Convenient and Inexpensive Synthesis of (1*R*,2*R*)-*trans*-1-Amino-6-nitroindan-2-ol

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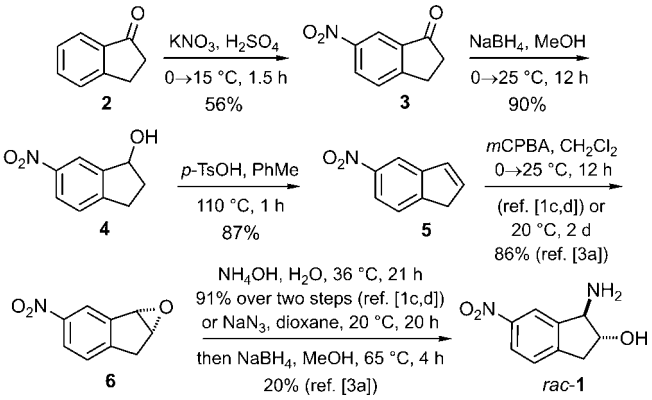
Abstract: Racemic *trans*-1-amino-6-nitroindan-2-ol (*rac*-**1**) has been prepared in five steps from inexpensive indene (**7**) in 96% overall yield. The key step was a direct nitration of the known *trans*-1-aminoindan-2-ol (*rac*-**9**) which gave sulfuric acid mono-(*rac*-*trans*-1-amino-6-nitroindan-2-yl) ester (*rac*-**10**) in quantitative yield. The latter was quantitatively converted into *rac*-**1** by treatment with aqueous 6 N HCl and then ammonia solutions. The same transformations of (1*R*,2*R*)-**9** [prepared by deracemization of *rac*-**9** with (−)-dibenzoyl-L-tartaric acid (DBT)] proceeded without loss of the optical activity. Deracemization of *rac*-**1** applying (+)-(*S*)-L-mandelic acid (MA) furnished (1*R*,2*R*)-**1** and (1*S*,2*S*)-**1** in 34 and 17% yield, respectively, with *e.e.* $\geq$ 98 and 97.6%, respectively. Procedures for recycling of the chiral auxiliaries DBT and MA are also described. The structures of key intermediates were confirmed by X-ray crystal structure analysis.

Keywords: amino alcohols; aromatic substitution; chiral resolution; indene; nitration; structure elucidation

Introduction

During the last decade, (1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-ol [(1*R*,2*R*)-**1**] has been found to be a very important intermediate in medicinal chemistry for the preparation of muscarinic agonists,[1] bronchodilators and antihypertensives,[2] potassium channel regulators,[3] multidrug resistance protein inhibitors,[4] and antipsychotics[5] as well as in combinatorial chemistry to build small-molecule libraries consisting of substituted indanes.[6] Very recently this compound was also found to be an excellent auxiliary for deracemization of unfunctionalized, α-epimerizable non-racemic ketones and aldehydes.[7] In its racemic form, the title compound *rac*-**1** had first been prepared (but reported without detailed characterization) in three steps with 17% overall yield[3a] starting from 6-nitroindene **5** and applying a general synthetic approach to *trans*-1-aminoindan-2-ols, i.e., epoxidation with *m*CPBA, ring opening of the epoxide **6** with azide anion and finally reduction of the azido to an amino group (Scheme 1).

However, 6-nitroindene (**5**) is not commercially available, and must be prepared in three steps[8] from the rather expensive indan-1-one (**2**) (the lowest posted price is currently US $ 666.00 for 500 g). The synthesis of enantiomerically pure (1*R*,2*R*)-**1** has also been reported, but the original paper[7a] does not contain any experimental details. This compound and its preparation also are the subject of several patents filed mainly by Eli Lilly and Company, USA (see, for example,[1–6]); however, their synthetic approach[1c,d] was essentially the same as reported before,[3a,8] i.e., starting from indan-1-one (**2**), but more efficient, as the epoxide **6** was directly converted into *rac*-**1** *via* ring opening with ammonia (Scheme 1). The resolution of the racemate[1] (see also ref.[5] cited in ref.[7a]) can be achieved using (*S*)-(+)-mandelic acid (lowest posted price US $ 583.00 for 1 kg).[9]



Scheme 1. Known preparations of racemic (1*R**,2*R**)-*trans*-1-amino-6-nitroindan-2-ol (*rac*-**1**).[1c,d,3a,8]

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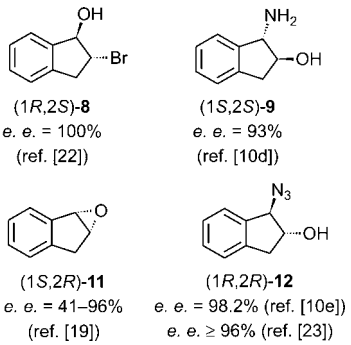
Results and Discussion

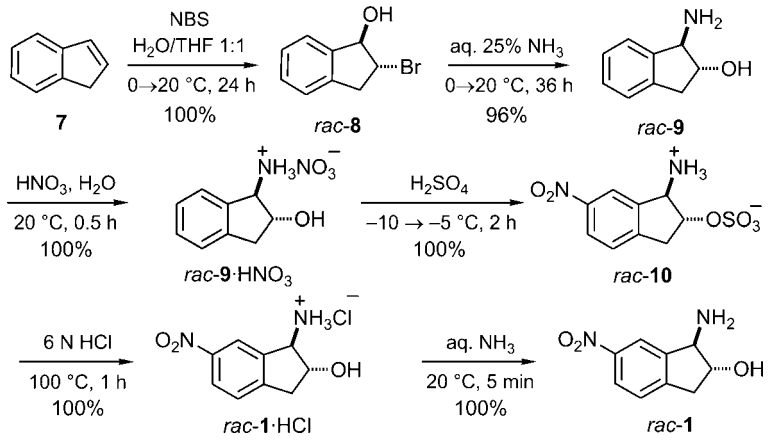
A more efficient access to *rac*-**1** would be by direct nitration of *trans*-1-aminoindan-2-ol (*rac*-**9**). Two synthetic approaches to *rac*-**9** have been reported. The first one starts with the transformation of indene (**7**) to the bromohydrin *rac*-**8**[10] with subsequent ring closure forming the corresponding epoxide **11**,[10d, e,11] ring opening of the epoxide **11** with azide anion[10d, e,11] and finally reduction of the azido to an amino group.[10d, e,11,12] In the second synthesis, formation of the epoxide **11** and its ring opening to directly yield *rac*-**9** are performed as a one-pot operation by working up the bromohydrin **8** with concentrated aqueous ammonia solution.[11,13]

Using the short second approach and, compiling the best published protocols and optimizing the procedures for isolation, *trans*-1-aminoindan-2-ol (*rac*-**9**) could be prepared from indene (**7**) in 96% overall yield (Scheme 2).

