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Enzymatic resolution of (±)-*cis*- and (±)-*trans*-1-aminoindan-2-ol and (±)-*cis*- and (±)-*trans*-2-aminoindan-1-ol

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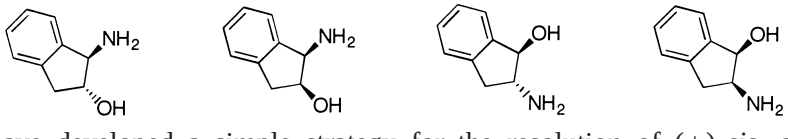
Abstract

Pseudomonas cepacia lipase (PSL) efficiently catalyses the kinetic resolution of (±)-*cis*- and (±)-*trans*-1-aminoindan-2-ol through the *O*-acylation reaction of the corresponding *N*-benzyloxycarbonyl derivative using vinyl acetate as the acyl donor. In a similar way, *cis*-*N*-Cbz-2-aminoindan-1-ol is resolved when isopropenyl acetate is used as the acylating agent. The enantioselectivity of the reaction was lower for (±)-*trans*-*N*-Cbz-2-aminoindan-1-ol due to the different steric requirements for the two conformers of this substrate.

1. Introduction

Chiral 1,2-aminoalcohols have proved to be a functionally diverse class of compounds with a wide range of applicability in coordination chemistry, organic synthesis and medicinal chemistry.[1] In particular, enantiomerically pure *cis*- and *trans*-1,2-cycloaminoalcohols are compounds of great interest due to its presence in many products with physiological activity.[2] Moreover, the cyclic *cis* isomers have special relevance as chiral auxiliaries in asymmetric synthesis.[3]



Recently, we have developed a simple strategy for the resolution of (±)-*cis*- and (±)-*trans*-1,2-aminocyclopentanol and 1,2-aminocyclohexanol.[4,5] In these studies, the best results were achieved through a lipase-catalysed *O*-acylation of the *N*-Cbz protected aminoalcohols.

Taking these results into account, it seemed very interesting to apply this methodology to the resolution of (±)-*cis*- and (±)-*trans*-1-aminoindan-2-ol and 2-aminoindan-1-ol. It is of note that the

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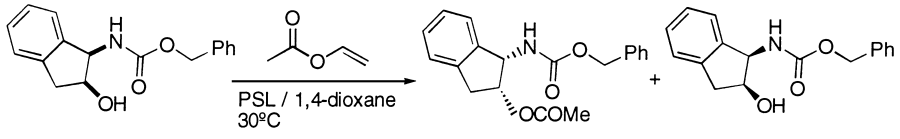
preparation of enantiomerically pure *cis*-1-aminoindan-2-ol has become a subject of special relevance in the last few years due to its importance in asymmetric synthesis.[6] Moreover, this compound is a key component of indinavir, which is a potent inhibitor of the protease of human inmunodeficiency virus[7] (HIV). Several enzymatic and non-enzymatic procedures have been described for the preparation of racemic[8] and optically active[9] *cis*-1-aminoindan-2-ol. The esterification reaction of the corresponding azidoindanols[10] and bromoindanols[11] has been the most common strategy when enzymes are used. Less attention has been paid to the *trans* isomers. However, enzymatic transesterification has been used to obtain enantiomerically pure *trans*-2-aminoindan-1-ol.[12] Finally, the synthesis of the four isomers of 1,2-diaminoindane with high enantiomeric excesses has been performed with the lipase-catalysed selective transesterification of (±)-*cis*-2-azidoindan-1-ol and (±)-*trans*-1-azidoindan-2-ol as the key step.[13]

2. Results and discussion

We have prepared the corresponding *N*-benzyloxycarbonyl derivatives of the *cis* and *trans* isomers of 1-aminoindan-2-ol, and 2-aminoindan-1-ol following the procedure described in earlier papers.[4,5] The protecting group (benzyloxycarbonyl) was chosen because it can be selectively introduced in good yield to give a substrate that is stable under the projected reaction conditions and which can be removed easily.[14] Initially, we tried the kinetic resolution of these *N*-protected aminoindanols by means of an enzymatic transesterification reaction.

