Highly Efficient Biocatalytic Resolution of *cis*- and *trans*-3-Aminoindan-1-ol: Syntheses of Enantiopure Orthogonally Protected *cis*- and *trans*-Indane-1,3-diamine

Mónica López-García, Ignacio Alfonso, and Vicente Gotor*[a]

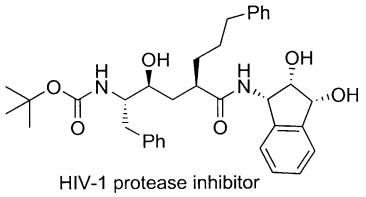
Abstract: The efficient chemoenzymatic synthesis of enantiopure 1,3-difunctionalized indane derivatives has been achieved. The corresponding *cis* and *trans* *N*-protected amino alcohols were successfully resolved by acetylation using lipase B, which is a biocatalyst isolated from *Candida antarctica*. All the possible isomers were obtained in very good chemical yields and *ee* values (>99%). The utility of these compounds was subsequently shown by the preparation of orthogonally protected *cis*- and *trans*-indane-1,3-diamine using a Mitsunobu reaction. Both enantiomers of the *trans* isomer and a desymmetrized *cis* diastereomer were prepared in enantiopure form. Complete inversion of configuration during the Mitsunobu reaction was demonstrated by a combination of NMR techniques and molecular modeling. The utility and versatility of the strategy was also demonstrated by the selective deprotection of each nitrogen atom under mild reaction conditions.

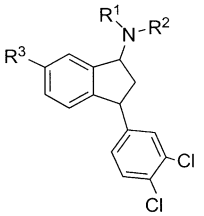
Keywords: biotransformations · chemoenzymatic synthesis · enzymes · Mitsunobu reaction

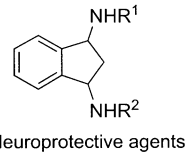
Introduction

Biocatalytic processes have been demonstrated to be a powerful tool for the preparation of chiral synthons in organic synthesis.[1] Simple enzymatic resolution of racemic mixtures,[2] sequential kinetic resolution,[3] parallel kinetic resolution,[4] dynamic kinetic resolution,[5] asymmetric redox processes,[6] and desymmetrization of prochiral substrates[7] have been used for the efficient and practical preparation of enantiopure drugs and chemicals. Moreover, enzymes often display high chemo- and stereoselectivities under mild reaction conditions; this enhances the value of these catalysts for modern organic chemistry.

In efforts devoted to explore new biotransformations that have subsequent synthetic applications, we became interested in 1,3-disubstituted substrates. The efficient enzymatic resolution of 1,2-amino alcohols[8] and 1,2-diamines[3c,e] has previously been accomplished in our group. In spite of the potential applications of 1,3-optically active compounds, they have received much less attention, especially in the field of biocatalytic processes.[9] One of the most interesting structures from this family is the 1,3-disubstituted indane core, as this moiety is present in some HIV protease inhibitors,[10] in drugs used for cocaine abuse treatment,[11] as well as in polyamine derivatives used against neurodegenerative diseases.[12] In addition, both optically active amino alcohols and diamines have possible interesting applications in asymmetric synthesis and in the design of new ligands for asymmetric catalysts.[13] Amino alcohol derivatives have been used to resolve acids because of the ability of their corresponding crystalline diastereomeric salts to form β-sheet-







[a] M. López-García, Dr. I. Alfonso, Prof. V. Gotor
Departamento de Química Orgánica e Inorgánica
Facultad de Química, Universidad de Oviedo
Oviedo (Spain)
E-mail: vgs@sauron.quimica.uniovi.es

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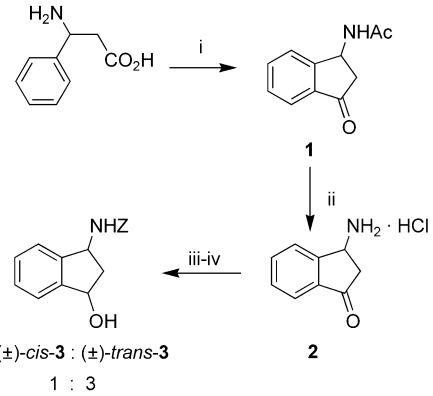
like structures.[14] Similarly, diamines constitute synthetic precursors for optically active polyamines and azamacrocycles.[15] As a result, we have been interested in the development of chemoenzymatic syntheses of new enantiopure diamines that then could have potential applications in all these fields. Moreover, it has emerged that the isomers of indane-1,3-diamine are interesting but as yet unexploited building blocks. Unfortunately, access to both enantiomers of these types of molecules still remains a difficult task. Indeed, only one paper describes the resolution of 3-aminoindan-1-ol isomers.[14] Several diastereomeric salt recrystallizations using a chiral acid were needed to resolve the *trans* isomer, and this was only achieved in poor yields, while tedious chiral HPLC separation yielded only enantioenriched rather than the enantiopure *cis* diastereomer, also in poor final yields.

On the basis of these facts, we embarked on the preparation of a number of different enantiopure 1,3-disubstituted indane synthons in which all possible relative stereochemistries were accounted for. To achieve this goal, we used a combination of both biocatalytic and nonenzymatic processes. In this way, all the enantiomers of *cis*- and *trans*-3-aminoindan-1-ol and *cis*- and *trans*-indane-1,3-diamine were obtained in enantiopure form. Our synthetic strategy afforded orthogonally protected diamines, which then allowed each nitrogen atom to be selectively deprotected. In addition, we will describe the unsymmetrical preparation of an enantiopure derivative of *cis*-indane-1,3-diamine that would be a *meso* compound if it were symmetrically substituted.

Results

Enzymatic resolution of (±)-*trans*- and (±)-*cis*-3-(*N*-benzyloxycarbonyl)aminoindan-1-ol: We built the 1,3-disubstituted indane moiety from commercially available racemic 3-amino-3-phenylpropanoic acid. Conventional acetylation of the amino group and transformation of the carboxylic acid group into the acyl chloride followed by in situ intramolecular Friedel–Craft acylation of the aromatic ring afforded (*N*-acetyl)-3-aminoindan-1-one (**1**) in 76% overall yield (Scheme 1).[14] Standard deprotection of the acetamide



Scheme 1. Reagents and conditions: i) Ref. [14]; ii) HCl; iii) $NaBH_4$, MeOH; iv) CbzCl, Na_2CO_3.

yielded aminoketone **2**, which was isolated as its hydrochloride salt. Borohydride reduction of **2** gave the corresponding amino alcohols, which were subsequently transformed in situ into their benzyl carbamate derivatives for easier isolation and manipulation (92% combined overall yield). The diastereomeric mixture of carbamates was readily separated by semipreparative HPLC to give (±)-*trans*-**3** and (±)-*cis*-**3**. The moderate diastereoselectivity (3:1 *trans*/*cis*) observed was determined both by ^{1}H NMR spectroscopy of the crude product and from signal integration of the HPLC traces. The result can be explained by analysis of the initial reaction between borohydride and the free amino group to form the corresponding boramide. In good agreement with previously published results, this reaction would favor an intramolecular reduction that would lead to a *trans* configuration.[14] The relative configurations of the compounds were unambiguously established by NOESY experiments. Results from these experiments are shown in Figure 1. Each proton

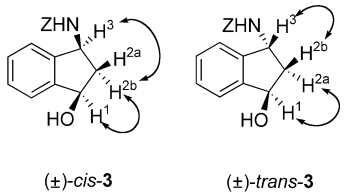


Figure 1. Cross-peaks observed in the NOESY spectra of *cis*-**3** and *trans*-**3**.