The nitration of an aromatic compound containing hydroxy and/or amino substituents on an aliphatic side chain usually requires these functionalities to be protected (cf.[14a]). Otherwise the nitration gives low yields,[14b] is accompanied by dehydration[8] and characterized by the formation of complex reaction mixtures.[14c] However, 1-aminoindane can be transformed into its 6-nitro derivative in high yield by initially forming its salt with nitric acid and slowly adding this salt to concentrated sulfuric acid at -5 to $-10\,^{\circ}C$.[15] Adopting this protocol, the nitration of *rac*-**9** could be performed in quantitative yield, however, the product was obtained as the betain-type monosulfate ester *rac*-**10** (Scheme 2). The zwitterionic nature of *rac*-**10** caused its low solubility in most organic solvents, and this probably is the reason, why the hydroxy group in *rac*-**10** could not be deprotected applying established methods[16] such as heating in a pyridine/dioxane mixture,[16a] stirring in dioxane in the presence of *p*-TsOH[16b] or stirring in THF in the presence of sulfuric acid.[16c] Fortunately, after simple heating of *rac*-**10** in 6 N aqueous hydrochloric acid for 1 h (cf.[16e]), beautiful crystals of the hydrochloride monohydrate *rac*-**1**·HCl·H_2O precipitated upon cooling the reaction mixture. Upon drying under vacuum over P_4O_{10}, *rac*-**1**·HCl was obtained and converted into the free base *rac*-**1** by treatment with aqueous ammonia in quantitative yield over both steps (Scheme 2). This corresponds to an overall yield of 96% over the whole sequence starting from inexpensive indene.

The enantiomerically pure target compound (1*R*,2*R*)-**1** can be prepared either by deracemization of *rac*-**1** or by nitration of the enantiomerically pure aminoindanol (1*R*,2*R*)-**9** as well. Initially, we turned our attention to the latter route. Over the last two decades, different synthetic approaches to enantiomerically pure materials of types **8**, **9**, **11**, and **12** have been investigated in great detail. The most elegant and, possibly, the most economical approach would be an enantioselective chemical transformation of an achiral precursor in the presence of a chiral catalyst, and this method has been exhaustively investigated applying the Jacobsen asymmetric epoxidation of indene (**7**) in the presence of different chiral Mn(III)-salen complexes. Indeed, when performing the epoxidation at low temperature with expensive reagents such as *m*-chloroperbenzoic acid (*m*CPBA) or *N*-methylmorpholine *N*-oxide (NMO), the epoxide





Scheme 2. Synthesis of racemic (1*R**,2*R**)-*trans*-1-amino-6-nitroindan-2-ol (*rac*-**1**) by direct nitration of 1-aminoindan-2-ol *rac*-**9**.

(1*S*,2*R*)-**11** was obtained with enantiomeric excesses (*e.e.*) of 91–96%,[10d,17] and the amino alcohol (1*S*,2*S*)-**9** prepared from this material had an *e.e.* of 93%. However, the enantiomeric excess in the epoxide **11** varied from 41 to 88%, when less expensive oxidizing reagents were applied.[18]

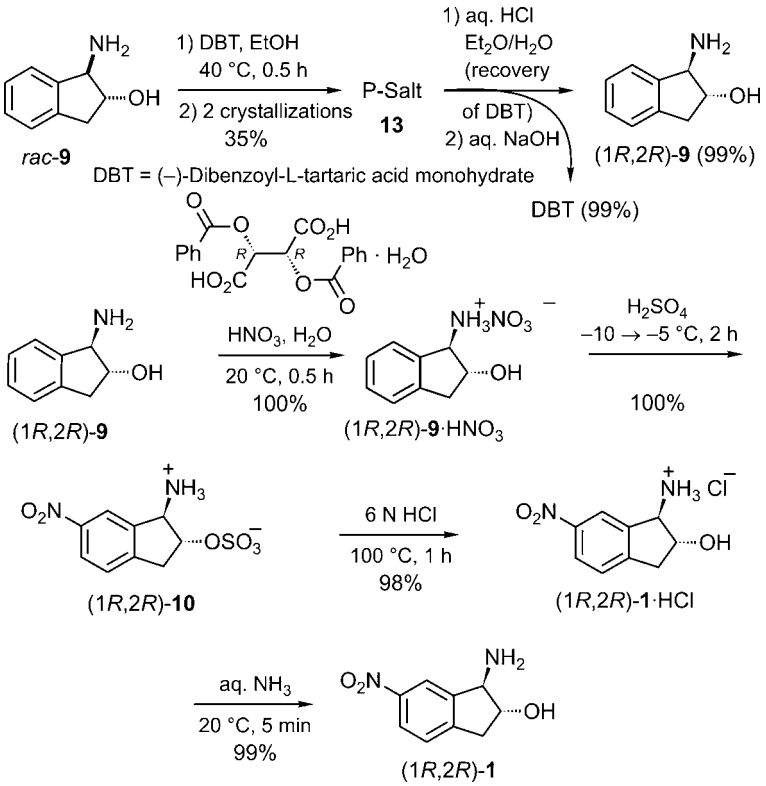
Enzymatic epoxidation of **7** applying *E. coli* JM 109 (pTaB19) gave better results, as *e.e.* values were better than 98% on a 10-g scale,[19] but enzymatic deracemization of the epoxide *rac*-**11** was less successful in that it provided lower yields.[20] At first glance, the enzymatically obtained epoxide (1*S*,2*R*)-**11** appears to be the most convenient starting material for the preparation of (1*R*,2*R*)-**9**, as it can be isolated by simple distillation without chromatography. However, apart from the necessity of having special experience and equipment, the superiority of this approach is limited by the low stability of the epoxide (1*S*,2*R*)-**11** itself.

Also successful were lipase-mediated resolutions of the bromohydrin **8**[21] and the azido alcohol **12**.[10e,22] However, these preparations require column chromatography for the isolation of enantiomerically pure materials.

Summarizing the results discussed above, it appeared that the most convenient large-scale preparation would be the deracemization of *rac*-**9** using an appropriate chiral auxiliary. Such resolutions have been known for almost a century,[13b,23] and the procedure of isolation of (1*S*,2*S*)-**9** applying (+)-dibenzoyl-D-tartaric acid reported by Lehr et al.[24] appeared to be the most promising. As was expected, with the less expensive (−)-dibenzoyl-L-tartaric acid (DBT)[25] the corresponding (1*R*,2*R*)-**9** was isolated in 35% yield (Scheme 3), while DBT could be recovered in almost quantitative yield and used again. However, this preparation takes more time than that reported by Lehr et al.[24] (see Experimental Section).

The salt **13** exhibited very similar values of melting point and specific rotation as the reported values,[24] however, the enantiomeric excess (*e.e.*) for the isolated free base (1*R*,2*R*)-**9**, which was determined by HPLC analysis of its *N*-Boc derivative, was only 77.6% (see Experimental Section; in ref.[24] the *e.e.* was not determined by an independent method). Nevertheless, the synthetic sequence was completed with this material, and enantiomerically enriched (1*R*,2*R*)-**1** with $[\alpha]_D^{20}$: +15.7 (*c* 1.16, THF) was obtained. This material was used to prepare seeding crystals of the salt with mandelic acid (see below). The structure and the absolute configuration of (1*R*,2*R*)-**10** and of (1*R*,2*R*)-**1**·HCl·H_2O obtained along this route were confirmed by X-ray crystal structure analysis (Figure 1), which indicates that no racemization occurred upon nitration and cleavage of the sulfuric acid monoester.