2.1. *Resolution of* cis-*1-aminoindan-2-ol*

Racemic *cis*-1-aminoindan-2-ol was prepared following the procedure described by Igarashi et al.[11] The aminoalcohol was conveniently protected and its Cbz derivative **1** was used as starting material. The resolution of **1** was carried out in 1,4-dioxane at 30°C using *Pseudomonas cepacia* lipase (PSL) as the biocatalyst and vinyl acetate as the acyl donor (Scheme 1 and Table 1).



(±)-*cis*-**1** (1*S*,2*R*)-**2** (1*R*,2*S*)-**1**

Scheme 1.

Under these reaction conditions, PSL exhibited high enantioselectivity towards the substrate. The enzyme preferred the *R* isomer of the carbamate, yielding the *O*-acetylderivative (1*S*,2*R*)-**2** with an enantiomeric excess of >99% ($[\alpha]_D^{23}$=−69.6 (*c* 0.775, EtOH)) and 2-hydroxycarbamate (1*R*,2*S*)-**1** was recovered in 78% ee ($[\alpha]_D^{23}$=−4.8 (*c* 0.25, $CHCl_3$)). These data correspond to a conversion value (*c*) of 44% and an enantiomeric ratio higher than 200 (Table 1, entry 2). The absolute configuration of the

Table 1

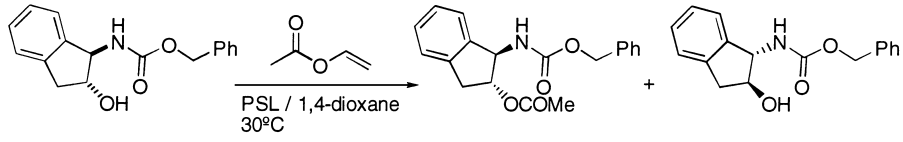
			product	(1*S*,2*R*)	Remaining	substrate	(1*R*,2*S*)		
Entry	t, d		yield[a](%)	ee[b](%)		yield[a](%)	ee[b](%)	Conv[c](%)	*E*[c]
1	3	**2**	74	>99	**1**	63	22	18	*E*>200
2	9	**2**	86	>99	**1**	55	78	44	*E*>200

[a]After flash chromatography. [b]determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD and Chiralcel-ODH. [c]See ref. 15.

remaining substrate (1*R*,2*S*) was assigned by comparison between the sign of the specific rotation for the corresponding unprotected *cis*-aminoalcohol with the value found in the literature.[10b]

2.2. *Resolution of* trans-*1-aminoindan-2-ol*

Racemic *trans*-1-aminoindan-2-ol was prepared by ammonolysis of racemic epoxyindane. This reaction was carried out in a similar way to that described for the preparation of the corresponding (±)-*trans*-1,2-aminocyclohexanol and (±)-*trans*-1,2-aminocyclopentanol.[4] The aminoindanol was converted into its *N*-benzyloxycarbonyl derivative **3**. We performed the resolution of compound **3** following the same methodology developed for **1** (Scheme 2 and Table 2). The very high enantiomeric ratio of this reaction made it possible to achieve both the product and the remaining substrate in enantiomerically pure form by controlling the percent conversion.



(±)-*trans*-**3** (1*R*,2*R*)-**4** (1*S*,2*S*)-**3**

Scheme 2.