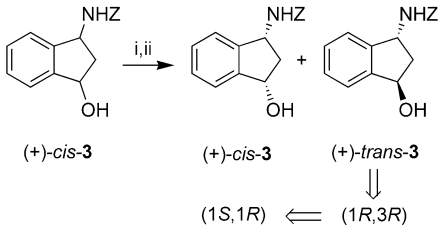
of the diastereotopic C2 methylene group in the (±)-*trans*-**3** isomer displays strong cross-peaks with a proton at either C1 or C3 (H1 correlates with H2a and H3 with H2b, respectively); this suggests that H1 and H3 are on opposite faces of the cylcopentane ring. On the other hand, in the *cis* isomer, both H1 and H3 show strong NOE effects with only

Abstract in Spanish: *Se ha conseguido la eficiente síntesis quimioenzimática de indanos 1,3-difuncionalizados enantiopuros. Los correspondientes* cis *y* trans *aminoalcoholes* N*-protegidos se resuelven mediante acetilación usando la lipasa B de* Candida antarctica *como biocatalizador. Así se obtienen todos los posibles isómeros de forma enantiopura y con muy buenos rendimientos. La utilidad de estos compuestos se muestra mediante la preparación de la* cis *y* trans *indano-1,3-diamina ortogonalmente protegidas, a través de una reacción de Mitsunobu. Para el isómero* trans*, ambos enantiómeros pueden ser preparados de forma enantiopura. En el caso del diastereoisómero* cis*, también se obtiene el correspondiente compuesto desimetrizado enantioméricamente puro. La inversión total de la configuración durante la reacción de Mitsunobu se demuestra mediante la combinación de técnicas de RMN y modelización molecular. La utilidad y versatilidad de la estrategia finalmente se pone de manifiesto con la desprotección selectiva de cada átomo de nitrógeno en condiciones suaves de reacción.*

one proton of the C2 methylene group (H1 and H3 correlate with H2b). This observation indicates that H1, H3, and H2b are all on the same side of the cyclopentane ring. It is also noteworthy that the chemical shift difference for the diastereotopic protons of the methylene group at C2 is more pronounced for the *cis* ($\Delta\delta = 1.20$ ppm) than for the *trans* ($\Delta\delta = 0.19$ ppm) isomer. This effect, which is in accord with reported data on similar structures, arises because the chemical environment of each C2 proton is different to a greater extent for the *cis* isomer.[16] We subsequently used these Z-amino-protected compounds to study enzymatic resolution by transesterification.

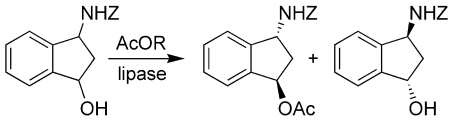
We started the enzymatic resolution screening with (±)-*trans*-**3**. Different enzymes, solvents, and acyl donors were tested (Table 1), and it was found that reactivity and enantioselectivity[17] depended largely on the enzyme used. For instance, the optimized reaction conditions for similar substrates previously obtained in our laboratory[8] (Table 1, entry 1) yielded low *E* values. When the solvent (entry 2), acyl donor (entry 3), or temperature (entry 4) was changed the results did not improve. We concluded from these observations that lipase isolated from *Pseudomonas cepacia* (PSL) displays low enantioselectivity towards this substrate. Moreover, the polymer-supported preparation of this enzyme (PSL-C) did not fare any better, and the substrate was almost completely converted into a virtually racemic product in six hours at 20 °C (Table 1, entry 5). However, lipase B (CAL-B) isolated from *Candida antarctica* displayed excellent enantioselectivities upon accurate control of both the reaction conditions (Table 1, entries 6–10) and the percentage of conversion (Table 1, entries 9 and 10), and allowed both the substrate and product to be obtained in enantiomerically pure form. Under optimized reaction conditions at 30 °C, vinyl acetate was used as the acyl donor and *tert*-butyl methyl ether was used as the solvent. The reaction, which is very fast, reached 49 % conversion in less than one hour and yielded the enantiopure acylated product (1*R*,3*R*)-**4** in 48 % yield (50 % is the limiting yield for a kinetic resolution). On the other hand, 55 % conversion was achieved after 3.5 h, and gave rise to a 43 % yield of the remaining alcohol in an enantiomeric excess of >99 % after chromatographic purification. The absolute configuration of the product was inferred by deprotecting the Z group of the unreacted substrate (Pd^0, HCOOH, MeOH) and comparing the sign of specific rotation with published data.[13] As a result, the fastest reacting enantiomer was determined to have a (1*R*,3*R*) configuration, which is in good agreement with the Kazlauskas' rule.

We used the optimized reaction conditions determined for (±)-*trans*-**3** in the enzymatic resolution of (±)-*cis*-**3**. Although the reaction is slower for the *cis* isomer, the enantioselectivity is better. Moreover, both the substrate and product are able to be isolated in enantiopure form from the same enzymatic reaction (Table 2, entry 3). The process is also very efficient, as enantiopure ester (1*R*,3*S*)-**4** and alcohol (1*S*,3*R*)-**3** were isolated in 48 and 49 % yield, respectively. The lower reactivity of *cis* isomers has previously been observed in our research group with respect to indane-1,2-amino alcohol derivatives,[8b] and could arise because of the presence of a bulkier (NH–Z) substituent on the same face as the reacting hydroxy group. The absolute configuration was determined by performing the sequence depicted in Scheme 2. The unreacted substrate from the enzymatic process was first oxidized with pyridinium chlorochromate (PCC), and was then reduced with borohydride to give a mixture of *cis*/*trans* diastereomers. The reaction is generally



Scheme 2. Reagents and conditions: i) PCC, CH_2Cl_2; ii) $NaBH_4$, MeOH.

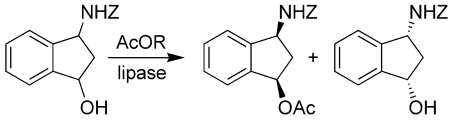
Table 1. Enzymatic resolution screening for (±)-*trans*-**3**.



