Efficient and Practical Syntheses of (*R*)-(5-Amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester

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Abstract: Efficient and practical syntheses of enantiomerically pure (*R*)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1**) by three different routes via the resolution of different aminoindan intermediates are described.

Keywords: bromination; nitration; palladium-catalyzed amination; resolution

Introduction

Enantiomerically pure (*R*)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1**) serves as an important intermediate in the synthesis of LAB687 (Figure 1), which is an inhibitor of microsomal triglyceride transfer protein (MTP).[1] Our goal was to develop a practical synthesis of **1** which is amenable for scale-up. Our retrosynthetic analysis (Scheme 1) revealed that enantiomerically pure **1** could be synthesized efficiently by three routes. The first route involved the resolution of (±)-5-bromo-2-aminoindan (**3**) followed by carbamoylation and palladium-catalyzed amination of **6** using the benzophenone imine as an ammonia equivalent. (±)-5-Bromo-2-aminoindan would be easily available by a regioselective bromination of commercially available 2-aminoindan (**2**). The second route was based on the resolution of (±)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1**) itself, which would also be easily available from commercially available 2-aminoindan (**2**) by regioselective nitration, carbamoylation, and reduction. The third route utilized the resolution of (±)-5-nitro-2-aminoindan followed by carbamoylation and reduction. Route 1 will be of significance for the early phase of development as it is the shortest and safest route, while routes 2 and/or 3 will be of commercial value due to the inexpensive nature of reagents used. In this paper we describe multi-kilogram scale syntheses of enantiomerically pure **1** based on all three of these approaches.

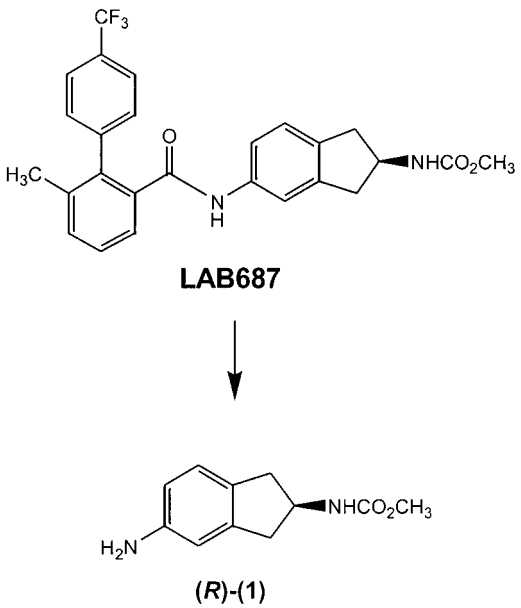

Figure 1.

Results and Discussion

Route 1: Synthesis of (R)-1 Based on Resolution of (±)-5-Bromo-2-aminoindan

Because in the early phase of development it is the speed which is critical and not the cost, we first investigated the route 1 as it will be the safest and shortest route.

An asymmetric synthesis of (*S*)-5-bromo-2-aminoindan, involving a total number of 11 steps and in

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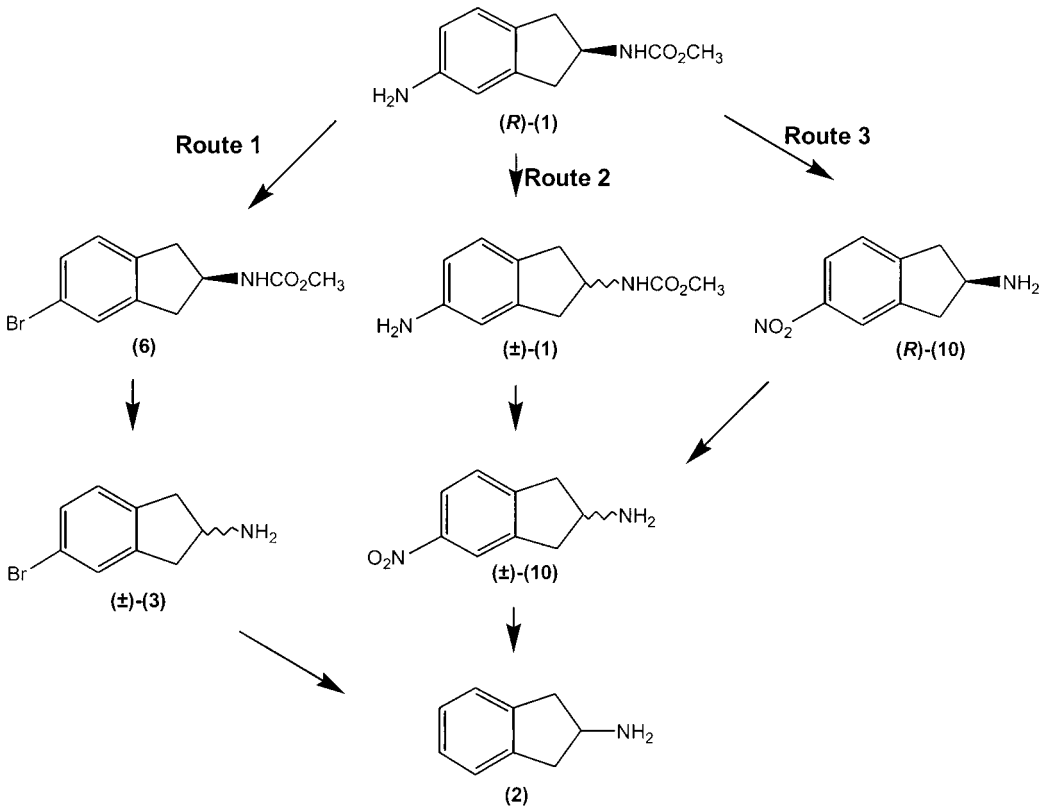
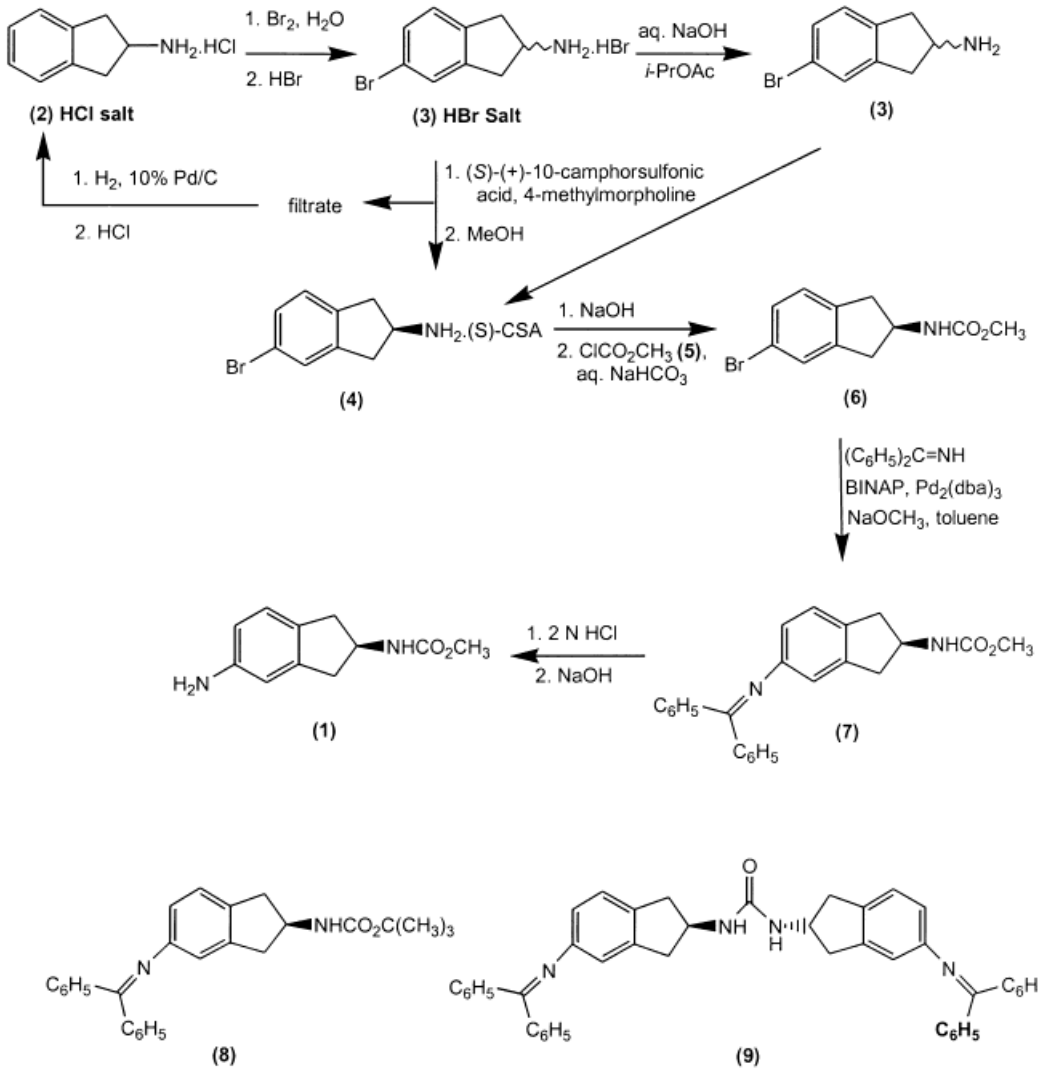


Scheme 1.