Both *trans*-1,2-disubstituted 6-nitroindanes (1*R*,2*R*)-**1**·HCl·H_2O and (1*R*,2*R*)-**10** possess similar molecular



Scheme 3. Deracemization of *rac*-**9** with (−)-dibenzoyl-L-tartaric acid (DBT) and conversion of (1*R*,2*R*)-**9** into (1*R*,2*R*)-**1** by nitration.

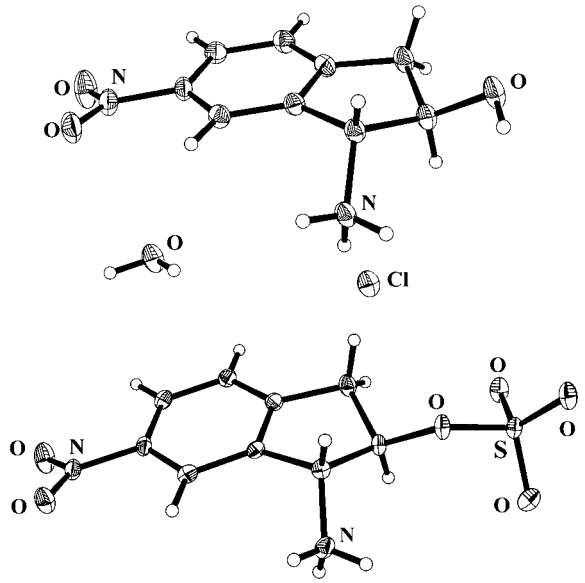
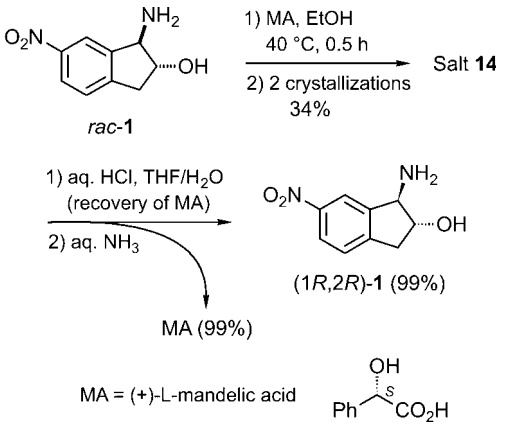


Figure 1. Molecular structures of (1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-ol hydrochloride monohydrate [(1*R*,2*R*)-**1**·HCl·H_2O] (top) and of sulfuric acid mono-[(1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-yl] ester [(1*R*,2*R*)-**10**] (bottom) in the crystal.[26]

geometries with a C(2)-envelope conformation of the 5-membered ring and a nitro group slightly rotated out of the plane of the aromatic ring [torsional angles around C(6)–N(1) bonds are 17.7 and 11.7° for (1*R*,2*R*)-**1**·HCl·H_2O and (1*R*,2*R*)-**10**, respectively]. No abnormal bond lengths and angles were found. The crystal packings of molecules (1*R*,2*R*)-**1**·HCl·H_2O (Figure 2, **A**) and (1*R*,2*R*)-**10** (Figure 2, **B**) are also remarkably similar to each other in spite of the differing number of hydrogen bond donors and acceptors in the two structures. A detailed scheme of the hydrogen bonding motifs is shown in Figure 2 (**C** and **D**). In both cases the molecules form two-dimensional H-bonded sheets, perpendicular to the *c*-axis of the unit cell, and a number of weak C(aryl)–H···O(NO_2) interactions connect the sheets with each other. Such packing is quite different from those observed in the crystals of similar compounds – the salts of *cis*-1-aminoindan-2-ol with 2-arylalkanoic acids which form H-bonded columns, and a derivative of *trans*-1-amino-6-nitroindan-2-ol which forms H-bonded chains.[27]

Eventually, the target compound (1*R*,2*R*)-**1** was prepared by deracemization of *rac*-**1** (cf.[1,7a]) applying (+)-(*S*)-L-mandelic acid (MA)[28] for the resolution (Scheme 4, for details see Experimental Section). MA can be recovered in almost quantitative yield and used again and again.

The (1*R*,2*R*)-**1**, obtained by this method, had mp 147–148.5 °C (dec.) and $[\alpha]_D^{20}$: +7.35 (*c* 1.146, MeOH) or $[\alpha]_D^{20}$: +19.9 (*c* 0.453, THF). As a bonus, (1*S*,2*S*)-**1** which had mp 146.5–148.5 °C (dec.) and $[\alpha]_D^{20}$: −6.90 (*c* 0.60, MeOH) or $[\alpha]_D^{20}$: −19.3 (*c* 0.450, THF) was also isolated. The enantiomeric excesses for the thus obtained (1*R*,2*R*)-**1** and (1*S*,2*S*)-**1** were determined by HPLC analysis of their *N*-Boc derivatives to be ≥98 and 97.6%, respectively. These compounds appear to be perfectly stable in the solid phase, but not very stable in solution, as diluted solutions in both MeOH and THF after measurements of the specific rotations slowly turned dark after standing for two weeks at ambient temperature.



Scheme 4. Preparation of (1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-ol [(1*R*,2*R*)-1] by deracemization of *rac*-1 with (+)-(*S*)-L-mandelic acid (MA).

Conclusion

A new efficient approach to the target compound (1*R*,2*R*)-**1** from inexpensive starting materials – indene (US $ 38.50/kg) and NBS (US $ 43.60/kg; most solvents and the chiral auxiliary MA can be recovered) – using the nitration of *rac-trans*-1-aminoindan-2-ol (*rac*-**9**) as a key step, has been elaborated. To the best of our knowledge, this ought to be the most efficient and least expensive of all the methods known up to now, at least for the preparation of **1** in racemic form. Of course, in terms of "atom economy" [29] the final deracemization is not perfect. However, this can easily be improved by employing the previously published ring opening with ammonia of enantiomerically pure (prepared by enzymatic epoxidation[19]) or at least enantiomerically enriched (prepared by Jacobsen asymmetric epoxidation with NaOCl[18k]) epoxide (1*S*,2*R*)-**11**, followed by nitration and, if necessary, final purification *via* the salt with MA.

Experimental Section

General

All chemicals were used as commercially available. Indene (**7**) was freshly distilled under reduced pressure, bp 70–72 °C/