Entry	Enzyme	Solvent	R	*T* [°C]	*t* [h]	ee_s[a] [%]	ee_p[a] [%]	*c*[b] [%]	*E*[b]
1	PSL	1,4-dioxane	vinyl	30	48	66	81	45	19
2	PSL	*t*BuOMe	vinyl	30	36	82	82	50	25
3	PSL	*t*BuOMe	isopropenyl	30	36	16	87	16	16
4	PSL	*t*BuOMe	vinyl	20	27	34	88	28	21
5	PSL-C	*t*BuOMe	vinyl	20	6	46	5	90	1.5
6	CAL-B	1,4-dioxane	vinyl	30	1	47	98	32	157
7	CAL-B	*t*BuOMe	vinyl	15	2	88	98	47	>200
8	CAL-B	*t*BuOMe	vinyl	15	0.5	81	>99	45	>200
9	CAL-B	*t*BuOMe	vinyl	30	0.5	94	>99	49	>200
10	CAL-B	*t*BuOMe	vinyl	30	3.5	>99	81	55	>200

[a] Determined by HPLC: $ee_s = ee$[(1*S*,3*S*)-**3**] and $ee_p = ee$[(1*R*,3*R*)-**4**]. [b] Determined from ee_s and ee_p as in ref. [17].

Table 2. Enzymatic resolution of (±)-*cis*-**3** by using the optimized reaction conditions determined for (±)-*trans*-**3**.



(±)-*cis*-**3** (1*R*,3*S*)-**4** (1*S*,3*R*)-**3**

Entry	Enzyme	Solvent	R	*T* [°C]	*t* [h]	ee_s[a] [%]	ee_p[a] [%]	*c*[b] [%]	*E*[b]
1	CAL-B	*t*BuOMe	vinyl	30	14	36	>99	27	>200
2	CAL-B	*t*BuOMe	vinyl	30	36	54	>99	35	>200
3	CAL-B	*t*BuOMe	vinyl	30	60	>99	>99	50	>200

[a] Determined by HPLC: $ee_s = ee$[(1*S*,3*R*)-**3**] and $ee_p = ee$[(1*R*,3*S*)-**4**)]. [b] Determined from ee_s and ee_p as in ref. [17].

diastereoselective, although only a 3:2 *cis*/*trans* mole ratio was obtained in this case. In particular, the carbonyl ketone is preferentially reduced from the face opposite the Z group to give the *cis* isomer. HPLC separation of the diastereomeric mixture afforded (+)-*trans*-**3**, in which the configuration was determined to be (1*R*,3*R*). Since the asymmetric carbon at the 3-position is not involved in any of the reactions depicted in Scheme 2, the absolute configuration of the unreacted substrate was unambiguously assigned as (1*S*,3*R*). This configuration is also in good agreement with the Kazlauskas' rule for enzymatic resolution of secondary alcohols.

Finally, the NMR spectra for the acetylated derivatives *cis*-**4** and *trans*-**4** were observed to be similar to the spectra for *cis*-**3** and *trans*-**3**. In particular, the difference in the chemical shifts of the diastereotopic methylene protons at C2 was found to be greater for the *cis* ($\Delta\delta = 1.15$ ppm) than for the *trans* ($\Delta\delta = 0.32$ ppm) isomer, and reflects that the cyclopentane faces in *cis*-**4** have considerably different chemical environments. In addition, the assigned stereochemistry was confirmed from the strongest cross-peaks found in the NOESY spectra of compounds (1*R*,3*R*)-**4** and (1*R*,3*S*)-**4** (Figure 2).

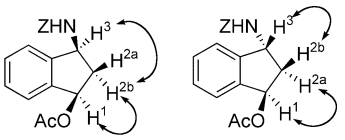
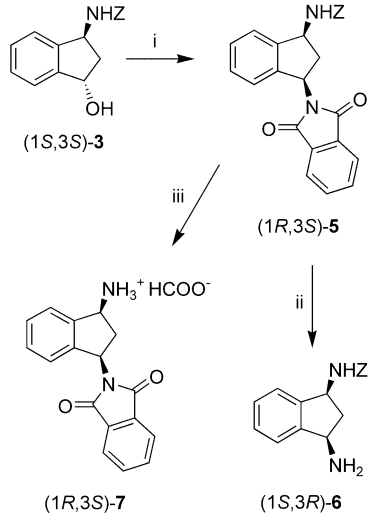


Figure 2. Cross-peaks observed in the NOESY spectra of (1*R*,3*R*)-**4** and (1*R*,3*S*)-**4**.

Synthesis of orthogonally protected enantiopure *cis*- and *trans*-indane-1,3-diamine: First of all, some structural characteristics must be considered. The *trans* isomer exists as a pair of enantiomers that possess C_2 symmetry, while the *cis* diastereomeric counterpart is a *meso* compound. Consequently, the *cis* isomer is only chiral when the substituents on the amino groups are different. Here we present a simple strategy, using the Mitsunobu reaction as the key step, for the synthesis of orthogonally protected *cis*- and *trans*-diamines. We will describe the preparation of both enantiomers of the *trans* diastereomer in enantiopure form, while orthogonal protection of the *cis* isomer has allowed us to synthesize an enantiopure, asymmetrically substituted *meso* compound that is chiral.

We used (1*S*,3*S*)-**3**, which was obtained as the unreacted substrate in the (CAL-B)-catalyzed acetylation described in the previous section (Table 1, entry 10), as the starting material for the synthesis of the *cis* diastereomer. Compound (1*R*,3*S*)-**5** was obtained in 76% yield after chromatographic purification when enantiopure (1*S*,3*S*)-**3** was subjected to Mitsunobu reaction conditions in the presence of PPh_3, diethylazodicarboxylate (DEAD), and phthalimide as the nucleophile (Scheme 3). As demonstrated from a combination



Scheme 3. Reagents and conditions: i) phthalimide, DEAD, PPh_3; ii) hydrazine, MeOH; iii) Pd, HCOOH, MeOH.

of NMR data and molecular modeling, the reaction took place with complete inversion of configuration at the 1-position. Figure 3 shows the observed cross-peaks in the NOESY spectrum and the optimized structure (HF/3-21G level of theory) for (1*R*,3*S*)-**5**. One of the diastereotopic C2 protons (labeled as H2a) displays an NOE effect with the NH of the carbamate, and strong cross-peaks arise between H1, H3, and H2b in good agreement with the measured distances in the optimized geometry (Figure 3). These data allowed the chemical shifts for H2a and H2b to be unambiguously assigned. Again, the anisochrony of the ^{1}H NMR chemical shifts for the diastereotopic methylene protons at