9.8% overall yield, was recently reported.[2] It was stated that this asymmetric synthesis approach was necessary because these compounds were not readily resolved by traditional means, due to the orientation of the 5-substituted group combined with the near planarity of the indan molecule.[3] Because the reported synthesis[2] was lengthy and utilized azide chemistry in one of the steps, which was a potential safety concern, it was deemed impractical for our purposes. We decided to re-examine the resolution route to prepare enantiomerically pure (*R*)-5-bromo-2-aminoindan because such an approach would result in a practical method, in particular if the racemic material could be prepared efficiently. We rationalized that racemic 5-bromo-2-aminoindan (**3**) should be readily available by a regioselective bromination of commercially available 2-aminoindan hydrochloride (**2** · HCl salt). Bromination of 2-aminoindan hydrochloride (Scheme 2) in water with 1.07 equivalents of bromine at 58 – 60 °C resulted in a mixture of (±)-**3** · HBr salt, its 4-bromo regioisomer, and dibrominated derivatives in minor amounts. The regioselectivity of 5- vs. 4-bromination was 8:1. The desired (±)-**3** · HBr salt crystallized from the reaction mixture and was isolated by filtration. An efficient washing of this solid with 2-propanol removed the undesired 4-bromo regioisomer and dibromo derivatives in the filtrate. A recrystallization of the crude solid from water, which removed any unreacted **2**, furnished (±)-**3** · HBr salt in 65% yield with >97% purity. This process was scaled-up on a multi-kilogram scale in the pilot plant.

With an efficient, one-step preparation of (±)-**3** in hand, our next goal was to develop the resolution conditions for this intermediate. To study the resolution of (±)-**3**, the HBr salt was first converted to the free base (±)-**3** by a treatment with aqueous NaOH in isopropyl acetate. Resolution of (±)-**3** free base was studied with several resolving agents: di-*p*-toluoyl-D-tartaric acid, dibenzoyl-D-tartaric acid, D-tartaric acid, L-malic acid, (*S*)-(+)-mandelic acid, (–)-menthoxyacetic acid, (1*R*,3*S*)-(+)-camphoric acid, (1*S*)-(+)-10-camphorsulfonic acid. Only (1*S*)-(+)-10-camphorsulfonic acid led to the resolution to afford the diastereomeric salt **4** which was enriched with the desired *R*-enantiomer of 5-bromo-2-aminoindan. The enantiomeric purity of **4** was determined by HPLC using a Chiralcel OJ column, using the free base which was generated by treatment of the salt **4** with aqueous NaOH in ethyl acetate. Resolution of (±)-**3** free base with (1*S*)-(+)-10-camphorsulfonic acid in a 2:1 mixture of isopropyl acetate and methanol yielded **4** in 45.5% yield (91% based on theory) with a ~88.5:11.5 (*R*:*S*) ratio. Further treatment of this diastereomeric salt with methanol furnished **4** in ~36% overall yield (72% based on theory) with a 98.8:1.2 (*R*:*S*) ratio. This methanol treatment was heterogeneous, as crude **4** did not dissolve even at reflux. How-



Scheme 2. Route 1.

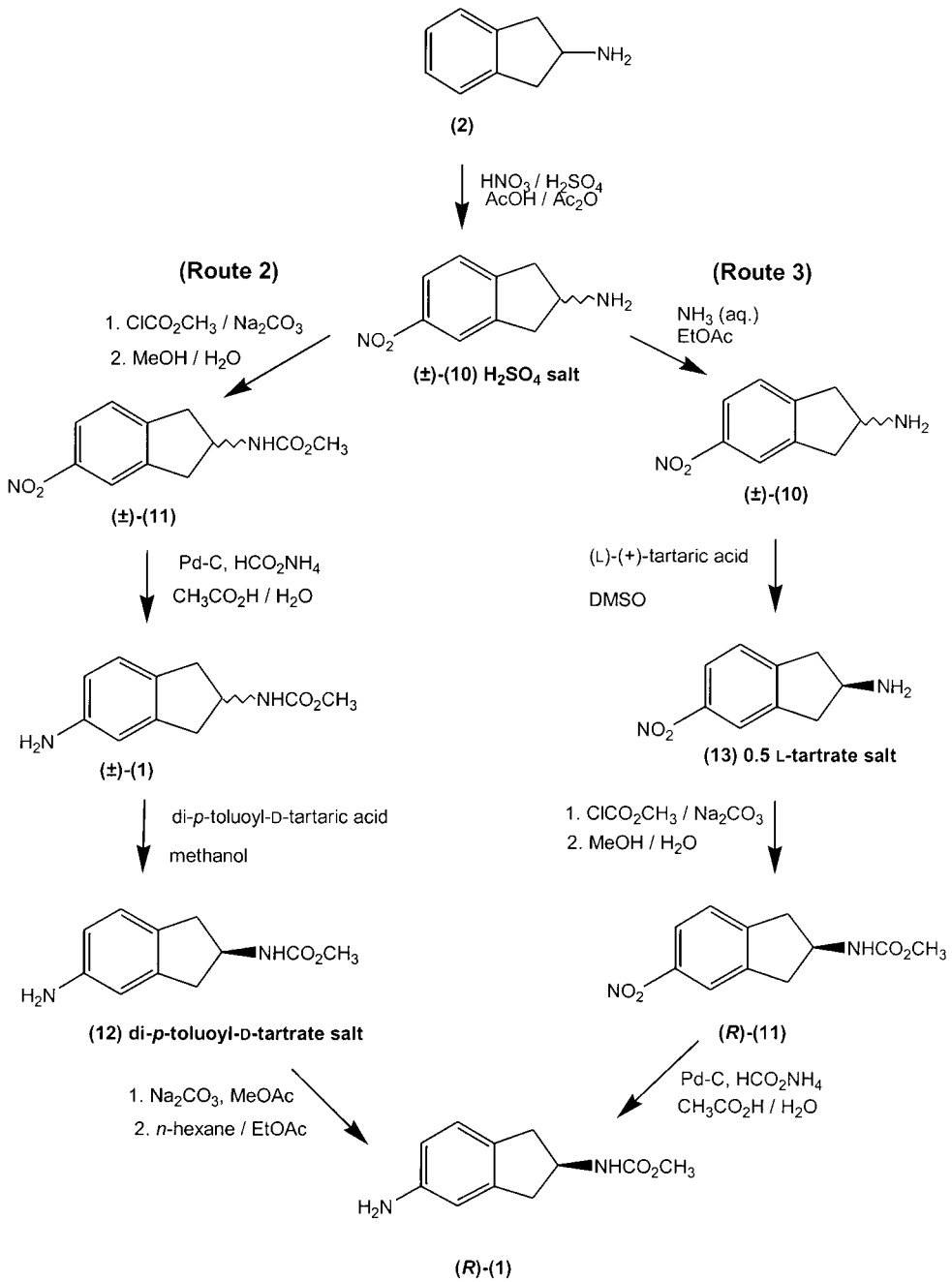
ever, it was a very efficient treatment as **4** even with an 80:20 (*R*:*S*) ratio could be enriched to a 98:2 (*R*:*S*) ratio. The solubilities of (*R*)- and (*S*)-5-bromo-2-aminoindan(1*S*)-(+)-10-camphorsulfonate diastereomeric salts at 20 °C were 2.0 and 12.4 mg/mL, respectively, in a 2:1 mixture of isopropyl acetate-methanol, and 8.6 and 76.9 mg/mL, respectively, in methanol. Several solvent mixtures of different compositions and different total volumes were also tried to optimize the resolution conditions. The diastereomeric salt **4** of the desired enantiomeric purity (*R*:*S* = >98:2) could not be obtained directly under any of these conditions.