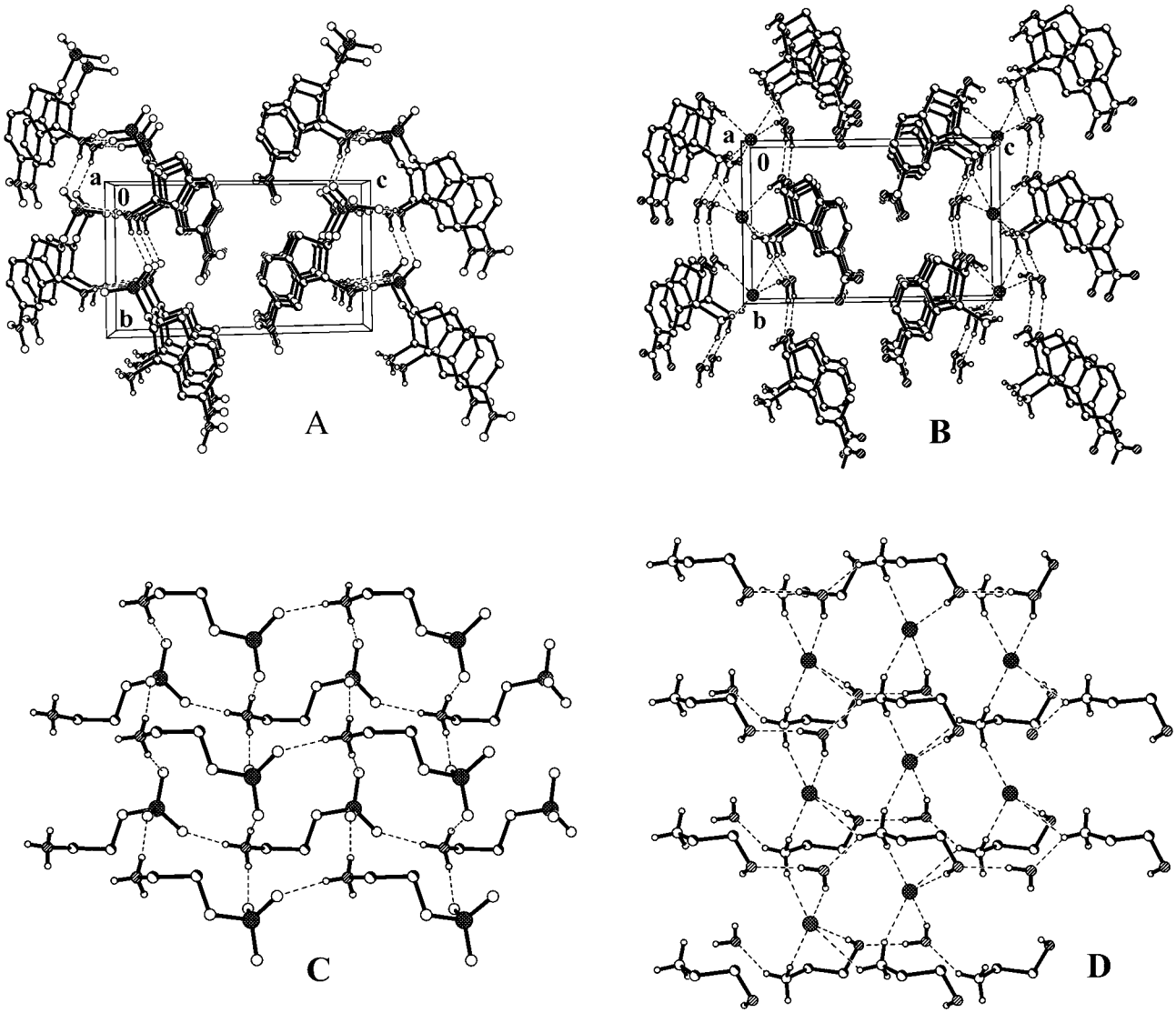


Figure 2. Crystal packing of (1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-ol hydrochloride monohydrate [(1*R*,2*R*)-**1**·HCl·H_2O] (**A**), of sulfuric acid mono-[(1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-yl] ester [(1*R*,2*R*)-**10**] (**B**) and detailed scheme of the hydrogen bonding motifs (**C** and **D**, respectively) in the crystal.

25 mbar. Anhydrous dichloromethane and THF for the preparation of *N*-Boc derivatives were obtained by distillation from P_4O_{10} and sodium benzophenone ketyl, respectively. THF for extractions was distilled from KOH using a rotary evaporator. Organic extracts were dried over $MgSO_4$. The ^1H and ^{13}C NMR spectra were recorded at 250 (^1H), and 62.9 MHz [^{13}C, additional DEPT (distortionless enhancement by polarization transfer)] on a Bruker AM 250 instrument in $CDCl_3$, D_2O and DMSO-d_6 solutions, $CHCl_3/CDCl_3$, DHO and CD_3SOCD_2H as internal reference. Chiral HPLC analyses were performed with a Chiracel OD column, hexane/2-propanol, 98:2 [for *N*-Boc-(1*R*,2*R*)-**9**] or 90:10 [for *N*-Boc-(1*R*,2*R*)-**1**], 0.9 mL/min. Melting points were determined on a Büchi 510 capillary melting point apparatus, values are uncorrected. TLC analyses were performed on precoated sheets (0.25 mm Sil G/UV_{254}, Macherey-Nagel).

Caution: The operations with compounds **1**, **9** and **10** should be performed carefully, as the handling of compounds containing amino and nitro groups is often hazardous, no safety data for these substances are as yet available.

rac-trans-2-Bromoindan-1-ol (*rac*-8)

This protocol was essentially adopted from published procedures[10d, e] taking the best details from each. A 2-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser and a thermometer was charged with a solution of indene (**7**)[30] (99.6 g, 100 mL, 0.857 mol) in a mixture of THF (700 mL) and water (700 mL). Under vigorous stirring and external cooling with ice-cold water, *N*-bromosuccinimide[31] (126,2 g, 0.709 mol) was added in small portions over a period of 2 h, maintaining the internal temperature around 20 °C, and the resulting mixture was stirred for an additional 22 h at ambient temperature. Brine (400 mL) was added, the two layers were separated in a 4-L separating funnel, and

the inorganic phase was extracted with ethyl acetate (2 × 600 mL). The combined organic phases were washed with 10% aqueous $Na_2S_2O_3$ solution (400 mL) and concentrated under reduced pressure. The residue was taken up in diethyl ether (1.2 L),[32] the solution was washed with water (500 mL), brine (400 mL), dried and concentrated under reduced pressure to give *rac*-**8** as a colorless solid; yield: 182.0 g (99.6%); mp 124–126 °C (lit. 127–128 °C,[10b] 130–131 °C[10e]). Its ^1H[10d] and ^{13}C NMR spectra[21] were identical to the published ones. According to its ^1H NMR spectrum, compound *rac*-**8** was pure enough to be used without further purification.

rac-trans-1-Aminoindan-2-ol (*rac*-9)

This protocol was essentially adopted from the published one.[13c] A 4-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer and a thermometer, was charged with 25% aqueous ammonia solution (2 L). Under vigorous stirring and external cooling with ice-cold water, *rac-trans*-2-bromoindan-1-ol (*rac*-**8**) (170.5 g, 0.8 mol) was added in small portions over a period of 2 h, maintaining the internal temperature around +5 °C, and the resulting mixture was vigorously stirred for an additional 34 h at ambient temperature. Excess ammonia and some water were evaporated directly from the reaction flask under reduced pressure (***Caution!*** Evaporation of ammonia should be done carefully by only slowly decreasing the pressure) to a volume of *ca.* 800 mL, then sodium hydroxide [(32.0 g, 0.8 mol, as a solution in 128 mL of water (20%)] was added, and the product was isolated by filtration. The mother liquor was percolated with *tert*-butyl methyl ether (2 L) over a period of 24 h.[33] The solvent was evaporated, and the residue was dried under vacuum over P_4O_{10} overnight to give *rac*-**9** as a colorless or light beige solid; yield: 114.6 g (96%); mp 123 °C (dec.) (lit.[13c] 128–129 °C), which was used without further purification. Its ^1H NMR spectrum was identical to the published one[13c]; ^{13}C NMR ($CDCl_3$): δ = 38.1 (CH_2), 64.0 (CH), 82.3 (CH), 123.2 (CH), 124.8 (CH), 127.1 (CH), 127.8 (CH), 138.9 (C), 144.0 (C).