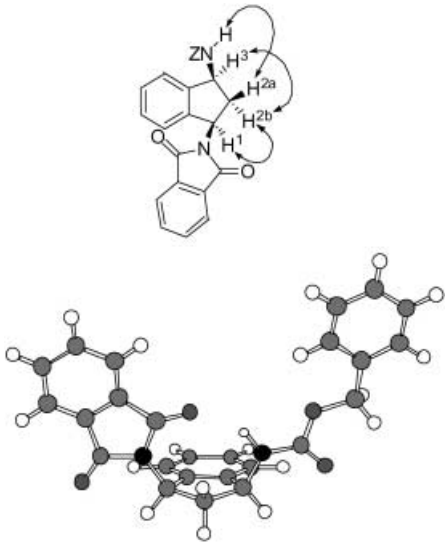
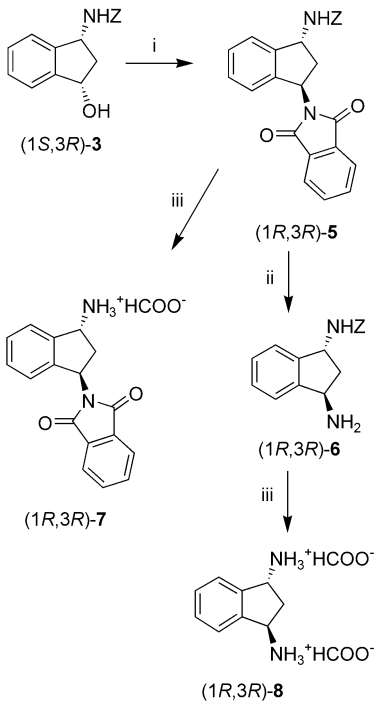


Figure 3. Cross-peaks observed in the NOESY spectrum (top) and the optimized structure (HF/3-21G level of theory) for (1*R*,3*S*)-**5** (bottom).

C2 were considerably greater ($\Delta\delta = 1.00$ ppm). Furthermore, both H1 and H3 showed large vicinal ($^3J_{H,H}$) coupling constants with one of the protons at C2 (H2b) and smaller coupling constants with the other proton (H2a). The minimized structure depicted in Figure 3 displays an almost planar geometry for the fused five-membered ring. Analysis of the energy minimum indicates that a stabilizing eight-membered-ring hydrogen bond exists between the carbamate NH at C3 and the phthalimide carbonyl group at C1, and explains the downfield shift observed for the NH proton signal in the ^{1}H NMR spectrum. The hydrogen bond renders a very rigid geometry within the molecule, as the conformation around C1–C2–C3 is nearly eclipsed. Therefore, large coupling constants are observed for the protons in a *cis* disposition ($^3J_{H1,H2b} = {}^3J_{H3,H2b} = 9.4$ Hz), while the *trans* disposed protons display smaller coupling constants ($^3J_{H1,H2a} = {}^3J_{H3,H2a} = 4.4$ Hz). All these observations strongly support that H1 and H3 have a *cis* configuration, and implies that the configuration at C1 has undergone inversion.

Compound (1*R*,3*S*)-**5** is also interesting because it is chiral and can be considered as a desymmetrized *meso* compound. Therefore, selective cleavage of each protecting group would access the free amino attached either to the *R* or *S* stereogenic center (Scheme 3). We thereby attempted to facilitate this transformation. Incubation of (1*R*,3*S*)-**5** in a methanolic solution of hydrazine led to deprotection of the nitrogen atom attached to the *R* chiral center in 98% yield. In contrast, conventional hydrogenolysis of (1*R*,3*S*)-**5** afforded the free amine at the *S* center in quantitative yield. Thus, two differently desymmetrized *cis* diamine derivatives have been successfully prepared in enantiomerically pure form from the same synthon.

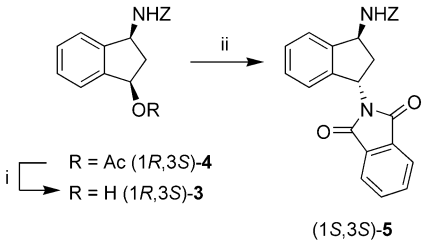
For the preparation of both enantiomers of the *trans* isomer, we used the substrate and product from the resolved *cis* amino alcohol derivatives (Table 2). Mitsunobu reaction of enantiopure (1*S*,3*R*)-**3** under the same reaction conditions as previously described (PPh_3, DEAD, phthalimide) afforded (1*R*,3*R*)-**5** in 68% yield (Scheme 4). The selective deprotection of each nitrogen atom in (1*R*,1*S*)-**5** was also successfully carried out. Hydrazine deprotection led to monoaminocarbamate (1*R*,3*R*)-**6**, while Pd(0) catalyzed hydrogenolysis afforded (1*R*,3*R*)-**7** in quantitative yield. Subsequent hydrogenolysis of (1*R*,3*R*)-**6** afforded diamine (1*R*,3*R*)-**8**, also in quantitative yield. The ^{1}H and ^{13}C NMR spectra of **8** indicated that the compound contains a C_2 symmetry, and thereby, the C2 protons are chemically equivalent (triplet at $\delta =$ 2.19 ppm).



Scheme 4. Reagents and conditions: i) phthalimide, DEAD, PPh_3; ii) hydrazine, MeOH; iii) Pd, HCOOH, MeOH.

The (*S*,*S*)-enantiomer was synthesized from the product isolated from the enzymatic resolution of (±)-*cis*-**3** (Table 2). Conventional saponification of enantiopure (1*R*,3*S*)-**4** led to the *N*-Z-protected amino alcohol (1*R*,3*S*)-**3**. This was subsequently transformed into (1*S*,3*S*)-**5** using the same Mitsunobu reaction as described above (Scheme 5).

The *trans* configuration in (1*R*,3*R*)-**5** was also demonstrated by NMR experiments. Figure 4 displays the observed cross-peaks in the NOESY spectrum of (1*R*,3*R*)-**5**, and



Scheme 5. Reagents and conditions: i) NaOH, MeOH; ii) phthalimide, DEAD, PPh_3.

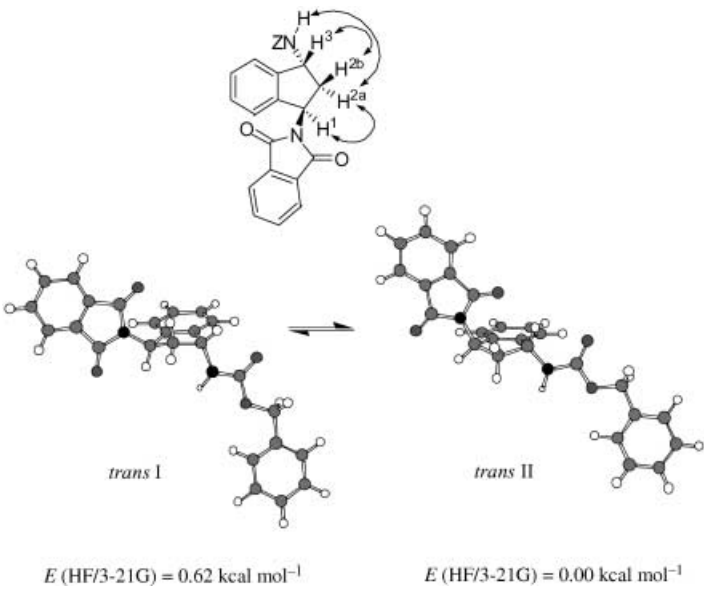


Figure 4. Cross-peaks observed in the NOESY spectrum of (1*R*,3*R*)-**5** (top), and results of molecular modeling (bottom; see text for details).

