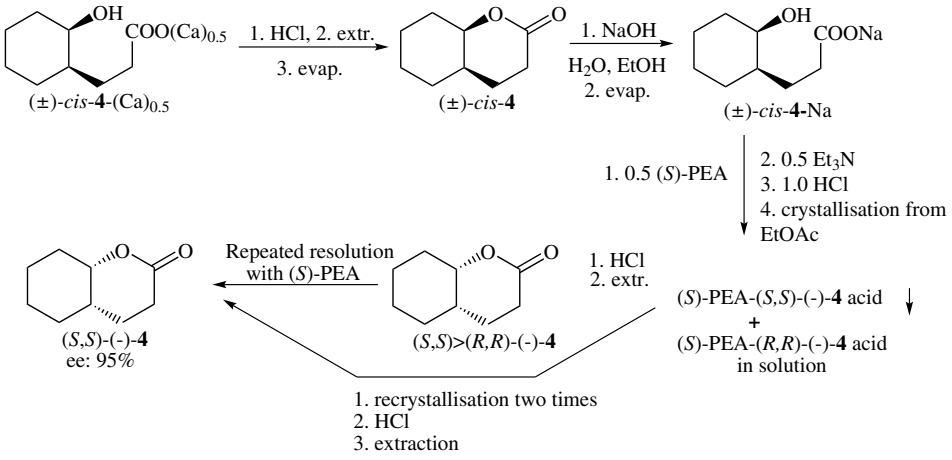
The resolution of (±)-*cis*-lactone-**4** (enriched in the *cis*-isomer) was carried out with (*S*)- and (*R*)-1-phenylethylamines PEA, respectively. Further purification of the obtained enantiomeric mixtures was performed by repeated resolution and by repeated recrystallization. Using this enantiomer separation procedure, (*S*,*S*)-*cis*-**4** was obtained in 95% ee and 28% yield (related to the enantiomer content of the (±)-*cis*-**4**) (Scheme 3). (*S*,*S*)-Lactone-**4** enantiomers



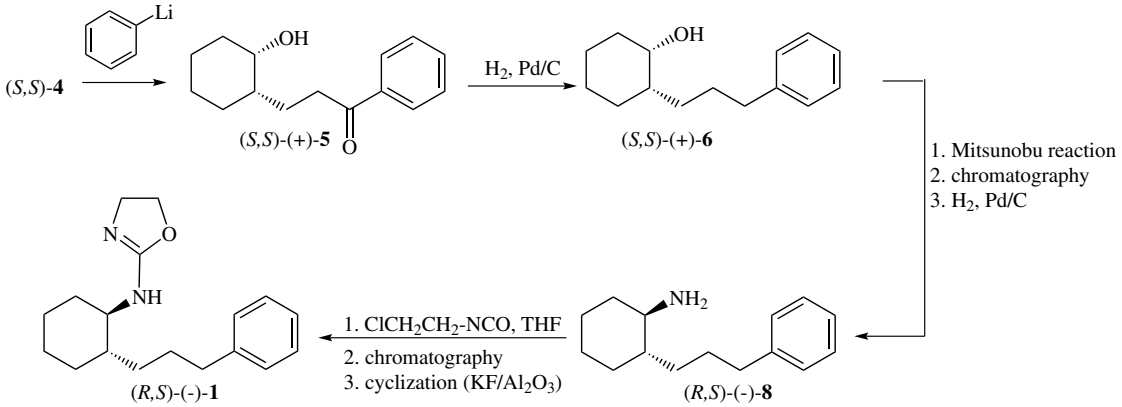
Scheme 1. The separation of (±)-*cis*,*trans*-octahydrocoumarin to *cis* and *trans* fractions, based on the solubility differences of their hydroxy acid Ca-salts.



Scheme 2. Synthetic route to (±)-*trans*-**1** from (±)-*cis*-**4**.



Scheme 3. Resolution of (±)-*cis*-**4**.



Scheme 4. Synthesis of (*R*,*S*)-2-(3-phenylprop-1-yl)cyclohexylamino-2-oxazoline **1**.

were separated with a yield of 28% and the (*R*,*R*)-lactone-**4** enantiomers were separated with a yield of 25% (this value refers to the enantiomer content of the racemic *cis*-lactone).

Optically active *cis*-**4** was reacted with phenyllithium (Scheme 4) to yield the ketone intermediate (*S*,*S*)-(+)-**5**. In this reaction, we observed an increase in the ee and de, respectively. Starting from (*S*,*S*)-**4** (ee: 94.3%, *cis*: 90.2%), (*S*,*S*)-**5** (ee: 94.0%, *cis*: 96.8%) was obtained in 82% yield, from (*R*,*R*)-**4** (ee: 94.5%, *cis*: 94.3%), (*R*,*R*)-**5** (ee: 96.1%, *cis*: 96.2%) was obtained in 81% yield.