rac-trans-1-Aminoindan-2-ol Nitrate (*rac*-9·HNO_3)

To a stirred suspension of *rac-trans*-1-aminoindan-2-ol (*rac*-**9**) (6.88 g, 46.1 mmol) in water in a 500-mL one-necked round-bottomed flask was added 65% aqueous nitric acid (2.5 mL, 1 equiv.). The mixture was stirred until a clear solution had formed (*ca.* 15 min), then water was evaporated under reduced pressure (40 °C bath temperature), and the residue was dried under vacuum over P_4O_{10} for 24 h to give *rac*-**9**·HNO_3 as a colorless or light yellow powder which is very well soluble in water; yield: 9.78 g (100%); mp 160–162 °C (dec.) (lit.:[13b] not reported); ^1H NMR (D_2O): δ = 2.73 (dd, *J* = 4.9, 16.4 Hz, 1H, CH_2), 3.21 (dd, *J* = 6.0, 16.4 Hz, 1H, CH_2), 4.42 (m, 2H, 2 CH), 7.11–7.28 (m, 4H, Ar-H); ^{13}C NMR (D_2O): δ = 40.8 (CH_2), 64.0 (CH), 77.9 (CH), 126.9 (CH), 128.0 (CH), 130.0 (CH), 132.4 (CH), 137.5 (C), 143.2 (C). If the solution is colored (this was observed when beige *rac*-**9** was used), it was stirred for 1 h with several spoons of charcoal and then filtered through a pad of Celite before evaporation.

Sulfuric Acid Mono-(*rac-trans*-1-amino-6-nitroindan-2-yl) Ester (*rac*-10)

This protocol for nitration was essentially adopted from a published procedure.[15] A 500-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, a nitrogen inlet and a thermometer, was charged with concentrated sulfuric acid (300 mL) and cooled to −10 °C under an atmosphere of nitrogen.[34] Under vigorous stirring and external cooling with acetone/dry ice, thoroughly powdered *rac*-**9**·HNO_3 (84.80 g, 0.4 mol) was added in small portions over a period of 2 h, maintaining the internal temperature in the range of −5 to −10 °C. The resulting mixture was vigorously stirred for an additional 1 h at −10 °C and for 0.5 h at 0 °C until a clear solution had formed, and was then poured onto cracked ice (700 g). The resulting very fine precipitate was filtered off, washed with ice-cold water (500 mL) and dried under vacuum over P_4O_{10} for 24 h to give *rac*-**10** as a colorless powder, decomposing slowly above 250 °C without melting; yield: 109.7 g (100%); ^1H NMR (DMSO-d_6): δ = 3.09 (dd, *J* = 6.6, 17.5 Hz, 1H, CH_2), 3.48 (dd, *J* = 7.4, 17.5 Hz, 1H, CH_2), 4.86–4.89 (m, 1H, CH), 4.98 (q, *J* = 6.5 Hz, 1H, CH), 7.59 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.23 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.48 (s, 1H, Ar-H), 8.57 (br. s, 3H, NH_3^+); ^{13}C NMR (DMSO-d_6): δ = 36.9 (CH_2), 59.4 (CH), 79.1 (CH), 120.2 (br., CH), 124.8 (br, CH), 126.5 (br, CH), 138.4 (C), 147.1 (C), 148.4 (C); (aromatic CH signals are close to coalescing); anal. calcd. for $C_9H_{10}N_2O_6S$ (274.3): C 39.41, H 3.67; found: C 39.17, H 3.52.

Sodium salt of *rac*-10: slow decomposition above 250 °C without melting; ^1H NMR (DMSO-d_6): δ = 2.16 (s, 2H, NH_2), 2.91 (dd, *J* = 4.1, 16.8 Hz, 1H, CH_2), 3.32 (dd, *J* = 6.2, 16.8 Hz, 1H, CH_2), 4.22 (br.s, 1H, CH), 4.54 (q, *J* = 6.0 Hz, 1H, CH), 7.45 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.06 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.11 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 37.0 (CH_2), 61.7 (CH), 85.1 (CH), 119.1 (br., CH), 121.8 (br., CH), 125.7 (br, CH), 146.6 (C), 147.0 (C), 147.8 (C); (aromatic CH signals are close to their coalescence temperature); anal. calcd. for $C_9H_9N_2O_6SNa$ (296.2): C 36.48, H 3.06; found: C 36.36, H 3.06.

rac-trans-1-Amino-6-nitroindan-2-ol (*rac*-1)

A 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and a reflux condenser, was charged with *rac*-**10** (53.5 g, 0.195 mol) and 6 N aqueous HCl (600 mL; by increasing this quantity one can accelerate the reaction, but the yield drops to 67–74%, as the product is rather well soluble in water at ambient temperature). The reaction mixture was stirred at 100 °C until *rac*-**10** had completely dissolved and a clear solution had formed (*ca.* 1 h), it was then stored in ice for 15 h. Still cold, the mixture was quickly filtered to give 48.47 g (100%) of *rac-trans*-1-amino-6-nitroindan-2-ol hydrochloride monohydrate (*rac*-**1**·HCl·H_2O) as beautiful slightly yellow crystals which easily loose water upon drying under vacuum over P_4O_{10} (12 h) to give *rac-trans*-1-amino-6-nitroindan-2-ol hydrochloride (*rac*-**1**·HCl) (44.95 g, 100%) as a colorless powder, slowly decomposing above 241 °C without melting; ^1H NMR (D_2O): δ = 2.90 (dd, *J* = 3.8, 17.2 Hz, 1H, CH_2), 3.38 (dd, *J* = 5.7, 17.2 Hz, 1 H, CH_2), 4.52–4.57 (m, 2H, 2 CH), 7.41 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.12 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.17 (s, 1H, Ar-H); ^{13}C NMR (D_2O): δ = 41.0 (CH_2), 63.4 (CH), 77.9 (CH), 122.5 (br, CH), 127.9 (br, CH), 129.1 (br, CH), 139.3 (C), 149.7 (C), 151.5 (C); (aromatic CH signals

are close to coalescing); anal. calcd. for $C_9H_{11}ClN_2O_3$ (230.7): C 46.86, H 4.81; found: C 46.54, H 4.59.

This compound (44.2 g, 191.6 mmol) was magnetically stirred in a 2-L beaker with water (300 mL) for 10 min. Then THF (300 mL) was added, the mixture was stirred for an additional 10 min before 25% aqueous ammonia solution (*ca.* 65 mL) was added in one portion. After stirring for an additional 5 min, the aqueous layer was saturated with sodium chloride, the layers were separated, and the aqueous phase was extracted with THF (2×300 mL). The combined organic phases were dried, filtered and concentrated under reduced pressure. The residue was stirred with diethyl ether/hexane mixture (1:1) and filtered again to give *rac*-**1**; yield: 37.0 g (100%); mp 150–152 °C (EtOAc, dec.) (lit:[3a] 136–137 °C). Its ^{1}H-NMR spectrum (DMSO-d_6) was identical to the published one (supporting information in ref.[7a]); ^{13}C NMR (DMSO-d_6): $\delta = 38.7$ (CH_2), 63.5 (CH), 81.3 (CH), 119.1 (br, CH), 122.9 (br, CH), 125.8 (br, CH), 147.0 (C), 147.7 (C), 148.3 (C); (aromatic CH signals are close to coalescing). This product can also be purified by recrystallization from ethyl acetate, but this is less practical, as the precipitate from EtOAc is rather voluminous.