shows that the carbamate NH proton correlates with one C2 proton, which has been assigned H2a. This proton also shows a strong NOE effect with H1, while H2b correlates with H3. This suggests that H1 and H3 are *trans* disposed. Moreover, chemical shift differences for H2a/H2b were again found to be smaller ($\Delta\delta = 0.50$ ppm) for the *trans* isomers than for the *cis* diastereomer. Finally, the vicinal coupling constants for the protons at C1−C2−C3 also inferred a *trans* arrangement: H1 shows a large coupling constant (9.1 Hz) with H2a and a small one (4.6 Hz) with H2b, while H3 shows a large vicinal coupling constant with H2b (8.1 Hz) and a small one with H2a (5.1 Hz). On the basis of the coupling constants measured in cyclopentene,[18] we would expect ${}^{3}J_{\mathrm{H,H}cis} > {}^{3}J_{\mathrm{H,H}trans}$, and this was in fact observed in the experimental values obtained. However, for comparison purposes we also performed some molecular modeling (HF/3-21G level of theory). We found two energy minima with very similar stability ($\Delta E = 0.62$ kcal mol^{-1}), both of which displayed an envelope conformation for the cyclopentene rings (Figure 4). One conformer places the NH−Z group in an axial position and the phthalimide in an equatorial orientation (*trans* I), while the other has the inverse conformation (*trans* II). The observed coupling constants are better described by a combination of the calculated coupling constants obtained for each conformer. The ^{1}H NMR spectrum in deuterated chloroform indicated that interconversion between the different conformations was fast, and that the solution consisted of 32% *trans* I and 68% *trans* II. Interestingly, the HF/3-21G energy difference between the two conformers indicates that the distribution at room temperature should be 26:74 *trans* I/*trans* II; this is in good agreement with the experimental data if the number of approximations is taken into account. In addition, we also determined the transition state (TS) structure for the equilibrium between *trans* I and *trans* II. This showed that the five-membered ring was planar. The calculated energy barrier was determined to be 1.6 kcal mol^{-1}. This explains the rapid interconversion between both conformers at room temperature, and again is in good agreement with experimental data. Once again, all these data strongly support that during the Mitsunobu reaction the configuration at C1 is completely inverted.

Conclusion

All the possible isomers of 3-aminoindan-1-ol and indane-1,3-diamine were prepared in this work using a chemoenzymatic strategy. Both the *cis* and *trans* diastereomers of the *N*-protected amino alcohol were efficiently resolved by (CAL-B)-catalyzed transesterification reactions in processes that were highly efficient in terms of both chemical yields and enantiomeric excesses of the final products. These enantiopure compounds were then used to synthesize the corresponding 1,3-diamines using an easy one-step procedure based on the Mitsunobu reaction. The orthogonally protected diamines were obtained with complete inversion of configuration at C1. Both enantiomers of the *trans* diastereomer were synthesized with enantiomeric excesses >99%, while for the *cis* counterpart, the completely desymmetrized diamine was obtained in enantiomerically pure form. The versatility of these interesting synthons was also demonstrated by selective deprotection of each nitrogen atom under mild reaction conditions.

Experimental Section

Preparation of racemic (±)-*cis*- and (±)-*trans*-3-(*N*-benzyloxycarbonylamino)indan-1-ol (±)-*cis*-3 and (±)-*trans*-3: (±)-(*N*-acetyl)-3-aminoindan-1-one (2 mmol) was added to a 3 N HCl aqueous solution (4 mL) and the reaction mixture was stirred overnight at 80 °C. The reaction mixture was then washed with CH_2Cl_2 and the resultant aqueous layer was evaporated under reduced pressure. The residue was washed with heptane to remove acetic acid, and the product thus obtained was dissolved in MeOH (6 mL) and then cooled to 0 °C. Sodium borohydride was then gradually added and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated to dryness, the crude residue was dissolved in water (4 mL), and Na_2CO_3 (2.3 mmol) was added. The mixture was immediately cooled to 0–5 °C with vigorous stirring, and benzyl chloroformate (2.3 mmol) was added dropwise. The reaction mixture, which was allowed to warm to room temperature, was stirred overnight and the aqueous solution was then extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica using hexane/ethyl acetate (1:1) as eluent to give the title compound as a white solid (92%). The desired compound was obtained as a mixture of diastereoisomers [(±)-*cis*-**3**/(±)-*trans*-**3** (1:3)]. The isomers were separated by HPLC (Sample ~ 200 mg, Kromasil 60-silica 7 μm-250 × 20, 6 mL min^{-1}, CH_2Cl_2/EtOAc 80:20).

Enzymatic acylation of (±)-*trans*-3-(*N*-benzyloxycarbonylamino)indan-1-ol (±)-*trans*-3: Vinyl acetate (5.3 mmol) was added to a suspension of (±)-*trans*-**3** (0.53 mmol) and CAL-B (169 mg) in *t*BuOMe (4.5 mL) that had previously been dried to avoid enzymatic hydrolysis, under an atmosphere of nitrogen. The mixture was then shaken at 30 °C and 250 rpm for the time shown in Table 1. The enzyme was filtered off, washed with CH_2Cl_2, and the combined organic layers were evaporated under reduced pressure. The unreacted substrate and product were separated by column chromatography on silica using ethyl acetate as eluent.

(1*S*,3*S*)-(−)-3-(*N*-benzyloxycarbonylamino)indan-1-ol (1*S*,3*S*)-3: The previously described procedure gave the title compound as a white solid (98%) after 3.5 h: m.p. 147–149°C; conversion: 55%, *ee* > 99%; HPLC analysis (Chiralcel OD−H, hexane/EtOH 93:7, 0.6 mL min^{-1}, 30°C, 215 nm): (±)-*trans*-**3**, two peaks, t_R = 26.3 and 29.4 min; (−)-(1*S*,3*S*)-**3**, one peak, t_R = 29.4 min; $[\alpha]_D^{20} = -52.0$ (c = 1.0 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.18 (AB portion of an ABXY system, $J_{H2a,H2b}$ = 13.7, $J_{H2a,H3}$ = 5.2, and $J_{H2a,H1}$ = 5.1 Hz, 1H; H2a), 2.37 (AB portion of an ABXY system, $J_{H2b,H3}$ = 6.3 and $J_{H2b,H1}$ = 2.2 Hz, 1H; H2b), 5.12 (s, 2H; OCH_2Ph), 5.24 (dd, $J_{H1,H2a}$ = 5.1 and $J_{H1,H2b}$ = 2.2 Hz, 1H; H1), 5.36 (dd, $J_{H3,H2b}$ = 6.3 and $J_{H3,H2a}$ = 5.2 Hz, 1H; H3), 7.29–7.36 ppm (m, 9H; 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.2 (CH_2), 54.4 (CH), 66.8 (CH_2), 73.8 (CH), 124.5 (CH), 124.7 (CH), 128.1 (CH), 128.5 (CH),128.7 (CH), 129.2 (CH), 136.2 (C), 143.0 (C), 144.2 (C), 156.1 ppm (NCOO); IR (KBr): $\tilde{\nu}$ = 3511, 3339, 1671 cm^{-1}; MS (60 eV, ESI): *m/z* (%): 284 (4) $[M+H]^+$, 306 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{17}NO_3$ (283.3): C 72.07, H 6.05, N 4.94; found: C 71.92, H 6.25, N 4.89.