Table 2

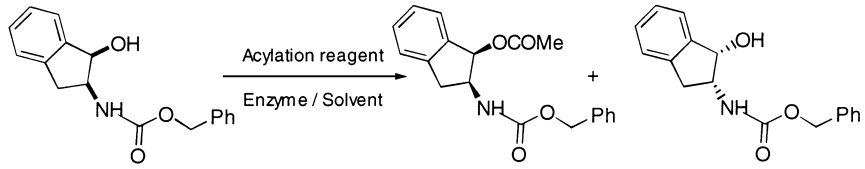
			product	(1*R*,2*R*)	Remaining	Substrate	(1*S*,2*S*)		
Entry	t, d		yield[a](%)	ee[b](%)		Yield[a](%)	ee[b](%)	Conv[c](%)	*E*[c]
1	2	**4**	100	>99	**3**	60	50	34	*E*>200
2	3	**4**	82	98	**3**	75	>99	50	*E*>200

[a]After flash chromatography. [b]determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD.[c]See ref. 15.

The enzyme showed preference for the *R* isomer of the carbamate, yielding the (1*R*,2*R*) *O*-acetylcarbamate **4** with 98% ee $[\alpha]_D^{23}$=−57.6 (*c* 0.25, $CHCl_3$). The substrate (1*S*,2*S*) 2-hydroxycarbamate **3** was recovered with 99% ee $[\alpha]_D^{23}$=−29.6 (*c* 0.25, $CHCl_3$). The absolute configuration of (1*S*,2*S*) was assigned after its transformation to the corresponding *trans*-aminoalcohol and comparison of its specific rotation with the data given in the literature.[9b]

2.3. *Resolution of* cis-*2-aminoindan-1-ol*

Synthesis of racemic *cis*-2-aminoindan-1-ol was carried out following the procedure developed by Corey et al.[16] As in the above cases, the corresponding carbamate derivative **7** was prepared. We accomplished its resolution under the same conditions used for their isomers (±)-*cis*- and (±)-*trans*-1-aminoindan-2-ol. Even though the enantiomeric ratio was very high, the process took place very slowly, achieving only 2% conversion even after 5 days of reaction (Table 3, entry 1). We tried changing the reaction conditions such as lipase type, acyl donor, solvent and increasing the temperature to 60°C in order to improve the reaction rate. In all cases the *E* value was higher than 200, but it seems to be clear that the main role in increasing the conversion in this reaction was played by the solvent. When *tert*-butyl methyl ether (TBME) was used instead of 1,4-dioxane, it was possible to reach a conversion value of about 50% and product **6** and substrate **5** could be obtained enantiomerically pure (Table 3, entry 3; Scheme 3).



Scheme 3.

Table 3

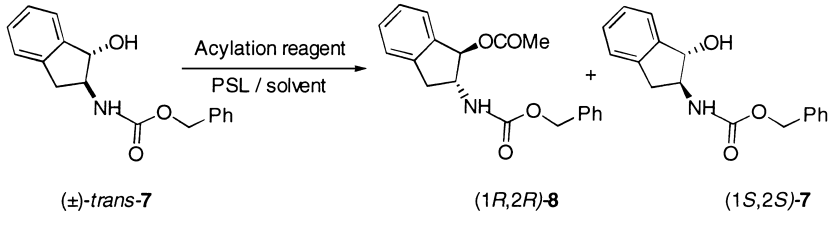
Entry	Acyl donor	Enzyme	Solvent	T°C	t,d	Product (1*R*,2*S*)	yield (%)	ee[b] (%)	substrat e(1*S*,2*R*)	Yield (%)	ee[b] (%)	Conv.[c] (%)	E[c]
1	V.A.[d]	PSL	1,4-diox.[f]	30	5	**6**	100	>99	**5**	86	2	2	*E*>200
2	I.P.A.[e]	PSL	TBME	40	6	**6**	100	>99	**5**	94	65	40	*E*>200
3	V.A.[d]	PSL	TBME	40	6	**6**	82	>99	**5**	78	96	49	*E*>200

[a]After flash chromatography. [b]determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD.[c]See ref. 15. [d]vinyl acetate. [e]isopropenyl acetate. [f]1,4-dioxane.