The carbonyl group of (*S*,*S*)-**5** and (*R*,*R*)-**5** was hydrogenated to a methylene one over a 10% Pd/C catalyst (Selcat Q),[8] in methanol, at ambient temperature. From (*S*,*S*)-**5**, (*S*,*S*)-(+)-**6** was obtained in 91% yield, from (*R*,*R*)-**5**, (*R*,*R*)-(−)-**6** was produced in 96% yield.

These *cis*-**6** alcohol enantiomers were then converted to the *trans*-azide enantiomers by a Mitsunobu reaction. Since the inversion was not accompanied by racemization and the further steps did not attach any asymmetric carbon atoms, the purity of the oxazoline enantiomers became higher than the ee of **5**. Next, the *trans*-azide enantiomers were transformed to *trans*-**8** amines by catalytic hydrogenation over palladium on carbon and *trans*-**8** enantiomers were converted to carbamide derivatives using 2-chloroethyl isocyanate in THF. Finally, the product was cyclized in the presence of KF catalyst obtaining the corresponding **1** oxazoline enantiomers (Scheme 4 shows the synthesis of the (*R*,*S*)-**1** isomer, the other was prepared analogously starting from (*R*,*R*)-**4**).

3. Conclusions

A new method for preparing the pure enantiomers of 2-(3-phenylprop-1-yl)cyclohexylamino-2-oxazoline has been developed using octahydrocoumarin as a starting material. The key step of the synthesis is the diastereoisomeric separation and optical resolution of *cis*-**4** starting from the commercially available *cis*,*trans*-**4** mixture. The developed new isomer separation and enantiomeric enrichment methods offer a new route to the synthesis of optically active 1,2-disubstituted cyclohexane analogues of compound **1** because one can start from optically active precursors such as compounds **4**, **5**, **6** or **7** and can avoid the enantiomer separation of the end products or other difficult to resolve 1,2-cyclohexane derivatives.

4. Experimental

Chemicals were purchased Aldrich (Steinheim, Germany). The 10% Pd/C catalyst (Selcat Q) was supplied by Five-Coop Fine Chemicals (Budapest, Hungary). Optical rotation data were measured with a Perkin–Elmer 241 automatic polarimeter. The ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM250 spectrometer. The ee values were determined by GC (HP-4890 Agilent with β-Dex column (30 m, 0.25 mm ϕ, 0.25 μm film), carrier N_2, FID detector) and HPLC (Jasco UV-1575 detector, PU-1580 pump) with Chiralpack AD column.

4.1. Separation of racemic *cis*-4

Racemic *cis*/*trans*-octahydrocoumarin **4** (20.0 g, 0.13 mol, $c/t = 54/46$) was dissolved in a mixture of aqueous NaOH solution (5.19 g, 0.13 mol NaOH in 30 mL water) and 140 mL ethanol. To this solution, $CaCl_2{\cdot}2H_2O$ (9.24 g, 0.063 mol in 20 mL water) was added. After standing overnight, the crystals were separated by filtration and washed with EtOH (2 × 4 mL) to give 8.76 g ($c/t = 22/78$) of the Ca-salt of hydroxy acid of octahydrocoumarin **4**. The mother liquor, after the evaporation of ethanol, was acidified with HCl (16 mL 32% aqueous solution, diluted with in 16 mL of water). After 1 h of stirring, the mixture obtained was extracted with dichloromethane (3 × 40 mL), the united solutions were dried over Na_2SO_4 and evaporated.

4.2. Preparation of *cis*-5

cis-Octahydrocoumarin ($c/t = 78/22$, 10.1 g, 0.065 mol) was dissolved in abs THF (100 mL) and a solution of phenyllithium in dibutyl ether (31 mL, 1.8 mol/L solution) was added at −78 °C into it dropwise. After 1 h of stirring (during this time the mixture warmed up to room temperature), the solvents were evaporated and HCl (6 mL 32% aqueous solution diluted with 30 mL water) was added. The reaction mixture was extracted with dichloromethane (3 × 100 mL). The combined solutions were dried over Na_2SO_4, and the solvent was evaporated to give 14.38 g *cis*-**5** (94.5%). MS (FAB) $m/z = 233$ [$(MH)^+$]. ^{1}H NMR ($CDCl_3$): 0.80–1.10 (1H, m), 1.10–1.35 (5H, m), 1.45 (1H, d), 1.50–1.93 (7H, m), 3.00–3.30 (1H, m), 7.10–7.65 (5H, m).