(1*R*,3*R*)-(+)-1-acetoxy-3-(*N*-benzyloxycarbonylamino)indan (1*R*,3*R*)-4: The previously described procedure gave the title compound as a white solid (97%) after 0.5 h: m.p. 117–119°C; conversion: 49%, *ee* > 99%; HPLC analysis (Chiralcel OD−H, hexane/*i*PrOH 93:7, 0.6 mL min^{-1}, 30°C, 215 nm): (±)-*trans*-**4**, two peaks, t_R = 26.9 and 29.4 min; (+)-(1*R*,3*R*)-**4**, one peak, t_R = 29.4 min; $[\alpha]_D^{20} = +127.3$ (c = 1.0 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.03 (s, 3H; CH_3), 2.23 (AB portion of an ABXY system, $J_{H2a,H2b}$ = 14.2, $J_{H2a,H3}$ = 7.4, and $J_{H2a,H1}$ = 6.3 Hz, 1H; H2a), 2.55 (AB portion of an ABXY system, $J_{H2b,H3}$ = 7.2 and $J_{H2b,H1}$ = 1.7 Hz, 1H; H2b), 5.15 (s, 2H; OCH_2Ph), 5.39 (dd, $J_{H3,H2a}$ = 7.4 and $J_{H3,H2b}$ = 7.2 Hz, 1H; H3), 6.21 (dd, $J_{H1,H2a}$ = 6.3 and $J_{H1,H2b}$ = 1.7 Hz, 1H; H1), 7.28–7.49 ppm (m, 9H; 2×Ph); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.1 (CH_3), 41.2 (CH_2), 54.4 (CH), 66.8 (CH_2), 75.6 (CH), 124.0 (CH), 126.1 (CH), 128.0 (CH), 128.1 (CH),128.4 (CH), 128.5 (CH), 129.7 (CH), 136.2 (C), 140.1 (C), 144.4 (C), 156.2 (NCOO), 170.9 ppm (OCO); IR (KBr): $\tilde{\nu}$ = 3311, 1735, 1684 cm^{-1}; MS (90 eV, ESI): *m/z* (%): 348 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{19}NO_4$ (325.4): C 70.14, H 5.89, N 4.30; found: C 70.02, H 6.01, N 4.10.

Enzymatic acylation of (±)-*cis*-3-(*N*-benzyloxycarbonylamino)indan-1-ol (±)-*cis*-3: The reaction was carried out as described above for the (±)-*trans*-**3** isomer. In this case, both the substrate and product were obtained in enantiopure form after 60 h (Table 2, entry 3).

(1*S*,3*R*)-(+)-3-(*N*-benzyloxycarbonylamino)indan-1-ol (1*S*,3*R*)-3: The previously described procedure gave the title compound as a white solid (97%): m.p. 162–164°C; conversion: 50%, *ee* > 99%; HPLC analysis (Chiralcel OD−H, hexane/EtOH 90:10, 0.6 mL min^{-1}, 30°C, 215 nm): (±)-*cis*-**3**, two peaks, t_R = 12.6 and 16.7 min; (+)-(1*S*,3*R*)-**3**, one peak, t_R = 16.7 min; $[\alpha]_D^{20} = +58.5$ (c = 1.0 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.73 (AB portion of an ABXY system, $J_{H2a,H2b}$ = 13.4, $J_{H2a,H1}$ = 7.1, and $J_{H2a,H3}$ = 6.2 Hz, 1H; H2a), 2.93 (AB portion of an ABXY system, $J_{H2b,H1}$ = 7.0 and $J_{H2b,H3}$ = 6.6 Hz, 1H; H2b), 5.03 (dd, $J_{H1,H2a}$ = 7.1 and $J_{H1,H2b}$ = 7.0 Hz, 1H; H1), 5.11 (dd, $J_{H3,H2b}$ = 6.6 and $J_{H3,H2a}$ = 6.2 Hz, 1H; H3), 5.17 (s, 2H; OCH_2Ph), 7.27–7.43 ppm (m, 9H; 2×Ph); ^{13}C NMR (75 MHz, CD_3OD): δ = 44.9 (CH_2), 53.8 (CH), 67.6 (CH_2), 73.2 (CH), 124.7 (CH), 125.0 (CH), 128.8 (CH), 129.0 (CH), 129.1 (CH), 129.3 (CH), 129.5 (CH), 138.4 (C), 143.8 (C), 145.9 (C), 158.8 ppm (NCOO); IR (KBr): $\tilde{\nu}$ = 3443, 3293, 1683 cm^{-1}; MS (90 eV, ESI): *m/z* (%): 306 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{17}NO_3$ (283.3): C 72.07, H 6.05, N 4.94; found: C 71.98, H 6.31, N 4.78.

(1*R*,3*S*)-(−)-1-acetoxy-3-(*N*-benzyloxycarbonylamino)indan (1*R*,3*S*)-4: The previously described procedure gave the title compound as a white solid (96%): m.p. 153–155°C; conversion: 50%, *ee* > 99%; $[\alpha]_D^{20} = -9.3$ (c = 1.0 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.88 (AB portion of an ABXY system, $J_{H2a,H2b}$ = 13.3, $J_{H2a,H3}$ = 8.3, and $J_{H2a,H1}$ = 7.2 Hz, 1H; H2a), 3.03 (AB portion of an ABXY system, $J_{H2b,H3}$ = 7.9 and $J_{H2b,H1}$ = 7.8 Hz, 1H; H2b), 2.11 (s, 3H; CH_3), 5.10 (dd, $J_{H3,H2a}$ = 8.3 and $J_{H3,H2b}$ = 7.9 Hz, 1H; H3), 5.16 (s, 2H; OCH_2Ph), 6.08 (dd, $J_{H1,H2b}$ = 7.8 and $J_{H1,H2a}$ = 7.2 Hz, 1H; H1), 7.31–7.43 ppm (m, 9H; 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 40.6 (CH_2), 53.2 (CH), 66.7 (CH_2), 75.0 (CH), 124.4 (CH), 125.1 (CH), 128.0 (CH), 128.4 (CH), 128.6 (CH), 129.4 (CH), 136.2 (C), 140.3 (C), 143.0 (C), 155.8 (NCOO), 170.6 ppm (OCO); IR (KBr): $\tilde{\nu}$ = 3296, 1734, 1685 cm^{-1}; MS (90 eV, ESI): *m/z* (%): 348 (100) $[M+Na]^+$, 348 (4) $[M+K]^+$; elemental analysis calcd (%) for $C_{19}H_{19}NO_4$ (325.4): C 70.14, H 5.89, N 4.30; found: C 70.32, H 5.73, N 4.52.