The different behaviour shown by *cis*-2-aminoindan-1-ol with respect to its 1-amino isomer in terms of rate of reaction, could be due to the fact that the hydroxyl group in this form is more hindered than in the *cis*-1-aminoindan-2-ol. Nevertheless, the enzyme showed preference towards the (*R*)-configuration of the carbon that bears the hydroxyl group. The absolute configuration of the remaining substrate was assigned after the deprotection reaction and recovery of the *cis*-2-aminoindan-1-ol and comparison of its specific rotation with the data given in the literature.[12]

2.4. *Resolution of* trans-*2-aminoindan-1-ol*

Synthesis of *trans*-2-amino-1-indanol was possible through a Mitsunobu[9a] reaction of the *cis*-2-azidoindan-1-ol (Scheme 4). After this, the carbamate **7** was prepared as starting material for the enzymatic resolution. Reaction conditions were the same as those used for *cis*-2-amino-1-indanol (Table 3, entry 3). In this case the acylated product (1*R*,2*R*)-**8** was obtained with a high enantiomeric excess (96%), along with the substrate (1*S*,2*S*)-**7** with 20% ee after 10 days of reaction (Table 4, entry 1). In order to improve these results, we tried other reaction conditions. We used vinyl acetate as acyl donor, and with the aim of increasing the temperature to accelerate the acetylation reaction rate, 1,4-dioxane was used at 60°C. However, the results obtained were disappointing (Table 4, entry 2). The best result (*E*=59) was obtained when (±)-*trans*-2-amino-1-indanol was exposed to PSL as a biocatalyst and isopropenyl acetate as the acylating agent in *tert*-butyl methyl ether at 40°C. The absolute configuration of (1*S*,2*S*)-**7** was assigned after its conversion to the corresponding *trans*-2-aminoindan-1-ol and comparison of its specific rotation with the value given in the literature.[12]



Scheme 4.

Table 4

Entry	Acyl donor	solvent	T°C	t,d	Product (1*R*,2*R*)	Yield (%)	ee[b] (%)	Substrate (1*S*,2*S*)	Yield (%)	ee[b] (%)	Conv.[c] (%)	*E*[c]
1	I.P.A.[d]	TBME	40	10	**8**	75	96	**7**	79	20	17	*E*=59
2	V.A.[d]	1,4-diox.[f]	60	8	**8**	100	95	**7**	78	15	14	*E*=45

[a]After flash chromatography. [b]determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD and Chiralcel-ODH. [c]See ref. 15. [d]isopropenyl acetate. [e]vinyl acetate. [f]1,4-dioxane.

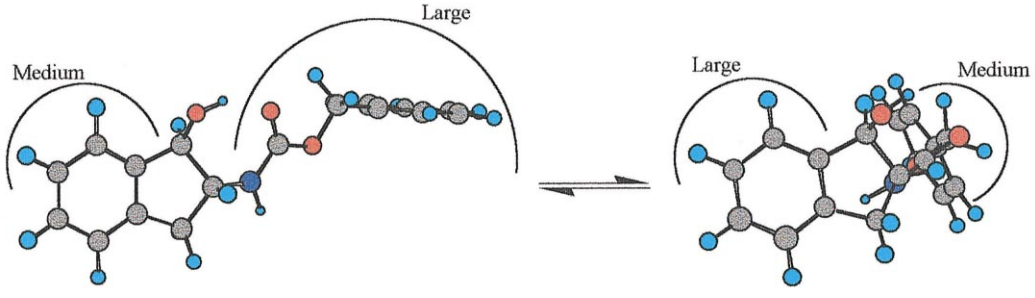


Figure 1.

Based on the observed reactivity of the four diastereoisomers towards the enzymatic *O*-acylation process, it must be pointed out that the reactivity of the (*R*)-enantiomer was faster in all the cases. These results are in accordance with Kazlauskas' rule[17] for resolution of secondary alcohols.