Because the throughput in the resolution step using a 2:1 mixture of isopropyl acetate-methanol was very low [5.3 L of solvent to resolve 130 g of (±)-**3** HBr], it was desirable to further optimize this step to increase the throughput for the next phase of development. We found that (±)-**3** · HBr salt could be resolved directly with (1*S*)-(+)-10-camphorsulfonic acid in methanol in the presence of 4-methylmorpholine as a base,[4] which generated the (±)-**3** free base *in situ*. This afforded the diastereomeric salt **4** in ~43% yield (86% based on theory) with a ~90:10 (*R*:*S*) ratio. A further treatment of this diastereomeric salt with methanol, as before, enhanced the ratio to >98:2 (*R*:*S*). The overall yield of **4** was 36.5% (73% based on theory). These new conditions not only enhanced the throughput 9.5 times (555 mL of methanol was used to resolve 130 g of (±)-**3** · HBr) but they also made the process simpler by eliminating the extra step used to generate the (±)-**3** free base. This process was scaled-up on a multi-kilogram scale in the pilot plant.

Having developed efficient resolution conditions for (±)-**3**, the next step was to convert the diastereomeric salt **4** to the methyl carbamate **6**. Treatment of **4** with aqueous NaOH in isopropyl acetate yielded a solution of the free base of **4**. Reaction of this solution with methyl chloroformate (**5**) at 0 °C in the presence of aqueous sodium bicarbonate as a base furnished **6**

in 86% yield. This process was also scaled-up on a multi-kilogram scale in the pilot plant.

With **6** in hand, we turned our attention to the last step involving a palladium-catalyzed amination of **6** using benzophenone imine as an ammonia equivalent. Reaction of **6** with benzophenone imine in toluene in the presence of (±)-BINAP (1.5 mol %), $Pd_2(dba)_3$ (0.5 mol %), and sodium *tert*-butoxide at 105 or 80 °C afforded the desired product **7** along with substantial amounts of two by-products, that were isolated by silica gel chromatography; their structures were assigned based on spectroscopic data to be *tert*-butyl carbamate (**8**, 9%) and dimeric urea (**9**, 11%). To eliminate the formation of **8** and minimize the formation of **9**, we discovered[5] that sodium *tert*-butoxide could be replaced by sodium methoxide as a base in palladium-catalyzed amination reactions. Thus, reaction of **6** with benzophenone imine (1.0 equivalent) in the presence of sodium methoxide (1.2 equivalents), (±)-BINAP (1.06 mol %), and $Pd_2(dba)_3$ (0.5 mol %) in toluene at 78 – 82 °C afforded the Schiff base intermediate **7**, which contained only <3% of dimeric urea **9**. Intermediate **7** was not isolated, and the crude reaction mixture from the ami-



Scheme 3. Routes 2 and 3.

nation step was subjected to hydrolysis with 6 N HCl, which yielded crude **1**. When excess benzophenone imine was used, it was observed that **1** reacted with unhydrolyzed benzophenone imine during work-up to regenerate the Schiff base **7** because it hydrolyzed much slower than **7**. The crude **1** contained palladium, which had to be removed to meet a specification of <4 ppm. To achieve this, crude **1** was treated with activated carbon (PICA P1400) in methanol, followed by filtration and recrystallization from methanol and water to afford pure **1** with the desired chemical and enantiopurity in 63% yield. The palladium content was <1 ppm. This process was successfully scaled-up in the pilot plant to a 15.4-kg scale giving **6** in 63% yield.

One of the well-known drawbacks with resolutions is that more than half of the material is wasted. Thus, it would be highly desirable to racemize/recycle the undesired enantiomer. We developed a unique and simple route to recycle the undesired enantiomer of **3** in the filtrate via its debromination by hydrogenolysis, which destroyed the asymmetry, to afford 2-aminoindan (**2**). The resulting **2** was then subjected to bromination to regenerate the (±)-**3** · HBr salt.

Crystalline (*R*)-5-bromo-2-aminoindan hydrochloride was prepared by a treatment of the free base of **4** with aqueous HCl. The overall yield of this HCl salt from (±)-**3** · HBr salt was 35.6%. The enantiomeric (*S*)-5-bromo-2-aminoindan hydrochloride was also prepared from (±)-**3** · HBr salt in 34.6% overall yield using the same procedure but replacing (1*S*)-(+)-10-camphorsulfonic acid with (1*R*)-(–)-10-camphorsulfonic acid in the resolution step. This resolution-based synthesis of the *S*-enantiomer, starting from cheap and commercially available **2**, was shorter and more efficient (overall yield 22.6% in 3 steps) than the previously reported synthesis (overall yield 9.8% in 11 steps).[2]

Route 2: Synthesis of (*R*)-1 Based on its Resolution

Because of the expensive ligand and the catalyst used in the above palladium-catalyzed amination step, we developed an alternative route to improve the economy. It was based on the resolution of (±)-**1** itself, which can be obtained by a regioselective nitration of 2-aminoindan followed by carbamoylation and reduction of the nitro group (Scheme 3).

Nitration of 2-aminoindan hydrochloride was known from the literature to afford (±)-5-nitro-2-aminoindan (**10**) in 60% yield.[6] The process involved neutralization of large amounts of acid, extractions, and evaporations. In our hands, 5-nitro-2-aminoindan (**10**) proved to be a thermally sensitive compound. In dynamic DSC, decomposition of **10** started at ca. 150 °C with a fairly high enthalpy of decomposition (–1680 kJ/kg). In DSC under isothermal conditions, decomposition was observed at temperatures above 90 °C. Therefore, it was important to avoid long thermal stress during work-up and during isolation of the product in the pilot plant. Hence, a safe and large-scale process for the nitration of 2-aminoindan (**2**) was developed, which involved the treatment of 2-aminoindan (**2**) with stoichiometric amounts of HNO_3 and a slight excess of H_2SO_4 in acetic acid, in the presence of acetic anhydride as a water scavenging agent (Scheme 3). Under these conditions, 60% aqueous HNO_3 could be used as nitration agent, which was preferable in the pilot plant from safety point of view. *HNO_3 is known to form highly explosive mixtures with acetic anhydride. Therefore, it is very important to ensure that different addition lines are used for acetic anhydride and HNO_3 when reproducing the nitration experiment described in this work.* Best results were obtained when 1 equivalent of acetic anhydride was used compared to the water present in the reaction mixture, calculated from the theoretically formed water in the reaction and water present in the reagents (H_2SO_4, HNO_3, and acetic acid). The regioselectivity of the nitration was slightly dependent on the reaction temperature: at lower temperatures, the formation of the desired product was preferred over its 4-nitro-regioisomer. The nitration was performed at –5 to 0 °C to obtain a ratio of 86:14 of 5- and 4-nitro regioisomers respectively. At lower temperatures in the above described solvent system, precipitation occurred and the nitration could not be drawn to completion. When the reaction was completed, the product **10** was isolated as the hydrogen sulfate salt by a simple dilution of the reaction mixture with methyl acetate and filtration of the resulting precipitate. Fortunately, the undesired 4-nitro regioisomer remained mainly in the mother liquor and the desired product (**10** · H_2SO_4 salt) was obtained in 75.6% yield, containing 2.5% of its 4-regioisomer as a single impurity. The hydrogen sulfate salt of **10** was significantly more thermally stable than the free base **10**, also during handling and storage. In dynamic DSC, decomposition of the hydrogen sulfate salt started at ca. 195 °C with an enthalpy of decomposition of –1260 kJ/kg. No exotherms were observed under isothermal conditions at 90 °C over 12 h. More than 500 kg of the hydrogen sulfate salt of **10** were produced in the pilot plant by this process at a 50-kg scale.

Methoxycarbonylation of the amino group was performed under modified Schotten-Baumann conditions with aqueous Na_2CO_3 as a base and methyl acetate as a solvent to obtain compound **11** in 98% yield. For the subsequent reduction of the nitro group, both catalytic hydrogenation under H_2 pressure as well as catalytic transfer hydrogenation were considered. Both methods gave the desired product (±)-**1** in excel-

lent yields and quality. Hydrogenation of **11** with 5% Pd/C under an initial hydrogen pressure of 5 bar in MeOH and subsequent crystallization of the product from MeOH/H_2O gave pure (±)-**1** in 98% yield. Alternatively, **11** was subjected to transfer hydrogenation with 10% Pd/C as catalyst and ammonium formate as the hydrogen-donor in MeOH/H_2O in the presence of acetic acid to obtain 93% of crystalline (±)-**1**. In the pilot plant, 240 kg of (±)-**1** were produced by the transfer hydrogenation method in multi-purpose reactors on a scale of 40 kg/batch.

The resolution of (±)-**1** was achieved by diastereomeric salt formation with 1 molar equivalent of di-*p*-toluoyl-D-tartaric acid in methanol. The crude diastereomeric salt was obtained in 56.9% yield with a ratio of ca. 81:19 (*R:S*). The crude salt was recrystallized from methanol to obtain the enriched salt of the desired (*R*)-enantiomer with 98:2 (*R:S*) ratio in 37.4% overall yield (74.8% based on theory). The stoichiometry of the salt was determined to be 1:1 (base:acid) from the ^{1}H NMR signals at δ = 6.83 ppm [1H of (*R*)-**1**] and 7.90 ppm (4H of tartaric acid). Enantiomeric ratios > 99:1 (*R:S*) could easily be achieved by a second recrystallization from methanol with an overall yield of 32% (64% based on theory). The resolution of (±)-**1** was performed on a 70-kg scale in the pilot plant.