4.3. Preparation of *cis*-6

Over 10% Pd/C catalyst (Selcat Q) (2.0 g) 3-(2-hydroxycyclohexyl)propiophenone (10.0 g) was hydrogenated in methanol (100 cm^3), in the presence of concd H_2SO_4 (0.3 g), in a 250 cm^3 stainless steel autoclave equipped with a magnetic stirrer (stirring speed: 1100 rpm). The reduction was carried out at 4 bar and room temperature. After finishing the hydrogen uptake, typically 4 h reaction time, the catalyst was filtered off and the filtrate was evaporated under vacuum. The amount of the crude product was 8.5 g of *cis*-**6** (90.9%). MS (FAB) $m/z = 219$ [$(MH)^+$]. ^{1}H NMR ($CDCl_3$): 0.80–1.10 (1H, m), 1.10–1.35 (5H, m), 1.45 (1H, d), 1.50–1.93 (7H, m), 2.45–2.63 (2H, m), 3.00–3.30 (1H, m), 7.10–7.65 (5H, m).

4.4. Preparation of *trans*-7

Triphenylphosphine (0.40 g, 1.52 mmol), a solution of diethyl azadicarboxylate (0.65 mL) and diphenyl phosphoryl azide (0.42 g, 1.52 mmol) were added to racemic alcohol (0.30 g, 1.37 mmol) dissolved in THF (3 mL) (cooled and stirred continuously). After 3 h of stirring, the solvent was evaporated to give the crude product. Flash chromatography over silica gel (30 g) with ethyl acetate/hexane = 1:50 eluent afforded 0.28 g pure *trans*-**7** (84.3%). ^{1}H NMR ($CDCl_3$): 0.80–1.35 (6H, m), 1.45–1.83 (8H, m), 2.45–2.70 (2H, m), 7.15 (3H, d), 7.25 (2H, d).

4.5. Preparation of racemic *trans*-8

Over 10% Pd/C catalyst (Selcat Q) (1.5 g), *trans*-**7** (5.0 g) was hydrogenated in methanol (80 cm^3), in a 250 cm^3 stainless steel autoclave equipped with a magnetic stirrer (stirring speed: 1100 rpm). The reduction was carried out at 5 bar and 25–30 °C. A pressure decrease could not be observed due to the nature of azido group hydrogenation (N_2 evolves!), but after 2 h of reaction time, the conversion was complete. The catalyst was filtered off and the filtrate was evaporated under vacuum giving 1.40 g of *trans*-**8** (32.1%) crude product. MS (FAB) $m/z = 218$ [$(MH)^+$]. ^{1}H NMR ($CDCl_3$): 0.80–1.45 (8H, m), 1.45–1.83 (8H, m), 2.45–2.70 (2H, m), 7.15 (3H, d), 7.25 (2H, d).

4.6. Preparation of racemic *trans*-1

Racemic *trans*-**8** (0.5 g, 2.3 mmol) dissolved in THF (20 mL) and 2-chloroethyl isocyanate (0.205 mL, 2.3 mmol) was stirred at room temperature for 1 h. After removal of the solvent, the residue was purified via flash chromatography over silica gel (first with hexane, next with ethyl acetate/hexane = 4:1) to give the desired intermediate (0.7 g). It was then treated with KF/Al_2O_3 (1.30 g) (40%), in acetonitrile (22 mL) and heated for 2 h. After the removal of the solvent, the residue was purified via flash chromatography over silica gel (using first ethyl acetate, next ethyl acetate/methanol/triethylamine = 10:2:1) giving the title compound as a white solid (0.54 g, 81.9%). MS (FAB) $m/z = 287$ [$(MH)^+$]. ^{1}H NMR ($CDCl_3$): 0.85–1.45 (6H, m), 1.45–2.10 (8H, m), 2.45–2.70 (2H, m), 3.75 (2H, t), 4.10–4.22 (2H, t), 7.15 (2H, d), 7.22 (3H, d), 3.16 (1H, t).