In the cases of (±)-*cis*- and (±)-*trans*-1-aminoindan-2-ol the large substituent is *N*-benzyloxycarbonyl, and the methylene group is the medium substituent. The great difference in size for both groups could confirm the very high enantioselectivity observed. For the resolution of (±)-*cis*-2-aminoindan-1-ol, the difference of size between the medium substituent and the large substituent is smaller, but this difference might be enough to explain the high *E* value measured in this compound.

On the other hand, the poorer resolution of (±)-*trans*-2-aminoindan-1-ol could be explained using the same empirical rule. ^{1}H NMR spectrum showed a broad signal for C*H*-OH suggesting a fast conformational equilibrium between two conformers in the NMR time-scale. MM† studies revealed the existence of two conformers with similar energy (Fig. 1). As is shown in Fig. 1, both conformers would present different steric requirements and would lead to a reverse order in the size of the substituents. This could give an explanation for the moderate enantioselectivity value of this isomer.

In conclusion, we have developed an efficient method for the resolution of (±)-*cis*- and (±)-*trans*-

† MM:MMX force field calculations[18] predict an energy difference of about 0.2 kcal/mol between both conformations and the energy barrier (for the transformations of one to the other) lower than 2 kcal/mol.

1-aminoindan-2-ol and (±)-*cis*- and (±)-*trans*-2-aminoindan-1-ol through their *N*-benzyloxycarbonyl derivatives, in order to obtain enantiomerically pure products and substrates. The relative position of the hydroxyl and amino group has a special relevance in the enzymatic *O*-acylation of these compounds.

3. Experimental

3.1. General

Pseudomonas cepacia lipase (PSL) was purchased from Amano Pharmaceutical Co. All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Precoated TLC plates of silica gel 60 F254 from Merck were used, while for column chromatography, Merck silica gel 60/230–400 mesh was applied. Mps were measured with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer Mattson 3000 Fourier transform infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC-300 (^{1}H 300 MHz and ^{13}C 75 MHz) spectrometer. Mass spectra were recorded on a Hewlett–Packard 5897 A spectrometer and HPLC analyses were carried out on a Shimadzu LC liquid chromatograph.

3.2. Preparation of racemic benzyl N-(1 and 2-hydroxyindane)carbamates

To a solution of amino alcohol (2 mmol) and sodium carbonate (0.254 g, 2.4 mmol) in water (3.4 mL), benzyl chloroformate (2.4 mmol) was added dropwise over a 0.5 h period at 0–5°C. The reaction mixture was stirred for an additional 6 h at room temperature and extracted with dichloromethane. The organic layer was dried and evaporated to dryness, to give the desired product in 85–100% yield.

3.2.1. (±)-cis-Benzyl N-(1-hydroxyindan-2-yl)carbamate **1**

The racemic 1-hydroxycarbamate **1** was purified by flash chromatography, using ethyl acetate:hexane (1:2) as eluent; it was a white solid, mp 140–142°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (br. s, 1H, OH), AB portion of ABX multiplet (δ_A 2.89, δ_B 3.10, J_{AB} 16.78), 4.56 (br. s, 1H, C*H*-OH), 5.16 (m, 3H, O-C*H*$_2$-Ph and C*H*-NH), 5.53 (m, 1H, N*H*), 7.24–7.40 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.4 (CH_2), 59.2 (CH), 67.0 (CH_2), 73.5 (CH), 124.4 (CHarm), 125.3 (CHarm), 127.1 (CHarm), 128.1 (CHarm), 128.2 (CHarm), 128.3 (CHarm), 128.5 (CHarm), 136.2 (Carm), 139.7 (Carm), 140.4 (Carm), 156.8 (CO carbamate); IR (KBr) 3476, 3339, 1668, 1549, 1254 cm^{-1}. MS (FAB$^+$, nitrobenzyl alcohol) m/z: 284 [(M+1)$^+$, 100], [(M+Na)$^+$, 70].