(*R*)-**1** was obtained from **12** by treatment with aqueous Na_2CO_3 and extraction with methyl acetate. The crude (*R*)-**1**, obtained by subsequent evaporation of the solvent, was already of sufficient purity and quality to be used directly for the next step. Alternatively, the product was recrystallized from methyl acetate/*n*-hexane to obtain crystalline (*R*)-**1** in 80% yield.

Route 3: Synthesis of (*R*)-1 Based on the Resolution of (±)-5-Nitro-2-aminoindan

Although proceeding with reasonable yields, the resolution of (±)-**1** at a late stage of the synthesis was the main drawback of the above route, and the resolution of (±)-5-nitro-2-aminoindan [(±)-**10**] instead of (±)-**1** was deemed to be highly desirable. The free base (±)-**10** was obtained from the hydrogen sulfate salt (**10** · H_2SO_4 salt) in almost quantitative yield by stirring with aqueous ammonia and extraction into ethyl acetate (Scheme 3). Compound (±)-**10** was a greenish oil, that darkened on storage at room temperature. The resolution of (±)-**10** was screened with different acids in different solvents. A resolution could finally be achieved with the cheap and natural L-(+)-tartaric acid in DMSO. The crude diastereomeric salt was obtained from (±)-**10** and L-(+)-tartaric acid in DMSO with an (*R:S*) ratio of 89:11. The crude product was heated twice in DMSO according to a temperature program to obtain products with a 96:4 (*R:S*) ratio after the first treatment and a 98:2 ratio after the second treatment, respectively. The overall yield of the resolution of (±)-**10** was 39.3% (78.6% based on theory). The tartrate salt **13** with a 98:2 (*R:S*) ratio had $[\alpha]_D^{25}$: –11.3 (*c* 0.5, H_2O) and showed decomposition at $T > 245$ °C without a defined melting point. According to ^{1}H NMR, the stoichiometry of the salt **13** was 2:1 (base:acid). The $[\alpha]_D$ value of **13** should be considered only as indicative, since the optical rotation was not corrected for residual solvent (DMSO), which may be present in the tartrate salt **13**. Treatment of **13** with aqueous NH_3 afforded (*R*)-**10** as a greenish oil, $[\alpha]_D^{25}$: –29.2 (*c* 1.0, CH_3OH). Methoxycarbonylation of **13** with methyl chloroformate and aqueous Na_2CO_3 with subsequent reduction of the nitro group on Pd/C under transfer hydrogenation conditions with ammonium formate and acetic acid gave (*R*)-**1** in similar yields as described for the corresponding conversions in the racemic series [**10** · H_2SO_4 salt to (±)-**11** to (±)-**1**]. This result demonstrated the feasibility of the resolution of (±)-**10** for the preparation of (*R*)-**1**. Preliminary calculations revealed that implementation of this route for the synthesis of (*R*)-**1** would reduce the costs of goods by a factor of > 3 and at the same time would increase the output by another factor of 3, compared to the route based on the direct resolution of (±)-**1**.

Conclusions

In summary, efficient and practical syntheses of enantiomerically pure (*R*)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1**) by three different routes via the resolution of different aminoindan intermediates are described. A comparison of these three routes is listed in Table 1 which demonstrates that process research is evolutionary and that in the early phase of development the cost is not

Table 1. Comparison of routes 1 – 3.

	Number of Steps	Overall Yield (%)	Advantages	Concerns
Route 1	4	12.9	Safe, short, recycling of undesired enantiomer is possible	Cost of ligand and catalyst, removal of palladium
Route 2	5	17.6	Higher yield, cost	Safety, recycling of undesired enantiomer is not possible
Route 3	5	24.7	Highest yield, Cost	Safety, recycling of undesired enantiomer is not possible

so important as the speed, which was achieved by the safest and shortest route 1. Route 3 will be of commercial value. In contrast to the report by Leiby and Romero,[3] our results clearly demonstrate that 5-substituted near planar 2-aminoindans are readily resolvable by classical methods.

Experimental Section

General Methods

Melting points were measured on a Büchi 535 melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker 300 instrument. The enantiopurities of 5-bromo-2-aminoindans were determined by chiral HPLC on a Rainin Dynamax system using a Daicel Chiralcel OJ column (4.6 × 250 mm) and a mixture of hexanes:ethanol:methanol:TFA (96:2:2:0.1) as the mobile phase (isocratic at a flow rate of 0.9 mL/min and UV detector at λ = 270 nm) at 35 °C. The retention times of (*R*)- and (*S*)-5-bromo-2-aminoindans were 19.6 and 18.4 min, respectively. The enantiopurity of **1** was determined by chiral HPLC on a Rainin Dynamax system using a Chiralcel AD column (4.6 × 250 mm) and a mixture of hexanes:2-propanol (80:20) as the mobile phase (isocratic at a flow rate of 1.0 mL/min and UV detector at λ = 254 nm) at 25 °C. The retention times of (*R*)- and (*S*)-**1** were 13.0 and 11.5 min, respectively. Enantiopurity of **12** was determined by converting it to the free base **1**. The enantiopurity of **10** was determined by first converting the free base into the benzoate derivative under classical Schotten-Baumann conditions and subsequent chiral HPLC of the benzoate on a Daicel Chiralpak AD column (4.6 × 250 mm) with hexanes:2-propanol (77:23) as the mobile phase (isocratic at a flow rate of 0.5 mL/min and UV detection at λ = 220 nm) at 40 °C. The retention times of the benzoates of (*R*) and (*S*)-**10** were 23.7 and 20.4 min, respectively.

(±)-5-Bromo-2-aminoindan Hydrobromide (3)

A 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, condenser with nitrogen inlet-outlet, and heating mantle was charged with 2-aminoindan hydrochloride (**2**; 118.8 g, 0.7 mol) and water (594 mL). The mixture was stirred and heated to an internal temperature of 58 – 60 °C to obtain a solution. To the resulting solution was added bromine (120.0 g, 0.75 mol) over a period of 50 min while maintaining an internal temperature of 58 – 60 °C. A solid precipitated when half of the bromine had been added. The mixture was stirred at an internal temperature of 60 – 62 °C for an additional 1 h and 48% HBr (107 mL) was added over a period of 5 min while maintaining the same internal temperature. After stirring for additional 10 min, the reaction mixture was cooled to an internal temperature of 20 – 23 °C over a period of 1 h. The solids were collected by filtration, washed with 2-propanol (3 × 133 mL), and dried at 58 – 60 °C (10 – 30 torr) to afford crude (±)-5-bromo-2-aminoindan hydrobromide; yield: 158.0 g. This crude material was charged to a 1-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, condenser with nitrogen inlet-outlet, and heating mantle and was suspended in water (390 mL). The suspension was heated to an internal temperature of 95 – 100 °C to obtain a clear solution. The solution was cooled to an internal temperature of 20 – 23 °C over a period of 2.5 h and stirred at this temperature for an additional 30 min. The solids were collected by filtration, washed with water (3 × 20 mL, precooled to 0 – 5 °C), and dried at 60 – 65 °C (10 – 30 torr) to afford (±)-5-bromo-2-aminoindan hydrobromide (**3**): Yield: 134.1 g (65.4%); mp >300 °C; ^{1}H NMR (DMSO-d_6): δ = 2.95 (m, 2H), 3.27 (m, 2H), 4.02 (m, 1H), 7.25 (d, 1H, *J* = 8.1 Hz), 7.39 (d, 1H, *J* = 8.1 Hz), 7.50 (s, 1H), 8.16 (bs, 3H); MS: *m/e* = 213.7 (MH^+); anal. calcd. for $C_9H_{11}Br_2N$: C, 36.89; H, 3.78; N, 4.78; Br, 54.54; found: C, 37.29; H, 3.88; N, 4.71; Br, 54.92.

In the pilot plant, 54.8 kg of **1** afforded 59.6 kg of **2**.