4.7. Resolution of racemic *cis*-4

To racemic *cis*-**4** (88.8 g, 0.577 mol) (*cis*-content is 78%) dissolved in methanol (80 mL), NaOH (23.0 g, 0.575 mol) dissolved in distilled water (15 mL) was added (under continuous cooling). After the removal of the solvent, the residue was treated with triethylamine (29.2 g, 0.289 mol) and (*S*)-1-phenylethylamine (PEA) (35.0 g, 0.289 mol) in methanol (200 mL). A mixture of HCl (32%, 57 mL) and methanol (50 mL) were added to the solution, and it was cooled with iced water (1 h) and the NaCl precipitate was removed by filtration. After the complete removal of the solvent, the residue was dissolved in ethyl acetate, and during the cooling, crystallization was observed. After a day staying, the crystals were separated by filtration and washed with ethyl

acetate (3 × 20 mL). The diastereomeric salt obtained (45.43 g) (53.8%, ee: 56.4%, *cis*: 80.8%) was dissolved in water (70 mL) and treated with HCl (32%) (28 mL) and it was extracted with dichloromethane (3 × 40 mL). After the removal of the solvent from the collected fractions, the weight of the *cis*-**4** obtained was 21.2 g (47.8%) (ee: 57.0%, *cis*: 81.0%). After removing of the solvent from the mother liquor of the diastereomeric salt, the residue was dissolved in water (200 mL) (it contained 18 g NaOH). The resolving agent was extracted from the solution with dichloromethane (3 × 100 mL). To the aqueous solution concd HCl (50 mL) was added, and then extracted with dichloromethane (3 × 100 mL). The collected fractions were evaporated to provide the *cis*-**4** (61.5 g, 69.3% calculated to racemic lactone, ee: 18.3%, *cis*: 79.1%). *cis*-**4** (61.5 g, 0.4 mol, ee: 18.3%, *cis*: 79.1%) was dissolved in methanol (50 mL), under cooling NaOH (16.0 g, 0.4 mol) dissolved in methanol (100 mL) was added. The solvent was completely removed and treated with (*R*)-1-phenylethylamine (PEA) (28.7 g, 0.237 mol) and triethylamine (16.50 g, 0.166 mol) in methanol (100 mL). To this solution a mixture of HCl (32%, 39.6 mL) and methanol (100 mL) was added. After filtration of the precipitated NaCl, the solvent was completely removed. The residue was dissolved in boiling ethyl acetate (330 mL) and it was filtered after 1 h of stirring at room temperature and the residue was washed in ethyl acetate (3 × 10 mL). The weight (first generation) of (*R*)-PEA-(+)-diastereomeric salt: 26.00 g (40.0% related to the (+)-enantiomer content of the measured *cis*-**4** enantiomer mixture, ee: 71.2%, *cis*: 82.6%). The solvent was completely removed from the mother liquor and the residue was dissolved again in ethyl acetate (200 mL) and cooled to room temperature. After 1 h stirring, it was then filtered and washed with ethyl acetate (2 × 10 mL). The weight (second generation) of (*R*)-PEA-(+)-diastereomeric salt was 18.70 g (28.8% related to (+)-enantiomer content of the measured *cis*-**4** enantiomer mixture, ee: 58.1%, *cis*: 82.1%). The total amount of the two diastereomeric salt generations was 44.70 g (68.8%). The united diastereomeric salts were dissolved in water (80 mL), concd HCl (35 mL) was added and the mixture was extracted with dichloromethane (3 × 50 mL). The fractions were dried over Na_2SO_4, and evaporated to give (+)-*cis*-**4**. (24.90 g) [64.4% related to the (+)-enantiomer content of the starting mixture] (ee: 65.7%, *cis*: 82.4%).

4.8. Purification of the mixture of *cis*-4 enantiomers

4.8.1. Re-resolution and recrystallization. A mixture of (−)-*cis*-**4** enantiomers (31.30 g, 0.203 mol) (ee: 57.0%, *cis*: 80.6%) was treated with NaOH (7.6 g, 0.153 mol) dissolved in methanol (46 mL), and a mixture of (*S*)-PEA (18.50 g, 0.153 mol) and triethylamine (4.30 g, 0.043 mol) dissolved in methanol (75 mL) was added. Next a mixture of HCl (32%, 18 mL), methanol (30 mL) and acetone (70 mL) was added. The solution was evaporated after the removal of the NaCl precipitated. The residue was dissolved in ethyl acetate (70 mL). In the first fraction, the (*S*)-PEA-(*S*,*S*)-(−)-diastereomeric salt (24.65 g) was precipitated (ee: 85%, *cis*: 83.4%). The mother liquor was evaporated and the second fraction (*S*)-PEA-(*S*,*S*)-(−)-diastereomeric salt (16.21 g) was precipitated by crystallization from ethyl acetate (ee: 85%, *cis*: 83.4%). The salt obtained from the second fraction was recrystallized from distilled water (10 mL). The crystals were separated by filtration and washed with acetone (3 × 4 mL) to give (*S*)-PEA-(*S*,*S*)-(−)-diastereomeric salt (8.31 g, the third fraction) (ee: 80.8%, *cis*: 84.3%). The combined fractions (32.96 g, the first and third fractions) were dissolved in distilled water (16 mL) to give the crystalline salt (21.7 g, ee: 95.0%, *cis*: 91.6%). The diastereomeric salt was dissolved in distilled water (20 mL), after which concd HCl (10 mL) was added and this solution was extracted with dichloromethane (3 × 50 mL). The combined fractions were dried over Na_2SO_4, and the solvent was evaporated to give 12.00 g of (*S*,*S*)-(−)-*cis*-**4** (ee: 94.3%, *cis*: 90.2%). The crude lactone was distilled (bp: 149–150 °C, 3 mmHg) to give 9.38 g of (*S*,*S*)-(−)-*cis*-lactone. $[\alpha]_D^{20} = -40.3$ (*c* 1, $CHCl_3$).