3.2.2. (±)-trans-Benzyl N-(1-hydroxyindan-2-yl)carbamate **3**

The racemic 1-hydroxycarbamate **3** was purified by flash chromatography, using ethyl acetate:hexane (1:2) as eluent; it was a brown solid, mp 135–137°C. ^{1}H NMR (300 MHz, $CDCl_3$) AB portion of ABX multiplet (δ_A 2.92, δ_B 3.28, J_{AB} 16.13), 4.44 (m, 1H, C*H*-OH), 4.99 (m, 1H, C*H*-NH), 5.16 (m, 3H, OH and O-C*H*$_2$-Ph), 5.33 (d, 1H, N*H*), 7.18–7.38 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.2 (CH_2), 64.2 (CH), 67.3 (CH_2), 81.6 (CH), 123.0 (CHarm), 125.1 (CHarm), 126.9 (CHarm), 127.2 (CHarm), 127.5 (CHarm), 128.1 (CHarm), 128.3 (CHarm), 128.4 (CHarm), 128.5 (CHarm), 135.9 (Carm), 138.9 (Carm), 140.0 (Carm), 157.6 (CO carbamate); IR (KBr) 3405, 3281, 1691, 1563, 1265 cm^{-1}. MS (FAB$^+$, nitrobenzyl alcohol) m/z: 284 [(M+1)$^+$, 52], [(M+Na)$^+$, 26].

*3.2.3. (±)-*cis*-Benzyl N-(2-hydroxyindan-1-yl)carbamate **5***

The racemic 2-hydroxycarbamate **5** was purified by flash chromatography, using ethyl acetate:hexane (1:2) as eluent; it was a white solid, mp 84–86°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (br. s, 1H, OH), AB portion of ABX multiplet (δ_A 2.87, δ_B 3.19, J_{AB} 16.08), 4.36 (m, 1H, C*H*-NH), 4.96 (br. s, 1H, C*H*-OH), 5.08 (m, 2H, O-CH_2-Ph), 5.67 (d, 1H, N*H*), *7*.20–7.38 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.5 (CH_2), 54.7 (CH), 66.7 (CH_2), 74.2 (CH), 125.0 (CHarm), 127.0 (CHarm), 128.0 (CHarm), 128.4 (CHarm), 129.0 (CHarm), 136.2 (Carm), 140.7 (Carm), 141.9 (Carm), 156.4 (CO carbamate); IR (KBr) 3246, 1691, 1549, 1291 cm^{-1}. MS (FAB$^+$, nitrobenzyl alcohol) m/z: 284 [(M+1)$^+$, 53], [(M+Na)$^+$, 52].

*3.2.4. (±)-*trans*-Benzyl N-(2-hydroxyindan-1-yl)carbamate **7***

The racemic 2-hydroxycarbamate **7** was purified by flash chromatography, using ethyl acetate:hexane (1:2) as eluent; it was a light yellow solid, mp 162–164°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (br. s, 1H, OH), AB portion of ABX multiplet (δ_A 2.72, δ_B 3.33, J_{AB} 15.26), 4.17 (m, 1H, C*H*-NH), 5.13 (m, 3H, N*H* and O-CH_2-Ph), 5.24 (m, 1H, C*H*-OH), 7.18–7.44 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9 (CH_2), 61.9 (CH), 67.1 (CH_2), 81.5 (CH), 124.3 (CHarm), 124.4 (CHarm), 127.4 (CHarm), 128.2 (CHarm), 128.3 (CHarm), 128.5 (CHarm), 136.0 (Carm), 138.0 (Carm), 142.1 (Carm), 156.4 (CO carbamate); IR (KBr) 3371, 3292, 1688, 1563, 1274 cm^{-1}. MS (FAB$^+$, nitrobenzyl alcohol) m/z: 284 [(M+1)$^+$, 85], [(M+Na)$^+$, 76].