Resolution of (±)-5-Bromo-2-Aminoindan Free Base (3) in Isopropyl Acetate-Methanol Mixture

A 5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, addition funnel, and heating cooling bath was charged with (±)-5-bromo-2-aminoindan hydrobromide (**3**; 130.0 g, 0.444 mol) and isopropyl acetate (1.5 L). The mixture was stirred at 20 – 25 °C and a solution of sodium hydroxide (26.62 g) and sodium chloride (186.35 g) in water (0.75 L) was added over 5 min while maintaining the internal temperature at 20 – 25 °C. The suspension was stirred efficiently until all the solids dissolved. The organic layer was separated and the aqueous layer was extracted with isopropyl acetate (0.75 L). The combined organic layers (~2.33 L), containing free base (±)-**3**, were transferred to a 12-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, addition funnel, condenser and heating mantle and diluted with isopropyl acetate (1.3 L) and methanol (0.93 L). The resulting solution was heated to reflux (internal temperature 65 °C) and to it was added a solution of (1*S*)-(+)-10-camphorsulfonic acid (103.1 g, 0.444 mol) in methanol (0.66 L) over 15 min while maintaining the internal temperature at 60 – 65 °C. The addition funnel was washed with methanol (0.185 L) and was added to the reaction mixture. To the clear solution were added (*R*)-5-bromo-2-aminoindan (1*S*)-(+)-10-camphorsulfonate salt (**4**) seeds (100 mg), and the mixture was cooled to 20 – 23 °C over 2 h. The mixture was allowed to stir at 20 – 23 °C for additional 2 h. The solids were collected by filtration, washed with a 2:1 mixture of isopropyl acetate-methanol (2 × 250 mL; precooled to 0 – 2 °C), and dried at 50 – 55 °C (10 – 30 torr) to obtain (*R*)-5-bromo-2-aminoindan (*1S*)-(+)-10-camphorsulfonate salt (**4**); (*R*):(*S*) = 88.5:11.5; yield: 90.0 g.

This crude **4** (90.0 g) was transferred to a 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, addition funnel, condenser, and heating mantle. Methanol (0.9 L) was added, and the resulting slurry was heated to reflux (internal temperature 65 °C). The refluxing was continued for an additional 1 h. The suspension was cooled to 20 – 23 °C over 2 h and stirred at this temperature for additional 2 h. The solids were collected by filtration, washed with a 1:1 mixture of isopropyl acetate-methanol (2 × 95 mL; precooled to 0 – 2 °C), and dried at 50 – 55 °C (10 – 30 torr) to afford (*R*)-5-bromo-2-aminoindan (1*S*)-(+)-10-camphorsulfonate salt

(**4**); yield: 71.4 g (36%; 72% of theory); mp 253 – 255 °C; $[\alpha]_D^{25}$: +10.4 (*c* 1.0, MeOH); (*R*):(*S*) = 98.8:1.2; ^{1}H NMR (DMSO-d_6): δ = 0.74 (m, 3H), 1.04 (s, 3H), 1.27 (m, 2H), 1.88 (d, 1H, *J* = 27 Hz), 1.93 (m, 1H), 2.39 (m, 1H), 2.45 (d, 1H, *J* = 27 Hz), 2.51 (m, 2H), 2.67 (m, 1H), 2.91 (m, 2H), 3.27 (m, 2H), 4.0 (m, 1H), 7.25 (d, 1H, *J* = 8.0 Hz), 7.39 (d, 1H, *J* = 8.0 Hz), 7.58 (s, 1H), 8.03 (bs, 3H); anal. calcd. for $C_{19}H_{26}BrNO_4S$: C, 51.35; H, 5.90; N, 3.15; S, 7.21; Br, 17.98; found: C, 51.22; H, 5.90; N, 3.12; S 7.20; Br, 18.13.

In the pilot plant, 16.5 kg of **3** afforded 9.4 kg of **4**.

Direct Resolution of (±)-5-Bromo-2-Aminoindan HBr Salt (3) in Methanol

A 1-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, addition funnel, and heating mantle was charged with (±)-5-bromo-2-aminoindan hydrobromide (**3**; 130.0 g, 0.444 mol), 4-methylmorpholine (47.12 g, 0.466 mol), and methanol (277 mL). The resulting suspension was heated to an internal temperature at 58 – 62 °C and a solution of (1*S*)-(+)-10-camphorsulfonic acid (134.0 g, 0.578 mol) in methanol (222 mL) was added over 15 min while maintaining the internal temperature at 60 – 65 °C. The addition funnel was washed with methanol (55 mL) and added to the reaction mixture. The reaction mixture was stirred at 60 – 65 °C for additional 10 min to obtain a clear solution. To this clear solution were added seeds of (*R*)-5-bromo-2-aminoindan (1*S*)-(+)-10-camphorsulfonate salt (**4**; 50 mg), and the mixture was cooled to 20 – 23 °C over 2 h. The mixture was allowed to stir at 20 – 23 °C for additional 2 h. The solids were collected by filtration, washed with a 2:1 mixture of isopropyl acetate-methanol (2 × 100 mL; precooled to 0 – 2 °C) and water (2 × 100 mL), and dried at 50 – 55 °C (10 – 30 torr) to obtain (*R*)-5-bromo-2-aminoindan (*1S*)-(+)-10-camphorsulfonate salt (**4**); (*R*):(*S*) = 90.6:9.4; yield: 85.75 g. Save the filtrate for recycling/racemization.

This crude **4** (85.75 g) was transferred to a 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, addition funnel, condenser, and heating mantle. Methanol (0.68 L) was added, and the resulting slurry was heated to reflux (internal temperature 65 °C). The refluxing was continued for an additional 5 h. The suspension was cooled to 20 – 23 °C over 2 h and stirred at this temperature for additional 2 h. The solids were collected by filtration, washed with a 1:1 mixture of isopropyl acetate-methanol (2 × 75 mL; precooled to 0 – 2 °C), and dried at 50 – 55 °C (10 – 30 torr) to afford (*R*)-5-bromo-2-aminoindan (1*S*)-(+)-10-camphorsulfonate salt (**4**); yield: 72.4 g (36.5%, 73% of theory); (*R*):(*S*) = 98.0:2.0. Save the filtrate for recycling/racemization.

In the pilot plant, 59.6 kg of **3** yielded 33.0 kg of **4**.

(*R*)-(5-Bromo-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester (6):

A 1-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, and a nitrogen inlet was charged with (*R*)-5-bromo-2-aminoindan (1*S*)-(+)-10-camphorsulfonate salt (**4**; 111.1 g, 0.25 mol) and isopropyl acetate (300 mL). To the resulting slurry was added a solution of sodium hydroxide (15.0 g) and sodium chloride (75.0 g) in water (300 mL) over a period of 10 min while maintaining an internal temperature at 20 – 25 °C. The suspension was stirred efficiently until all the solids dissolved (30 min). The organic layer was separated and the aqueous layer was extracted with isopropyl acetate (100 mL). The combined organic layers afforded a clear solution of (*R*)-5-bromo-2-aminoindan free base (430 mL). To this solution, in a 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, a nitrogen inlet, and an addition funnel, was added a solution of sodium bicarbonate (60.0 g) in water (600 mL). The mixture was cooled to an internal temperature of 0 – 5 °C and a solution of methyl chloroformate (**5**; 35.4 g, 0.375 mol) in isopropyl acetate (200 mL) was added over a period of 45 min while maintaining an internal temperature at 0 – 5 °C. The mixture was stirred at this temperature for an additional 1 h. The organic layer was separated and washed with 1 N sulfuric acid (150 mL), 10% aqueous sodium bicarbonate (110 mL), and water (150 mL). The organic layer was concentrated under reduced pressure (100 – 300 torr) at an internal temperature of 40 – 50 °C to collect ~500 mL of solvent and obtain ~150 mL of a slurry. To this slurry was added heptane (500 mL) and the concentration was continued to collect ~400 mL of solvent and obtain ~300 mL of a slurry. Heptane (500 mL) was added and the slurry was cooled to an internal temperature of 0 – 5 °C over a period of 30 min. The solid was collected by filtration over a Buchner funnel with suction, washed with heptane (40 mL), and dried at 60 – 65 °C under reduced pressure (10 – 30 torr) with nitrogen bleeding to obtain a constant weight (17 h) of (*R*)-(5-bromo-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**6**) as a crystalline white solid; yield: 58.2 g (86%); mp 108 – 110 °C; $[\alpha]_D^{25}$: –10.63 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.77 (m, 2H), 3.25 (m, 2H), 3.67 (s, 3H), 4.5 (br, 1H), 4.86 (br, 1H), 7.08 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.35 (s, 1H); anal. calcd. for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19; Br, 29.58; found: C, 48.93; H, 4.37; N, 5.13; Br, 29.73.

In the pilot plant, 30.8 kg of **4** yielded 15.4 kg of **6**.

(*R*)-(5-Amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester (1)

A 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, heating and cooling bath, and Dean-Stark condenser, was charged with toluene (900 mL). The solvent was refluxed for 5 h under nitrogen and 25 mL of solvent was collected to azeotrope out water with the Dean-Stark condenser. The solvent was cooled to 20 – 25 °C and saved for the next step under a nitrogen atmosphere.