HPLC analysis: (−)-(1*R*,3*S*)-**4** (0.07 mmol) was dissolved in MeOH (0.25 mL) and was subsequently treated with 1N NaOH (0.07 mL). After the mixture had been stirred for 20 min at room temperature, the solvent was removed under reduced pressure. The residue was acidified with 1N HCl and was then extracted with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 and filtered. Removal of the solvent under vacuum gave (−)-(1*R*,3*S*)-**3** in quantitative yield. Previously optimized conditions were used for the HPLC analysis: (±)-*cis*-**3**, two peaks, t_R = 12.6 and 16.7 min; (−)-(1*R*,3*S*)-**3**, one peak, t_R = 12.6 min.

General procedure for the Mitsunobu reaction: Phthalimide (0.12 mmol), PPh_3 (0.12 mmol), and DEAD (0.12 mmol) were added to a solution of either (1*S*,3*S*)-**3**, (1*S*,3*R*)-**3**, or (1*R*,3*S*)-**3** (0.11 mmol) in dry THF (1.5 mL) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 24 h and was then evaporated under reduced pressure. The desired compound, (1*R*,3*S*)-**5**, (1*R*,3*R*)-**5**, or (1*S*,3*S*)-**5**, was purified by column chromatography on silica using CH_2Cl_2/Et_2O (95:5) as eluent.

(+)-*cis*-1-(*N*-benzene-1,2-dicarbonyl)amino-3-(*N*-benzyloxycarbonyl)aminoindan, (1*R*,3*S*)-5: The previously described procedure gave the title compound as a white solid (76%): m.p. 201–203°C; *ee* > 99%; $[\alpha]_D^{20} = +106.7$ (c = 1.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (AB portion of an ABXY system, $J_{H2a,H2b}$ = 14.6, $J_{H2a,H1}$ = 4.4, and $J_{H2a,H3}$ = 4.4 Hz, 1H; H2a), 3.21 (AB portion of an ABXY system, $J_{H2b,H1}$ = 9.4 and $J_{H2b,H3}$ = 9.4 Hz, 1H; H2b), 5.20 (s, 2H; OCH_2Ph), 5.50 (ddd, $J_{H3,NH}$ = 9.7, $J_{H3,H2b}$ = 9.4, and $J_{H3,H2a}$ = 4.4 Hz, 1H; H3), 5.80 (dd, $J_{H1,H2b}$ = 9.4 and $J_{H1,H2a}$ = 4.4 Hz, 1H; H1), 6.30 (d, $J_{NH,H3}$ = 9.7 Hz, 1H; NHCbz), 7.13–7.49 (m, 9H; 2×Ph), 7.74–7.85 ppm (m, 4H; Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.5 (CH_2), 51.5 (CH), 53.8 (CH), 66.4 (CH_2), 123.2 (CH), 123.4 (CH), 124.8 (CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 128.8 (CH), 131.5 (CH), 134.0 (CH), 136.5 (C), 139.6 (C), 143.4 (C), 156.1 (NCOO), 167.7 ppm ($N(CO)_2$); IR (KBr): $\tilde{\nu}$ = 3335, 1712, 1682 cm^{-1}; MS (60 eV, ESI): *m/z* (%): 413 (100) $[M+H]^+$, 435 (64) $[M+Na]^+$; elemental analysis calcd (%) for $C_{25}H_{20}N_2O_4$ (412.4): C 72.80, H 4.89, N 6.79; found: C 72.67, H 5.18, N 6.57.

(+)-*trans*-1-(*N*-benzene-1,2-dicarbonyl)amino-3-(*N*-benzyloxycarbonyl)aminoindan (1*R*,3*R*)-5: The previously described procedure gave the title compound as a white solid (68%): m.p. 202–204°C; *ee* > 99%; $[\alpha]_D^{20} = +177.0$ (c = 0.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (AB portion of an ABXY system, $J_{H2a,H2b}$ = 14.3, $J_{H2a,H1}$ = 9.1, and $J_{H2a,H3}$ = 5.1 Hz, 1H; H2a), 2.93 (AB portion of an ABXY system, $J_{H2b,H3}$ = 8.1 and $J_{H2b,H1}$ = 4.6 Hz, 1H; H2b), 5.14 (d, $J_{NH,H3}$ = 8.3 Hz, 1H; NHCbz), 5.18 (s, 2H; OCH_2Ph), 5.80 (ddd, $J_{H3,NH}$ = 8.3, $J_{H3,H2b}$ = 8.1, and $J_{H3,H2a}$ = 5.1 Hz, 1H; H3), 6.00 (dd, $J_{H1,H2a}$ = 9.1 and $J_{H1,H2b}$ = 4.6 Hz, 1H; H1), 7.17–7.46 (m, 9H; 2×Ph), 7.72–7.84 ppm (m, 4H; Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.4 (CH_2), 52.4 (CH), 55.7 (CH), 66.7 (CH_2), 123.2 (CH), 123.9 (CH), 124.6 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 131.8 (CH), 133.9 (CH), 136.4 (C), 140.1 (C), 143.6 (C), 156.0 (NCOO), 167.6 ppm ($N(CO)_2$); IR (KBr): $\tilde{\nu}$ = 3335, 1708, 1675 cm^{-1}; MS (90 eV, ESI): *m/z* (%): 413 (33) $[M+H]^+$, 435 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{25}H_{20}N_2O_4$ (412.4): C 72.80, H 4.89, N 6.79; found: C 72.97, H 4.96, N 6.60.

(−)-*trans*-1-(*N*-benzene-1,2-dicarbonyl)amino-3-(*N*-benzyloxycarbonyl)-aminoindan (1*S*,3*S*)-5. (1*R*,3*S*)-**4** (0.26 mmol) was dissolved in MeOH (1 mL) and was subsequently treated with 1N NaOH (0.27 mL). After the mixture had been stirred for 20 min at room temperature, the solvent was removed under reduced pressure. The residue was acidified with 1N HCl and was then extracted with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to give compound (1*R*,3*S*)-**3** in quantitative yield. Mitsunobu reaction of (1*R*,3*S*)-**3** was carried out as previously described to give the title compound as a white solid (64%): m.p. 201–203°C; *ee* > 99%; $[\alpha]_D^{20} = -170.8$ (c = 0.9 in $CHCl_3$); elemental analysis calcd (%) for $C_{25}H_{20}N_2O_4$ (412.4): C 72.80, H 4.89, N 6.79; found: C 72.68, H 5.04, N 6.95.

General procedure for hydrazinolysis of the phthalimide group: Diamine (1*R*,3*S*)-**5** or (1*R*,3*R*)-**5** (0.1 mmol) was dissolved in 2M methanolic hydrazine (2.2 mL), and was then stirred at room temperature for 2 h. The solvent was evaporated to dryness and the residue was washed with $CHCl_3$

and filtered. The filtrate was concentrated under reduced pressure to give either (1*S*,3*R*)-**6** or (1*R*,3*R*)-**6**, respectively.