4.8.2. The recrystallization of diastereomeric salt. The (*R*)-PEA-(*R*,*R*)-(+)-diastereomeric salt (57.1 g) (ee: 64.3%, *cis*: 82.0%) was recrystallized from distilled water (27 mL) (the weight of obtained salt (1st)): 31.56 g (ee: 83.6%, *cis*: 86.0%). This first salt was recrystallized from distilled water (15 mL); the weight of obtained salt (2nd): 20.00 g (ee: 95.3%, *cis*: 94.3%). The second salt was dissolved in water (20 mL) and concd HCl (10 mL) was added to it. The solution was extracted with dichloromethane (3 × 50 mL). The combined fractions were dried over Na_2SO_4 and the solvent was evaporated to give 11.06 g of (*R*,*R*)-(+)-*cis*-**4** (ee: 95.4%, *cis*: 94.3%). The crude lactone was distilled (bp: 149–150 °C, 3 mmHg) giving 10.10 g of (*R*,*R*)-(+)-*cis*-lactone. $[\alpha]_D^{20} = +43.2$ (*c* 1, $CHCl_3$).

4.9. Preparation of (*R*,*R*)-*cis*-5 enantiomer

To (+)-*cis*-**4** (10.03 g, 0.651 mol) dissolved THF solution of phenyl-Li in dibutyl ether (27.5 mL) (1.8 molar) was added dropwise at −78 °C, and then stirred for 1 h. The solution was heated to room temperature. After evaporation of the solvent, concd HCl (5 mL) in distilled water (5 mL) was added, and it was extracted with dichloromethane (3 × 50 mL). The united fractions were washed with distilled water (10 mL), and the solvent was evaporated after drying over Na_2SO_4 to give the (*R*,*R*)-(−)-*cis*-**5**: 12.17 g (80.5%). $[\alpha]_D^{20} = -1.5$ (*c* 1, $CHCl_3$) (ee: 96.1%, *cis*: 96.2%). MS (FAB) $m/z = 233$ $[(MH)^+]$.

4.10. Preparation (*R*,*R*)-*cis*-6 enantiomer

The mixture of (*R*,*R*)-*cis*-**5** (12.10 g) dissolved in methanol (60 mL) and 0.3 g of concd sulfuric acid was hydrogenated (4 bar and 25–30 °C). After hydrogenation the catalyst was filtered off and washed with methanol (2 × 5 mL). Next, 5 mL of concd HCl was added and the solution was evaporated. The residue was dissolved in dichloromethane (150 mL) and washed with water (2 × 25 mL), dried over Na_2SO_4 and the solvent was evaporated. The amount of (*R*,*R*)-(−)-*cis*-alcohol was 10.94 g (95.7%). $[\alpha]_D^{20} = -9.5$ (*c* 1, $CHCl_3$), FAB-MS $m/z = 219$ $[(MH)^+]$.

4.11. Preparation of (*S*,*R*)-*trans*-8 enantiomer

Starting from (−)-*cis*-alcohol, the reaction is similar to the preparation of racemic *trans*-**7** and *trans*-**8** and (*S*,*R*)-(+)-*trans*-**8** was obtained with the same yield as in Sections 4.4 and 4.5. $[\alpha]_D^{20} = +49.0$ (*c* 1, $CHCl_3$), FAB-MS $m/z =$ 218 $[(MH)^+]$.

4.12. Preparation of (*S*,*R*)-*trans*-1 enantiomer

Starting from (*S*,*R*)-(+)-*trans*-**8** enantiomer and following the description of the preparation of racemic (*S*,*R*)-*trans*-**1**, the (+)-*trans*-**1** enantiomer was achieved with a yield of 60.7%. $[\alpha]_D^{20} = +30.5$ (*c* 1, $CHCl_3$). FAB-MS $m/z = 287$ $[(MH)^+]$.

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