A 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, heating mantle, and condenser was evacuated and flushed with nitrogen. This operation was repeated once more. The flask was charged with (*R*)-(5-bromo-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**6**; 94.55 g, 0.35 mol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (2.32 g, 3.73 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.6 g, 1.75 mmol), sodium methoxide (22.69 g, 0.42 mol), and benzophenone imine (63.43 g, 0.35 mol).

The flask was evacuated and flushed with nitrogen three times. Deoxygenated and dry toluene (875 mL, prepared in the pervious step) was transferred to this flask under nitrogen. While stirring, the flask was evacuated and flushed with nitrogen twice. The mixture was stirred and heated to an internal temperature at 78 – 82 °C over a period of 50 min with nitrogen outlet valve open. The nitrogen outlet valve was closed when the internal temperature had reached 78 – 82 °C. (A continuous flow of nitrogen over the course of the reaction had an adverse effect. No pressure was built-up during the reaction. The nitrogen outlet valve could be opened to release the pressure, if necessary, and then closed). The mixture was stirred at 78 – 82 °C for 16 h. The mixture was cooled to an internal temperature of 60 – 65 °C over a period of 15 min and 6 N HCl (175 mL) was added. The mixture was stirred at an internal temperature of 60 – 65 °C for 1.5 h and then transferred to a 5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, heating mantle, and digital thermometer. To this mixture was added water (2.01 L) and stirred at an internal temperature of 28 – 33 °C for 1 h. The mixture was cooled to 20 – 25 °C and allowed to stand for 1 h. The aqueous layer (containing a fine solid) was separated and extracted with isopropyl acetate (2 × 500 mL). The clear aqueous layer was cooled to an internal temperature of 18 – 22 °C and basified (to adjust the pH to 8 – 10) by addition of 3 N NaOH (~320 mL) over a period of 15 min while maintaining the internal temperature at 18 – 22 °C. The resulting white slurry was stirred at this temperature for 1 h and then cooled to 0 – 10 °C. After stirring at this temperature for additional 1 h, the solid was collected by filtration, washed with water (2 × 220 mL), and dried at 50 – 55 °C under reduced pressure (10 – 30 torr) with nitrogen bleeding to obtain crude (*R*)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1**); yield: 50.0 g (69%).

A 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet, heating mantle, and condenser was charged with crude (*R*)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1**; 50.0 g), PICA P1400 activated carbon (15.0 g), and methanol (990 mL). The mixture was heated to an internal temperature of 63 – 67 °C to achieve a gentle reflux and stirred at this temperature for additional 5 h. The hot mixture was filtered through a pad of Celite® 521 (30.0 g) in a Buchner funnel with suction. The Celite® pad was washed with hot (40 – 50 °C) methanol (248 mL). The combined filtrates were concentrated at atmospheric pressure at an internal temperature of 65 – 70 °C to collect ~805 mL of solvent to obtain a solution (495 mL). To this solution was added water (495 mL) at 60 – 70 °C and the mixture was cooled to an internal temperature at 20 – 25 °C over a period of 2 h. This mixture was cooled to an internal temperature of 0 – 5 °C over a period of 30 min and stirred at this temperature for an additional 1 h. The solid was collected by filtration over a Buchner funnel with suction, washed with a precooled (0 – 5 °C) mixture of methanol (100 mL) and water (100 mL), and dried at 50 – 55 °C under reduced pressure (10 – 30 torr) with nitrogen bleeding to afford (*R*)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1**); yield: 45.36 g (63% from **6**); mp 139 – 141 °C; $[\alpha]_D^{25}$: –9.1 (*c* 1.0, MeOH); (*R*):(*S*) = 99.5:0.5; ^{1}H NMR (DMSO-K$_6$): δ = 2.63 (m, 2H), 2.96 (m, 2H), 3.53 (s, 3H), 4.17 (m, 1H), 4.87 (s, 2H), 6.36 (d, 1H, *J* = 7.92 Hz), 6.41 (s, 1H), 6.82 (d, 1H, *J* = 7.9 Hz), 7.38 (d, 1H, *J* = 6.8 Hz); anal. calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58; found: C, 63.94; H, 6.80; N, 13.59. Palladium content: 0.7 ppm.

In the pilot plant, 15.4 kg of **6** yielded 7.4 kg of **1**.

(*R*)-5-Bromo-2-aminoindan Hydrochloride from (*R*)-5-Bromo-2-aminoindan (*1S*)-(+)-10-Camphorsulfonate Salt (4)

(*R*)-5-Bromo-2-aminoindan (1*S*)-(+)-10-camphorsulfonate salt (**4**; 4.44 g) was converted to the free base as described above using isopropyl acetate and a solution of sodium hydroxide (0.6 g) and sodium chloride (5.0 g) in water (15 mL). The filtered organic layer, containing the free base, was cooled to 15 °C (internal temperature), and concentrated hydrochloric acid (1.2 g; 37%) was added over a period of 10 min while maintaining an internal temperature at 20 – 22 °C. The solids were collected by filtration, washed with isopropyl acetate (5 mL), and dried at 50 – 55 °C (10 – 30 torr) to afford (*R*)-5-bromo-2-aminoindan hydrochloride as a white powder; yield: 2.42 g (97.6%); mp >300 °C; $[\alpha]_D^{25}$: –19.8 (*c* 1.0, MeOH); (*R*):(*S*) = 98.3:1.7; ^{1}H NMR (DMSO-d_6): δ = 2.98 (m, 2H), 3.27 (m, 3H), 3.98 (bs, 1H), 7.24 (d, 2H, *J* = 8.1 Hz), 7.38 (d, 2H, *J* = 8.1 Hz), 7.5 (s, 1H), 8.41 (bs, 2H); anal. calcd. for $C_9H_{11}BrClN$: C, 43.49; H, 4.46; N, 5.64; Cl, 14.26; Br, 32.14; found: C, 43.56; H, 4.27; N, 5.53; Cl, 14.33; Br, 32.35.

(*S*)-5-Bromo-2-aminoindan Hydrochloride

(*S*)-5-Bromo-2-aminoindan hydrochloride was prepared by the resolution of (±)-**3** in a similar manner as described above for the (*R*)-enantiomer except (1*R*)-(–)-10-camphorsulfonic acid was used for the resolution step. This afforded (*S*)-5-bromo-2-aminoindan (1*R*)-(–)-10-camphorsulfonate salt; yield: 35.5% (71% of theory); mp 255 – 259 °C; $[\alpha]_D^{25}$: –10.3 (*c* 1.0, MeOH); (*R*):(*S*) = 98.0 : 2.0.

HCl salt: Yield: 97.5%; mp >300 °C; $[\alpha]_D^{25}$: +20.3 (*c* 1.0, MeOH); (*R*):(*S*) = 99.5:0.5; ^{1}H NMR (DMSO-d_6): δ = 2.98 (m, 2H), 3.27 (m, 3H), 3.98 (bs, 1H), 7.24 (d, 2H, *J* = 8.1 Hz), 7.37 (d, 2H, *J* = 8.1 Hz), 7.5 (s, 1H), 8.41 (bs, 2H); anal. calcd. for $C_9H_{11}BrClN$: C, 43.49; H, 4.46; N, 5.64; Cl, 14.26; Br, 32.14; found: C, 43.50; H, 4.28; N, 5.54; Cl, 14.28; Br, 32.22.

Recycling by Debromination of the Undesired Enantiomer of 5-Bromo-2-aminoindan

To the combined filtrates from the direct resolution step in a Parr bottle was added 10% Pd/C (7.0 g). The Parr bottle was flushed three times with H_2 (60 psi) and then vibrated at 50 °C with H_2 (60 psi) for 17 h. The catalyst was filtered over a pad of Celite and washed with methanol (2 × 10 mL). The filtrate was concentrated under vacuum to give a crude solid. This crude solid was suspended in isopropyl acetate (450 mL), and a solution of 2 N NaOH (600 mL) was added. The suspension was stirred at 20 – 25 °C for 2 h to obtain a biphasic solution. The organic layer was separated and the aqueous layer was extracted with isopropyl acetate (300 mL). The organic layers were combined and treated with 37% HCl (30 mL) at a rate to maintain an internal temperature below 22 °C. The solids were collected by filtration,

washed with isopropyl acetate (2 × 10 mL), and dried at 55 – 60 °C (10 – 30 torr) to afford 2-aminoindan hydrochloride (**2**); yield: 44.0 g (recovered yield: 58.5%; 92% of theory).