P-Salt of (1*R*,2*R*)-1-Aminoindan-2-ol and (−)-Dibenzoyl L-Tartrate [(−)-13]

This protocol was adopted from the published one.[24] A 2-L beaker equipped with a mechanical stirrer was charged with a solution of (−)-dibenzoyl L-tartrate monohydrate (DBT) (100.0 g, 0.266 mol) in 95% ethanol (350 mL), and the solution was warmed to *ca.* 35 °C. In another 1-L beaker, *rac-trans*-1-aminoindan-2-ol (*rac*-**9**) (39.69 g, 0.266 mol) was dissolved in warm (*ca.* 45 °C) 95% EtOH, and this solution was added to the solution of DBT under vigorous stirring. The mixture was stirred for an additional 30 min. After 12 h, the voluminous precipitate was filtered off and washed with EtOH (200 mL), transferred into a 2-L, one-necked round-bottom flask and heated under reflux for 3 h with 1450 mL of EtOH. After this, the solution was partially evaporated to a volume of *ca.* 1100 mL at ambient pressure, and a few seed crystals (prepared by repeated crystallization) were added. After the mixture had been left standing for 1 week at ambient temperature, the precipitate was filtered off, washed with EtOH (200 mL) and dried under vacuum over P_4O_{10} overnight to give the P-salt (−)-**13** as colorless crystals; yield: 47.26 g (35%); mp 199–200 °C (dec.), $[\alpha]_D^{20}$: −100.8 (*c* 1.18, MeOH) [lit. for (+)-**13**:[24] $[\alpha]_D^{20}$: +100.7 (*c* 1.11, MeOH)]. After repeated crystallizations, neither the mp nor $[\alpha]_D^{20}$: had changed; ^{1}H NMR (DMSO-d_6): $\delta = 2.69$ (dd, $J = 6.9$, 16.5 Hz, 1H, CH_2), 3.17 (dd, $J = 6.8$, 16.5 Hz, 1H, CH_2), 4.31–4.36 (m, 2H, 2 CH), 5.16 (s, 2H, 2 CH), 7.15–7.26 (m, 3H, Ar-H), 7.41–7.44 (m, 1H, Ar-H), 7.49–7.55 (m, 4H, Ar-H), 7.55–7.68 (m, 2H, Ar-H), 7.96–7.99 (m, 4H, Ar-H), 9.0 (br s, 5H, OH + NH). All the mother liquors from this preparation were collected for the recovery of DBT (see below).

In the second experiment, from *rac*-**9** (20.42 g, 0.137 mol) and regenerated DBT·H_2O (51.48 g, 0.137 mmol) using the corresponding quantity of regenerated EtOH, (−)-**13** (23.6 g, 34%) was obtained as described above. This sample had $[\alpha]_D^{20}$: −100.5 (*c* 1.065, MeOH).

(1*R*,2*R*)-*trans*-1-Aminoindan-2-ol [(1*R*,2*R*)-9]

The salt (−)-**13** (45.85 g, 90.34 mmol) was suspended in diethyl ether (150 mL), and the mixture was vigorously stirred for 30 min. Under cooling with ice-cold water 1 N aqueous HCl solution (226 mL) was added, and the mixture was stirred until two clear phases had formed (*ca.* 30 min) which were separated. The organic phase was dried, filtered and concentrated under reduced pressure to give DBT·H_2O as a colorless solid; yield: 33.66 g (99%); mp 95–98 °C; $[\alpha]_D^{20}$: −119.4 (*c* 1.055, MeOH). This corresponds to the data for the pure compound as commercially available.

The aqueous layer was transferred to a percolator and cooled to 5 °C. Sodium hydroxide (14.46 g, 0.362 mol) was added, the mixture was stirred with cooling (ice-cold water) until all of the sodium hydroxide had dissolved, and then was percolated with *tert*-butyl methyl ether (0.5 L) over a period of 24 h. The solvent was evaporated, and the residue was dried under vacuum over P_4O_{10} overnight to give (1*R*,2*R*)-**9** as colorless crystals; yield: 13.442 g (99.7%); mp 133–135 °C (dec.); $[\alpha]_D^{20}$: −21.5 (*c* 0.58, MeOH) [lit. for (1*S*,2*S*)-**9**:[10d,24] $[\alpha]_D^{20}$: +25.0 (*c* 0.14, $CHCl_3$); $[\alpha]_D^{20}$: +22.8 (*c* 1.112, MeOH)]. The enantiomeric excesses in (1*R*,2*R*)-**9** were determined according to the literature procedure.[10d] Both *rac*-**9** and (1*R*,2*R*)-**9** were converted into their *N-tert*-butoxycarbonyl derivatives adopting a published protocol.[10d] ^{1}H and ^{13}C NMR data of *N*-Boc-*rac*-**9** and *N*-Boc-(1*R*,2*R*)-**9** were identical to the published ones.[3e]

***N*-Boc-*rac*-9:** mp 114–115 °C (lit.[10d] 113–114 °C).

***N*-Boc-(1*R*,2*R*)-9:** mp 130–132 °C, $[\alpha]_D^{20}$: +55.7 (*c* 1.376, $CHCl_3$) [lit.[10d] for *N*-Boc-(1*S*,2*R*)-**9**: mp not reported, $[\alpha]_D^{20}$: −51.3 (*c* 0.15, $CHCl_3$)]. These two samples were analyzed by HPLC, $t_R = 22.13$ min for (1*R*,2*R*)-**9** and 28.28 min for (1*S*,2*S*)-**9**. The analysis disclosed an *e.e.* of 77.6%.

Recovery of (−)-Dibenzoyl L-Tartrate[35]

This procedure is partially described in the previous experiment. The combined mother liquors from the preparation of (1*R*,2*R*)-**9** were evaporated in a 1-L, one-necked, round-bottomed flask. The residue was vigorously stirred (mechanical stirrer) with diethyl ether (500 mL) overnight, filtered off and washed with diethyl ether (200 mL).[36] The salt was suspended in a mixture of diethyl ether (500 mL) and water (700 mL) in a 2-L beaker and vigorously stirred for 30 min (mechanical stirrer). With cooling in ice-cold water 12 N aqueous HCl solution (29 mL) was added, and the mixture was stirred until two clear phases had formed (*ca.* 1 h), which were separated. The inorganic phase[37] was extracted with Et_2O (250 mL), the combined organic phases were dried, filtered and concentrated under reduced pressure to give DBT·H_2O as a light yellow foam; yield: 64.41 g (99%); $[\alpha]_D^{20}$: −119.2 (*c* 1.160, MeOH).

(1*R*,2*R*)-*trans*-1-Aminoindan-2-ol Nitrate [(1*R*,2*R*)-9·HNO_3]

From (1*R*,2*R*)-**9** (13.28 g, 89.03 mmol) and 65% aqueous nitric acid (2.5 mL, 1 equiv.) in water (500 mL), (1*R*,2*R*)-**9**·HNO_3 was obtained under the conditions described above as a colorless powder; yield: 18.89 g (100%); mp 162–164 °C (dec.); $[\alpha]_D^{20}$: −24.3 (*c* 1.149, H_2O) [lit.[13b] $[\alpha]_D^{20}$: −27.8 (*c* 0.7, H_2O)].