*3.3. General procedure for the syntheses of benzyl carbamates **2** and **4***

Vinyl acetate (10 mmol) and carbamate (±)-*cis*-**1** or (±)-*trans*-**3** (1 mmol) were added to a suspension of PSL (320 mg) in 1,4-dioxane (9 mL) under nitrogen. The mixture was shaken at 30°C and 250 rpm during 9 and 3 days, respectively. The enzyme was then filtered off and washed with dichloromethane (2×10 mL) and the organic solvents were evaporated off. The crude residue was subjected to column chromatography, with ethyl acetate:hexane (1:2) as eluent.

Isopropenyl acetate (5 mmol) or vinyl acetate (10 mmol) and carbamate (±)-*cis*-**5** or (±)-*trans*-**7** (1 mmol) were added to a suspension of PSL (320 mg) in *tert*-butyl methyl ether (2 mL) under nitrogen. The mixture was shaken at 40°C and 250 rpm during 6 and 10 days. The enzyme was then filtered off and washed with dichloromethane (2×10 mL) and the organic solvents were evaporated off. The crude residue was subjected to column chromatography, with ethyl acetate:hexane (1:2) as eluent.

*3.3.1. Benzyl (1*R*,2*S*)-*N*-(1-hydroxyindan-2-yl)carbamate **1***

The previously described procedure gave 55% of (1*R*,2*S*)-**1** as a white solid, mp 127–129°C. $[\alpha]_D^{23}$=−4.8 (*c* 0.25 in $CHCl_3$). Determination of ee for (1*R*,2*S*)-**1**, 78% by chiral HPLC (Chiralcel OD), hexane:ethanol (97%, 3 v/v) in isocratic conditions (flux 0.8 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 33.63 min for the *SR* and 36.79 min for the *RS*; *R*s, 1.8.

*3.3.2. Benzyl (1*S*,2*S*)-*N*-(1-hydroxyindan-2-yl)carbamate **3***

The previously described procedure gave 75% of (1*S*,2*S*)-**3** as a white solid, mp 165–167°C. $[\alpha]_D^{23}$=−29.6 (*c* 0.25 in $CHCl_3$). Determination of ee for (1*S*,2*S*)-**3**, 99% ee was determined from its methyl ester derivative by chiral HPLC (Chiralcel OD), hexane:propan-2-ol (90%, 10 v/v) in isocratic conditions (flux 0.8 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 20.24 min for the *SS* and 23.04 min for the *RR*; *R*s, 2.02.

*3.3.3. Benzyl (1*S*,2*R*)-*N*-(2-hydroxyindan-1-yl)carbamate* ***5***

The previously described procedure gave 78% of (1*S*,2*R*)-**5** as a white solid, mp 75–77°C. $[\alpha]_D^{23}$=−26.0 (*c* 0.25 in $CHCl_3$). Determination of ee for (1*S*,2*R*)-**5**, 96% by chiral HPLC (Chiralcel OD), hexane:propan-2-ol (80%, 20 v/v) in isocratic conditions (flux 0.8 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 15.23 min for the *RS* and 23.07 min for the *SR*; *R*s, 4.94.

*3.3.4. Benzyl (1*S*,2*S*)-*N*-(2-hydroxyindan-1-yl)carbamate* ***7***

The previously described procedure gave 79% of (1*S*,2*S*)-**7** as a white solid, mp 161–163°C. $[\alpha]_D^{23}$=−4.0 (*c* 0.25 in $CHCl_3$). Determination of ee for (1*S*,2*S*)-**7**, 20% by chiral HPLC (Chiralcel OD), hexane:propan-2-ol (80%, 20 v/v) in isocratic conditions (flux 0.8 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 13.89 min for the *SS* and 16.72 min for the *RR*; *R*s, 2.4.