(±)-5-Nitro-2-aminoindan Hydrogen Sulfate Salt (10 · H_2SO_4 Salt)

A 1.5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser was charged with acetic acid (94.5 g) and 2-aminoindan (30.0 g, 0.225 mol) at 20 – 25 °C. The mixture was stirred for 15 – 30 min until a solution was formed. Concentrated H_2SO_4 (96%, 105.85 g) was added at 20 – 25 °C (with cooling), followed by the addition of acetic anhydride (101.2 g). The suspension was stirred for 15 – 30 min at 20 – 25 °C to obtain a clear solution. The solution was cooled to –5 °C and 60% HNO_3 (24.61 g, 0.234 mol) was added to the solution while maintaining an internal temperature of –5 to 0 °C. Intensive cooling and very slow addition were necessary to maintain the internal temperature between –5 and 0 °C. The mixture was stirred for 30 min at –5 to 0 °C and for additional 2 h at 0 – 5 °C. The progress and completion of the reaction was followed by GC. For work-up, methyl acetate (233 g) was added to the reaction mixture while maintaining an internal temperature of 0 – 5 °C. A suspension was formed during the addition. The suspension was warmed up to 20 °C and a second portion of methyl acetate (467 g) was added. The suspension was stirred for 1 h at 20 – 25 °C and 2 h at 0 °C. The product was collected by filtration and washed with a total of 224 g of methyl acetate in several portions to remove acetic acid and acetic anhydride residuals. The product was dried at 25 °C for 48 h under reduced pressure (1 – 5 mbar) to obtain (±)-**10** · H_2SO_4 salt; yield: 47.0 g (75.6%); mp 182 – 183 °C; ^{1}H NMR (DMSO-d_6): δ = 3.04 (m, 1H), 3.09 (d, *J* = 5 Hz, 1H), 3.385 (d, *J* = 8 Hz, 1H), 3.445 (d, *J* = 8 Hz, 1H), 4.11 (m, 1H), 7.565 (d, *J* = 8 Hz, 1H), 8.0–8.15 (m, 4H), 8.18 (m, 1H), 8.2–9.7 (broad s, 1H); MS: *m/e* = 178 (M^+, 100%), 161 ($M^+ - NH_3$), 130 (90%), 117 (75%), 103, 77, 63.

In the pilot plant, 350 kg of 2-aminoindan yielded 556.8 kg of (±)-**10** · H_2SO_4 salt.

(±)-(5-Nitro-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester (11)

A 1.5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser was charged with (±)-5-nitro-2-aminoindan hydrogen sulfate salt (45 g, 0.163 mol). Water (407 g) was added, and the mixture was stirred at 20 – 25 °C to obtain a solution. The solution was treated with methyl acetate (290 g) and with saturated aqueous Na_2CO_3 (267 g). The CO_2 gas, evolved during the addition of Na_2CO_3, was purged through the nitrogen outlet. The mixture was cooled to 0 – 4 °C in an ice bath and was treated with methyl chloroformate (23.57 g, 0.249 mol) dropwise over a period of 1 h, while maintaining an internal temperature at 0 – 4 °C. After completion of the addition, the mixture was warmed up to 20 – 25 °C and stirred for 1 h at this temperature. The layers were separated, and the water layer was extracted with methyl acetate (2 × 176 g). The combined organic layers were washed with brine (266 g), and the water layer was discarded. The solvent of the organic layer was evaporated at 45 °C under reduced pressure, and the residue was dissolved in methanol (352 g) at an internal temperature of 45 – 50 °C. The solvent was evaporated again at 40 – 45 °C under reduced pressure, and the residue was dissolved in methanol (246 g). To this solution, water (315 g) was added slowly while maintaining the internal temperature at 45 – 50 °C. Crystallization occurred during the addition of water, and a thick suspension was formed. The suspension was stirred for 2 h at 20 – 25 °C and for > 2 h at 0 – 4 °C. The product was collected by filtration and was washed with water (3 × 100 g). Drying at 25 °C under reduced pressure (1 – 5 mbar) for 48 h afforded crystalline (±)-**11**; yield: 37.6 g (97.8%); mp 137 °C; ^{1}H NMR (DMSO-d_6): δ = 2.87 (d, *J* = 6 Hz, 1H), 2.92 (d, *J* = 6 Hz, 1H), 3.23 (dd, *J* = 7.5 Hz and *J* = 2.0 Hz, 1H), 3.285 (d, *J* = 7.5 Hz, 1H), 4.33 (sextet, *J* = 7 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.54 (m, 1H), 8.0–8.1 (m, 3H); MS: *m/e* = 236 (M^+), 161 (100%), 144, 130, 115, 103, 76; anal. calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86; found: C, 55.97; H, 5.20; N, 11.85.

In the pilot plant, 442.5 kg of (±)-**10** · H_2SO_4 salt yielded 366.3 kg of (±)-**11**.

(5-Amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester (1)

A 1.5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser was charged with Pd/C (10% on charcoal, 1.75 g) and (±)-**11** (35 g, 0.148 mol). Methanol (420 g) was added, followed by the addition of acetic acid (36.5 g). The mixture was heated to an internal temperature of 38 – 42 °C and was stirred for 30 min at this temperature. A solution of ammonium formate (38.5 g, 0.592 mol) in methanol (68 g) and water (87 g) was added over 1 h, while maintaining the internal temperature at 38 – 42 °C. Whereas almost all of the generated H_2 was consumed and no gas evolution was observed in the beginning, significant gas evolution was observed toward the end of the addition. After completion of the addition, the reaction mixture was stirred for 2 h at 38 – 42 °C until the completion of the reaction was confirmed by HPLC. The catalyst was removed by filtration through a pad of Celite® (40.0 g) in a Buchner funnel with suction. The Celite® pad was washed with methanol (3 × 138 g). The filtrate was diluted with water (417 g), and the solution was concentrated by distillation at 35 – 45 °C and reduced pressure (150 – 200 mbar) to a final volume of approx. 400 mL. Crystallization of the product was observed during the distillation. The suspension was stirred for >2 h at 20 – 25 °C, and the product was collected by filtration. The product was washed with water (3 × 138 g) and dried for 24 h at 40 – 45 °C under reduced pressure (1 – 5 mbar) to afford (±)-**1**; yield: 28.44 g (93.1%); mp 145.5 – 146.5 °C; ^{1}H NMR (DMSO-d_6): δ = 2.6 (m, 2H), 2.95 (m, 2H), 3.52 (s, 3H), 4.16 (sextett, *J* = 7.3 Hz, 1H), 4.79 (s, 2H), 6.35 (dd, *J* = 7.9 and 2.1 Hz, 1H), 6.39 (broad s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 6.5 Hz, 1H); MS: *m/e* = 206 (M^+, 12%), 174 [$M - CH_3OH$]$^+$, 145, 131 (100%), 119, 91, 59; anal. calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.11; H, 6.90; N, 13.53.

In the pilot plant, 363.1 kg of **11** yielded 291.7 kg of (±)-**1**.

(5-Amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester, di-*p*-Toluoyl-D-tartrate Salt (12)

A 0.75-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser was charged with (+)-di-*p*-toluoyl-D-tartaric acid (57.35 g, 0.145 mol) and methanol (346 g). The suspension was stirred at 20 – 25 °C for 10 min until a clear a solution was obtained. To the solution was added (±)-**1** (30 g, 0.145 mol) as a solid at 20 – 25 °C to the solution under continuous stirring. Usually, a clear solution formed again within 10 min, before crystallization of the salt started to form a suspension. The reaction mixture was stirred for 5 h at an internal temperature of 22 – 25 °C. The product was isolated by filtration, washed with cold methanol/isopropyl acetate (1:1 v/v, 3 × 60 mL) and dried for 24 h at 50 °C to obtain the crude salt **12** with (*R*):(*S*) = 81.2 : 18.8; yield: 49.07 g. The crude salt **12** was placed in a 0.5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser. Methanol (235 mL) was added, and the suspension was heated to reflux until a clear solution was formed. The solution was cooled to an internal temperature of 30 – 32 °C within 30 min to initiate the crystallization, and the suspension was stirred for additional 30 min at this temperature. The suspension was heated to 42 – 45 °C (internal temperature) within 15 min. and was stirred for additional 45 min at this temperature, followed by cooling to 30 – 32 °C within 45 min and stirring at this temperature for additional 30 min. The heating and cooling cycle (between 42 – 45 °C and 30 – 32 °C) was repeated once again. Finally, the suspension was cooled to 20 – 22 °C, stirred for 1 h at this temperature, and the product was collected by filtration. The product was washed with cold methanol and isopropyl acetate (1:1 v/v, 3 × 60 mL) and dried for 24 h at 50 °C to furnish **12**. (*R*):(*S*) = 98:2; yield: 35.88 g. The product was a solvate containing ca. 10% of methanol.