(1*R*,2*R*)-*trans*-1-Amino-6-nitroindan-2-ol [(1*R*,2*R*)-1]

From (1*R*,2*R*)-**9**·HNO_3 (18.25 g, 85.98 mmol) and H_2SO_4 (60 mL), sulfuric acid mono-[(1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-yl] ester [(1*R*,2*R*)-**10**] under the conditions described above, was obtained as a colorless powder, slowly decomposing above 250 °C; yield: 23.57 g (100%). Its ^{1}H and ^{13}C NMR data were identical to those of *rac*-**10**.

This material (10.69 g, 38.98 mmol) was converted into (1*R*,2*R*)-*trans*-1-amino-6-nitroindan-2-ol hydrochloride [(1*R*,2*R*)-**1**·HCl] as indicated above; yield: 8.80 g (98%); $[\alpha]_D^{20}$: −6.2 (*c* 1.05, H_2O). ^{1}H and ^{13}C NMR data were identical to those of *rac*-1·HCl. Work-up of this salt with aqueous ammonia furnished (1*R*,2*R*)-**1** in 99% yield, mp 145–147 °C (dec.), $[\alpha]_D^{20}$: +15.7 (*c* 1.16, THF).

Salt [(+)-14] of (1*R*,2*R*)-*trans*-1-Amino-6-nitroindan-2-ol [(1*R*,2*R*)-1] and (+)-(*S*)-L-Mandelic Acid (MA)

A 2-L beaker equipped with a mechanical stirrer was charged with a solution of MA (41.46 g, 272.5 mmol) in ethanol (280 mL), and the solution was warmed to *ca.* 35 °C. In another 2-L beaker, *rac-trans*-1-amino-6-nitroindan-2-ol (*rac*-**1**) (51.26 g, 264 mmol) was dissolved in warm (*ca.* 45 °C) EtOH (800 mL), and this solution was added to the solution of MA with vigorous stirring. The mixture was stirred for an additional 30 min at *ca.* 40 °C. After 12 h, the voluminous precipitate was filtered off and washed with EtOH (240 mL) to give 72.54 g of the salt mixture. This was transferred into a 2-L, one-necked round-bottomed flask and heated under reflux for 1 h with 1500 mL of EtOH. After this, seeding crystals (prepared by repeated crystallization of the salt from enantiomerically enriched [(1*R*,2*R*)-**1**], the preparation of which is described in the previous experiment) were added. After standing of this mixture for 1 week at ambient temperature, the precipitate was filtered off and washed with EtOH (200 mL) to give the salt mixture; yield: 55.97 g (61%); mp 162–170 °C (dec.).[38]

A small portion of this material was converted into (1*R*,2*R*)-**1** as described above and then into its *N*-Boc derivative (see below). The HPLC analysis of the latter disclosed an *e.e.* of 61.8%. This salt was heated in THF (1100 mL) under reflux for 30 min (the material dissolved only partially) and, after standing for two days at ambient temperature, the precipitate was filtered off and washed with THF (200 mL) to give the salt; yield: 33.51 g (36.6%); mp 181–182 °C (dec.).

This was recrystallized again from EtOH (670 mL, seeding crystals were added) to give (+)-**14**; yield: 31.10 g (34%); mp 183–184 °C (dec.), which is essentially the same as the mp of the seeding crystals (183.5–184 °C, dec.); $[\alpha]_D^{20}$: +45.3 (*c* 1.672, MeOH).

The mother liquor from the first crystallization from EtOH was evaporated, and the residue was recrystallized from EtOH three times (40 mL of EtOH for every 10 g of the salt; the material which did not dissolve in this quantity was filtered off) to give the salt of MA with (1*S*,2*S*)-**1** [salt (+)-**14a**]; yield: 15.53 g (17%); mp 163–164 °C; $[\alpha]_D^{20}$: +47.0 (*c* 2.088, MeOH).[39]

(1*R*,2*R*)-*trans*-1-Amino-6-nitroindan-2-ol [(1*R*,2*R*)-1] and (1*S*,2*S*)-*trans*-1-Amino-6-nitroindan-2-ol [(1*S*,2*S*)-1]

The salt (+)-**14** (24.590 g, 71.0 mmol) was suspended in a mixture of diethyl ether (200 mL) and water (200 mL), and the mixture was vigorously stirred for 15 min. Under cooling with ice-cold water 1 N aqueous HCl (118 mL) was added, and the mixture was stirred at ambient temperature until two clear phases had formed (*ca.* 15 min) which were separated. The aqueous layer was extracted with diethyl ether (3 × 150 mL), the combined organic phases were dried, filtered and concentrated under reduced pressure to give MA as a colorless solid; yield: 10.69 g (99%); mp 129–131 °C; $[\alpha]_D^{20}$: +156.9 (*c* 3.318, H_2O). This corresponds to the data for the pure compound as commercially available [mp 130–132 °C and $[\alpha]_D^{20}$: +155.0 ± 5 (*c* 5.0, H_2O)]. The aqueous layer was magnetically stirred in a 1-L beaker with THF (200 mL) for 10 min before 25% aqueous ammonia (*ca.* 30 mL) was added in one portion. After stirring for an additional 5 min, the aqueous layer was saturated with sodium chloride, the layers were separated, and the aqueous phase was extracted with THF (3 × 150 mL). The combined organic phases were dried, filtered and concentrated under reduced pressure. The residue was stirred with diethyl ether/hexane mixture (1:1, 100 mL), filtered off and dried under vacuum over P_4O_{10} overnight to give (1*R*,2*R*)-**1**; yield: 13.64 g (99%); mp 147–148.5 °C (dec.), $[\alpha]_D^{20}$: +7.35 (*c* 1.146, MeOH), +19.9 (*c* = 0.453, THF).

Analogously, from the salt (+)-**14a** (12.432 g, 35.9 mmol), (+)-mandelic acid (5.46 g, 100%) and (1*S*,2*S*)-**1** (6.90 g, 99%) were obtained according to the same protocol. The latter compound had mp 146.5–148.5 °C (dec.) and $[\alpha]_D^{20}$: −6.90 (*c* 0.60, MeOH), −19.3 (*c* 0.450, THF). The NMR spectra of both enantiomers (DMSO-d_6) were identical to those of the racemic compound *rac*-**1**.