(1*S*,3*R*)-(−)-*cis*-3-amino-1-(*N*-benzyloxycarbonyl)aminoindan (1*S*,3*R*)-6: The previously described procedure gave the title compound as a white solid (98%): m.p. 121–123 °C; *ee* > 99%; $[\alpha]_D^{20} = -45.9$ ($c = 1.4$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.49$ (m, 1H; H2a), 2.06 (br s, 2H; NH_2), 2.97 (m, 1H; H2b), 4.28 (t, $J = 7.4$ Hz, 1H; H1), 5.16 (m, 1H; H3), 5.18 (s, 2H; OCH_2Ph), 5.41 (d, $J = 8.3$ Hz, 1H; NHCbz), 7.29–7.41 ppm (m, 9H; 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.9$ (CH_2), 53.4 (CH), 54.0 (CH), 66.7 (CH_2), 123.3 (CH), 123.7 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 136.4 (C), 142.5 (C), 146.1 (C), 156.1 ppm (NCOO); IR (KBr): $\tilde{\nu} = 3301$, 1684 cm^{-1}; MS (90 eV, ESI): *m/z* (%): 283 (100) $[M+H]^+$, 305 (51) $[M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{18}N_2O_2$ (282.3): C 72.32, H 6.43, N 9.92; found: C 72.08, H 6.58, N 9.71.

(1*R*,3*R*)-(+)-*trans*-1-amino-3-(*N*-benzyloxycarbonyl)aminoindan
(1*R*,3*R*)-6: The previously described procedure gave the title compound as an oil (74%): *ee* > 99%; $[\alpha]_D^{20} = +14.1$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.85$ (br s, 2H; NH_2), 2.18–2.38 (br m, 2H; CH_2), 4.53 (t, $J = 6.2$ Hz, 1H; H1), 4.94 (br d, 1H; NHCbz), 5.16 (s, 2H; OCH_2Ph), 5.37 (br m, 1H; H3), 7.28–7.38 ppm (m, 9H; 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.0$ (CH_2), 54.4 (CH), 54.8 (CH), 66.7 (CH_2), 123.9 (CH), 124.7 (CH), 128.1 (CH), 128.5 (CH), 128.7 (CH), 136.4 (C), 142.1 (C), 146.9 (C), 156.0 ppm (NCOO); IR (KBr): $\tilde{\nu} = 3310$, 1701 cm^{-1}; MS (90 eV, ESI): *m/z* (%): 283 (100) $[M+H]^+$, 305 (63) $[M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{18}N_2O_2$ (282.3): C 72.32, H 6.43, N 9.92; found: C 72.48, H 6.38, N 9.87.

General procedure for the cleavage of *N*-benzyloxycarbonylamides: To compound (1*R*,3*S*)-**5** or (1*R*,3*R*)-**5** (0.1 mmol) was added a 10% HCO_2H solution (2.2 mL in MeOH, purged with nitrogen prior to use) followed by Pd-black (14 mg). The mixture was vigorously stirred for 2 h and was then filtered through Celite and washed with MeOH. The solvent was removed to give the desired product (1*R*,3*S*)-**7** or (1*R*,3*R*)-**7**, respectively.

(1*R*,3*S*)-(+)-*cis*-3-amino-1-phthalimidoindan as its formic acid salt (1*R*,3*S*)-7: The previously described procedure gave the title compound in quantitative yield as a white solid: m.p. 165–167 °C; *ee* > 99%; $[\alpha]_D^{20} = +145.4$ ($c = 1.0$ in MeOH); ^{1}H NMR (300 MHz, D_2O): $\delta = 2.36$ (m, 1H; H2a), 3.04 (m, 1H; H2b), 4.83 (m, 1H; H3), 5.72 (m, 1H; H1), 7.12–7.70 (m, 8H; 2×Ph), 8.32 ppm (br s, 1H; $HCOO^-$); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 35.7$ (CH_2), 52.8 (CH), 54.5 (CH), 124.5 (CH), 125.3 (CH), 125.9 (CH), 130.4 (CH), 131.4 (CH), 133.0 (CH), 135.8 (CH), 139.7 (C), 142.4 (C), 169.5 ppm ($N(CO)_2$); IR (KBr): $\tilde{\nu} = 3446$, 2966, 1716 cm^{-1}; MS (60 eV, ESI): *m/z* (%): 262.1 (100) $[(M-HCOOH)-NH_2]^+$, 279.1 (40) $[(M-HCOOH)+H]^+$, 301.1 (11) $[(M-HCOOH)+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{16}N_2O_4$ (324.3): C 66.66, H 4.97, N 8.64; found: C 66.45, H 5.07, N 8.74.

(1*R*,3*R*)-(+)-*trans*-3-amino-1-phthalimidoindan as its formic acid salt (1*R*,3*R*)-7: The previously described procedure gave the title compound in quantitative yield as a white solid: m.p. 177–179 °C; *ee* > 99%; $[\alpha]_D^{20} = +167.7$ ($c = 1.1$ in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 2.61$ (br m, 1H; H2a), 2.99 (br m, 1H; H2b), 5.26 (br m, 1H; H3), 6.11 (m, 1H; H1), 7.26–7.87 (m, 8H; 2×Ph), 8.56 ppm (br s, 1H; $HCOO^-$); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 36.3$ (CH_2), 53.6 (CH), 56.1 (CH), 124.2 (CH), 125.5 (CH), 125.8 (CH), 130.4 (CH), 131.3 (CH), 133.1 (CH), 135.6 (CH), 140.9 (C), 142.8 (C), 169.1 ppm ($N(CO)_2$); IR (KBr): $\tilde{\nu} = 3446$, 2968, 1716 cm^{-1}; MS (60 eV, ESI): *m/z* (%): 262.1 (100) $[(M-HCOOH)-NH_2]^+$, 279.1 (55) $[(M-HCOOH)+H]^+$, 301.1 (8) $[(M-HCOOH)+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{16}N_2O_4$ (324.3): C 66.66, H 4.97, N 8.64; found: C 66.78, H 5.13, N 8.59.

(1*R*,3*R*)-(+)-*trans*-1,3-indandiamine as its formic acid salt (1*R*,3*R*)-8: The previously described procedure was applied to (1*R*,3*R*)-**6** to give the title compound (89%): *ee* > 99%; $[\alpha]_D^{20} = +20.1$ ($c = 0.37$ in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 2.19$ (t, $J = 6.0$ Hz, 2H; H2a and H2b), 4.56 (t, $J = 6.0$ Hz, 2H; H1 and H3), 7.18–7.47 ppm (m, 4H; Ph); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 46.6$ (CH_2), 56.5 (CH), 126.3 (CH), 130.3 (CH), 147.6 ppm (C); MS (30 eV, ESI): *m/z* (%): 132.1 (60) $[(M-2HCOOH)-NH_2]^+$, 149.1 (100) $[(M-2HCOOH)+H]^+$; elemental analysis calcd (%) for $C_{11}H_{16}N_2O_4$ (240.3): C 54.99, H 6.71, N 11.66; found: C 54.78, H 6.93, N 11.48.

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