For higher *R*/*S* ratios, the product was recrystallized as follows: dissolve 35.88 g of **12** in 180 mL of methanol at reflux, cool within 30 min to an internal temperature of 30 – 35 °C, stir for 1 h at this temperature, cool to 22 – 24 °C within 30 min and stir for >2 h at 22 – 24 °C. The product was isolated by filtration, washed with cold methanol:isopropyl acetate (1:1 v/v, 2 × 50 mL) and dried for 24 h at 50 °C to obtain **12** as a solvate, containing 9.4% of methanol and 0.3% of water, corresponding to 27.59 g of pure **12**; yield: 30.55 g (32%; 64% based on the theory); (*R*):(*S*) ratio 99.1:0.9; mp 160.2 – 160.4 °C; $[\alpha]_D^{25}$: +95 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6): δ = 2.41 (broad s, 6H), 2.61 (m, 2H), 2.96 (m, 2H), 3.52 (broad s, 3H), 4.17 (sextet, *J* = 7.2 Hz, 1H), 5.82 (s, 2H), 6.39 (d, *J* = 8 Hz, 1H), 6.44 (broad s, 1H), 6.83 (d, *J* = 8 Hz, 1H), 7.40 (d, *J* = 8 Hz, 4H), 7.90 (d, *J* = 8 Hz, 4H).

In the pilot plant, 143.9 kg of (±)-**1** yielded 249.8 kg of **12**.

(*R*)-(5-Amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester (1) (from 12):

(5-Amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester di-*p*-toluoyl-D-tartrate salt (**12**, 25 g) and water (80 g) were placed in a 0.75-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser. Saturated aqueous Na_2CO_3 (180 g) and methyl acetate (140 g) were added subsequently at 20 – 25 °C, and the reaction mixture was stirred for additional an 30 min to obtain two clear layers. The layers were separated, and the aqueous layer (pH > 9) was extracted with ethyl acetate (2 × 70 g). The organic layers were combined, cooled to 0 – 4 °C and stirred with 100 mL of a brine and water mixture (1:1) for 15 min at an internal temperature of 0 – 4 °C. The organic layer was separated and the solution was concentrated at 50 – 60 °C under reduced pressure (400 – 200 mbar) to a final volume of 100 – 110 mL, to obtain a suspension. *n*-Hexane (82.5 g) was added to the suspension at an internal temperature of 45 – 45 °C over a period of 15 min and the suspension was cooled to 20 – 25 °C. After stirring for 1 h at this temperature, the suspension was cooled to 0 – 4 °C and stirred for >2 h at this temperature to complete the crystallization. The product was collected by filtration and was washed with precooled (0 – 4 °C) hexane:ethyl acetate (3:1 v/v, 20 g). The product was dried under vacuum (1 – 5 mbar) at 60 °C for 20 h to obtain crystalline (*R*)-**1**; (*R*):(*S*) = 99.8:0.2; yield: 6.95 g (80%); mp 147 – 148 °C; $[\alpha]_D^{25}$: –9.0 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) was identical to the spectrum described above for (*R*)-**1**; anal. calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58; found: C, 63.97; H, 6.87; N, 13.51.

In the pilot plant, 249.2 kg of **12** yielded 68.7 kg of (*R*)-**1**.

(±)-5-Nitro-2-aminoindan (10)

NH_3 (25% aqueous solution, 75 g) was placed in a 0.75-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser. (±)-5-Nitro-2-aminoindan hydrogen sulfate salt (**10** · H_2SO_4 salt, 15 g) was added, and the mixture was stirred at 20 – 25 °C for 30 min. After addition of ethyl acetate (250 mL) to the mixture and stirring for additional 15 min, the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 200 mL) and the organic layers were combined. The organic layer was washed with water (250 mL), dried over sodium sulfate (30 g), and the solvent was evaporated at 40 – 45 °C under reduced pressure (200 to 20 mbar) to obtain the free base (±)-**10** as an oil; yield: 9.05 g (93.5%); ^{1}H NMR (DMSO-d_6): δ = 2.64 (d, *J* = 5.1 Hz, 1H), 2.70 (d, *J* = 5.1 Hz, 1H), 3.09 (m, 1H), 3.14 (dm, *J* = 6.6 Hz, 1H), 3.78 (m, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 8.01 (dm, *J* = 8.2 Hz, 1H), 8.04 (m, 1H); MS: *m/e* = 178 (M^+, 100%), 161 [M – NH_3]$^+$, 148, 130, 117, 103, 77, 63.

(*R*)-5-Nitro-2-aminoindan L-(+)-Tartrate Salt (13)

L-(+)-Tartaric acid (7.63 g, 1 equivalent) was placed in a 100-mL, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser. DMSO (25 mL) was added and the solution was heated to an internal temperature of 55 – 60 °C. A solution of (±)-**10** (9.05 g) in DMSO (20 mL) was added over a period of 45 min, while maintaining the internal temperature at 55 – 60 °C. Precipitation of the salt was observed during the addition. When the addition was completed, stirring was continued for 1 h at 55 – 60 °C. The reaction mixture, a gray suspension, was then allowed to cool to 20 – 25 °C and stirred for 24 h at this temperature. The product was collected by filtration (which proved to be a slow and difficult

operation). The product was washed with DMSO (3 × 5 mL) and subsequently with THF (3 × 5 mL), until a colorless filtrate was obtained. The product was dried under vacuum (1 – 5 mbar) at 45 °C for 48 h to obtain crude **13**; (*R*):(*S*) = 89:11; yield: 6.18 g. Crude **13** was treated in DMSO as follows to increase the enantiomeric purity: The crude product (6.15 g) was suspended in DMSO (30 mL), and the suspension was heated to an internal temperature of 66 – 68 °C. After stirring for 1 h, the suspension was allowed to cool to an internal temperature of 36 – 38 °C within 30 min and stirring was continued overnight (16 h) at this temperature. The suspension was stirred subsequently at 66 – 68 °C for 2 h and at 36 – 38 °C for 2 h. The stirring sequences at 66 – 68 °C and at 36 – 38 °C were repeated once again, and the product was finally isolated by filtration of the suspension at 36 – 38 °C. The filter cake was washed with DMSO (3 × 4 mL) and THF (3 × 5 mL) and dried under vacuum (1 – 5 mbar) at 45 °C for 24 h to afford **13**; (*R*):(*S*) = 96:4; yield: 5.44 g. The treatment in DMSO was repeated to obtain (*R*)-5-nitro-2-aminoindan, L-(+)-tartrate salt (**13**) with an enantiomeric ratio (*R*):(*S*) = 98.0:2.0; yield: 5.06 g [39.3% from (±)-**10**; 78.6% based on theory]; mp >245 °C (decomposition); $[\alpha]_D^{25}$: –11.3 (*c* 0.5, H_2O); ^{1}H NMR (DMSO-d_6): δ = 2.84 (m, 1H), 2.895 (d, *J* = 5 Hz, 1H), 3.24 (d, *J* = 7.2 Hz, 1H), 3.29 (d, *J* = 7.2 Hz, 1H), 3.76 (s, 1H), 3.945 (m, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 8.06 (dd, *J* = 8.3 and 2.2 Hz, 1H), 8.115 (m, 1H). The base:acid = 2:1 ratio was calculated from the integral ratio of the ^{1}H NMR signals at 3.76 ppm (2H of tartaric acid) and 3.945 ppm (1H of the base). This stoichiometry was confirmed by titration of **13** with $HClO_4$.

(*R*)-5-Nitro-2-aminoindan ((*R*)-10)

The free base (*R*)-**10** was prepared from its L-(+)-tartrate salt **13** by treating the salt with aqueous NH_3 according to the same procedure described above for the preparation of (±)-**10**. (*R*)-5-Nitro-2-aminoindan was obtained as a greenish oil; yield: 98%; $[\alpha]_D^{25}$: –29.2 (*c* 1.0, CH_3OH); ^{1}H NMR (DMSO-d_6): δ = 2.64 (d, *J* = 5.1 Hz, 1H), 2.70 (d, *J* = 5.1 Hz, 1H), 3.09 (m, 1H), 3.14 (dm, *J* = 6.6 Hz, 1H), 3.78 (m, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 8.01 (dm, *J* = 8.2 Hz, 1H), 8.04 (m, 1H); MS: *m/e* = 178 (M^+, 100%), 161 $[M - NH_3]^+$, 148, 130, 117, 103, 77, 63.

(*R*)-(5-Nitro-2,3-dihydro-1*H*-inden-2-yl)-carbamic Acid Methyl Ester ((*R*)-11)

Methoxycarbonylation of **13** with methyl chloroformate according to the same procedure as described for the preparation of (±)-**11** gave (*R*)-(5-nitro-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester; mp 147.5 – 148.0 °C; $[\alpha]_D^{25}$: –18.0 (*c* 1.0, CH_3OH). ^{1}H NMR and mass spectra of (*R*)-**11** were identical to those of (±)-**11** which were described above.

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