A sample each of *rac*-**1** (411 mg, 2.12 mmol), (1*R*,2*R*)-**1** (108 mg, 0.56 mmol) or (1*S*,2*S*)-**1** (92 mg, 0.47 mmol), respectively, was stirred in anhydrous THF (15 mL) with 1.1 equivs. of di-*tert*-butyl pyrocarbonate (Boc_2O) at ambient temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from EtOAc to give *N*-Boc-*rac*-**1** (488 mg, 78%), *N*-Boc-(1*R*,2*R*)-**1** (147 mg, 90%) and *N*-Boc-(1*S*,2*S*)-**1** (125 mg, 90%) as colorless crystals with mp 184–186 (dec.), 198–199 (dec.) and 199–201 °C (dec.), respectively. The latter two compounds had $[\alpha]_D^{20}$: −73.1 (*c* 0.884, THF) and $[\alpha]_D^{20}$: +70.0 (*c* 0.916, THF), respectively. ^{1}H NMR ($CDCl_3$) of all three compounds: δ = 1.51 (s, 9H, 3 CH_3), 2.99 (dd, *J* = 8.2, 16.8 Hz, 1H, CH_2), 3.39 (dd, *J* = 7.7, 16.8 Hz, 1H, CH_2), 4.10 (br. s, 1H, OH), 4.50 (q, *J* = 7.4 Hz, 1H, CH), 4.98 (t, *J* = 6.0 Hz, 1H, CH), 5.06 (br. s, 1H, NH), 7.38 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 8.16 (dd, *J* = 2.0, 8.3 Hz, 1H, Ar-H). The HPLC analyses [injection as a solution in THF, t_R = 12.5 min for (1*R*,2*R*)-**1** and 14.3 min for (1*S*,2*S*)-**1**] disclosed an *e.e.* of ≥98% for *N*-Boc-(1*R*,2*R*)-**1** and an *e.e.* of 97.6% for *N*-Boc-(1*S*,2*S*)-**1**.

All the mother liquors from the different recrystallizations were evaporated together, and (+)-mandelic acid was recovered in 98% yield under the conditions described above for DBT, but with several extractions with diethyl ether, as MA is rather well soluble in water.

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[26] Crystals of the compounds were obtained by recrystallization from water [(1*R*,2*R*)-**1**·HCl·H_2O] and by slow evaporation of a solution in THF/aqueous NH_3 [(1*R*,2*R*)-**10**]. The X-ray single crystal data were collected at 120(2) K on Bruker Proteum-M CCD (for **1**), equipped with Bede Microsource X-ray generator, and Bruker SMART CCD 6000 (for **10)** diffractometers using graphite monochromated Mo-K_α radiation. The structure solutions and refinements on F^2 were performed with the Bruker SHELXTL program suite. (1*R*,2*R*)-**1**·HCl·H_2O: $C_9H_{11}N_2O_3^+ \times Cl^- \times H_2O$ (*M* 248.66), crystal size $0.24 \times 0.20 \times 0.12$ mm^3, monoclinic, $a = 5.2952(2)$, $b = 8.0441(3)$, $c = 12.7859(4)$ Å, $\alpha = \gamma = 90$, $\beta = 90.90(1)^\circ$, $V = 544.55(3)$ Å^3, $Z = 2$, space group $P\,2_1$, $\rho = 1.517$ g·cm^{-3}, $\mu = 0.352$ mm^{-1}, intensities measured: 4936 ($2\theta_{max} = 57.98^\circ$), independent: 2743 ($R_{int} = 0.0381$), 197 parameters refined, $R_1 = 0.0322$ for 2743 reflections with $I > 2\sigma(I)$, wR_2 (all data) = 0.0836, GoF = 1.123, maximum and minimum residual electron density 0.373 and -0.256 e·Å^{-3}. (1*R*,2*R*)-**10**: $C_9H_{10}N_2O_6S$ (*M* 274.25), crystal size $0.14 \times 0.06 \times 0.02$ mm^3, monoclinic, $a = 5.2119(2)$, $b = 7.6336(3)$, $c = 13.4631(5)$ Å, $\alpha = \gamma = 90$, $\beta = 100.79(2)^\circ$, $V = 526.17(3)$ Å^3, $Z = 2$, space group $P\,2_1$, $\rho = 1.731$ g·cm^{-3}, $\mu = 0.333$ mm^{-1}, intensities measured: 5140 ($2\theta_{max} = 58.94^\circ$), independent: 2818 ($R_{int} = 0.0250$), 203 parameters refined, $R_1 = 0.0310$ for 2818 reflections with $I > 2\sigma(I)$, wR_2 (all data) = 0.0618, GoF = 1.020, maximum and minimum residual electron density 0.271 and -0.338 e·Å^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited as supplementary publication no. CCDC-250618 [(1*R*,2*R*)-**1**·HCl·H_2O] and CCDC-250617 [(1*R*,2*R*)-**10**] with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (+44)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[32] According to the original procedures,[10d, e] after work-up with aqueous 10% $Na_2S_2O_3$ solution, the organic layer was washed with brine, dried, concentrated and recrystallized from EtOAc[10d] or EtOH,[10e] respectively. However, this decreases the yield to 85 and 82.5%, respectively, as *rac*-**8** is rather well soluble in both solvents. Moreover, the main impurity – succinimide – remains even after recrystallization (from traces and up to 5%). As this impurity is very poorly soluble in diethyl ether, we have slightly modified the procedure in this point.

[33] According to the original protocol,[13c] the product was only filtered off and dried; however, this decreased the yield to 69%. Another procedure[24] recommends to perform an extraction with EtOAc in a percolator for 4 h. However, we have found that *rac*-**9** is not completely inert towards this solvent under the conditions of continuous extraction, and thus the *N*-acetyl derivative of *rac*-**9** was found in the resulting product as an impurity (1–8%, depending on the extraction time, 4–16 h) according to the ^{1}H NMR spectrum. Unlike this, the extraction with *tert*-butyl methyl ether proceeds at a lower temperature and without undesirable side reactions.

[34] The role of nitrogen in this reaction is to prevent the dilution of H_2SO_4 by atmospheric moisture only.

[35] The recovery of (−)-dibenzoyl L-tartrate has been described in the patents: a) S. Martin, D. Piergentili, *UK Pat. Appl.* GB 2382074 A1, **2003**; *Chem. Abstr.* **2003**, *138*, 385169; b) J. Jendrichovsky, L. Stibranyi, *Recovery of (+)- and (−)-dibenzoyltartaric acid monohydrate after resolution of optically active forms of α-methyl-β-dimethylaminopropiophenone. Czech. Patent*, **1975**; *Chem. Abstr.* **1975**, *83*, 78879. However, these patents do not cover our method, as in both patents the substituted tartaric acid derivatives from the resolution process were ***firstly*** neutralized by adding a base (for example, aqueous sodium bicarbonate), extracted into an aqueous phase, and ***secondly*** crystallized from the aqueous phase by addition of a mineral acid.

[36] This procedure is necessary to purify the salt, which after evaporation of EtOH has a yellow to green color. After stirring and washing with Et_2O, the salt is colorless again. Without this operation, the recovered $DBT \cdot H_2O$ can have a dark color.

[37] The aqueous layer can be used for the preparation of (1*S*,2*S*)-**9** by isolation of enriched **9** and applying the established procedure.[24]

[38] As the specific rotations of the two salts of MA with (1*R*,2*R*)-**1** [salt (+)-**14**] and (1*S*,2*S*)-**1** [salt (+)-**14a**] are very close to one another ($[\alpha]_D^{20}$: +45.3 (*c* 1.672, MeOH) and +47.0 (*c* 2.088, MeOH), respectively), the progress of purification can better be monitored by measuring the melting points. The second salt is better soluble in EtOH and in THF than the first one.

[39] Alternatively, the salts (+)-**14** and (+)-**14a** can be separated by low temperature crystallization from water/MeOH, 100:1.[1]