*3.3.5. Benzyl (1*S*,2*R*)-*N*-(1-acetoxyindan-2-yl)carbamate* ***2***

The previously described procedure gave 86% of (1*S*,2*R*)-**2** as a white solid, mp 147–149°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0 (s, 3H, CH_3), AB portion of ABX multiplet (δ_A 3.02, δ_B 3.20, J_{AB} 17.0), 5.2 (br. s, 2H, C*H*$_2$-Ph), 5.33 (d, 1H, N*H*), 5.43 (m, 1H, C*H*-NH), 5.58 (m, 1H, C*H*-OAc), 7.20–7.47 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (CH_3), 37.2 (CH_2), 57.3 (CH), 67.0 (CH_2), 75.6 (CH), 123.8 (CHarm), 125.0 (CHarm), 127.2 (CHarm), 128.2 (CHarm), 128.3 (CHarm), 128.5 (CHarm), 136.2 (Carm), 139.1 (Carm), 140.3 (Carm), 156.2 (CO carbamate), 170.2 (CO ester); IR (KBr) 3315, 1730, 1701, 1535, 1261 cm^{-1}. MS (FAB$^+$, nitrobenzyl alcohol) m/z: 326 [(M+1)$^+$, 78], [(M+Na)$^+$, 100]. $[\alpha]_D^{23}$=−69.6 (*c* 0.775 in EtOH). Determination of ee for (1*S*,2*R*)-**2**, 99% by chiral HPLC (Chiralcel OD-H), *T*=0°C, hexane:ethanol (97%, 3 v/v) in isocratic conditions (flux 0.5 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 44.74 min for the *SR* and 50.22 min for the *RS*; *R*s, 1.73.

*3.3.6. Benzyl (1*R*,2*R*)-*N*-(1-acetoxyindan-2-yl)carbamate* ***4***

The previously described procedure gave 82% of (1*R*,2*R*)-**4** as a white solid, mp 115–117°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H, CH_3), AB portion of ABX multiplet (δ_A 2.86, δ_B 3.37, J_{AB} 16.13), 5.18 (m, 4H, O-C*H*$_2$-Ph, C*H*-NH, C*H*-OAc), 5.38 (d, 1H, N*H*), *7*.13–7.43 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (CH_3), 35.95 (CH_2), 60.6 (CH), 66.7 (CH_2), 80.0 (CH), 124.0 (CHarm), 124.6 (CHarm), 127.2 (CHarm), 127.8 (CHarm), 128.3 (CHarm), 128.4 (CHarm), 136.13 (Carm), 138.6 (Carm), 139.4 (Carm), 156.1 (CO carbamate), 170.8 (CO ester); IR (KBr) 3319, 1739, 1696, 1539, 1240 cm^{-1}. MS (FAB$^+$, nitrobenzyl alcohol) m/z: 326 [(M+1)$^+$, 100], [(M+Na)$^+$, 67]. $[\alpha]_D^{23}$=−57.6 (*c* 0.25 in $CHCl_3$). Determination of ee for (1*R*,2*R*)-**4**, 98% by chiral HPLC (Chiralcel OD), hexane:propan-2-ol (90%, 10 v/v) in isocratic conditions (flux 0.8 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 20.24 min for the *SS* and 23.04 min for the *RR*; *R*s, 2.02.

*3.3.7. Benzyl (1*R*,2*S*)-*N*-(2-acetoxyindan-1-yl)carbamate* ***6***

The previously described procedure gave 82% of (1*R*,2*S*)-**6** as a white solid, mp 153–155°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H, CH_3), AB portion of ABX multiplet (δ_A 2.95, δ_B 3.27, J_{AB} 15.48), 4.67 (m, 1H, C*H*-NH), 5.16 (m, 2H, O-C*H*$_2$-Ph), 5.32 (m, 1H, C*H*-OAc), 6.06 (d, 1H, N*H*), *7*.24–7.51 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_3), 36.9 (CH_2), 53.1 (CH), 66.9 (CH_2), 76.0 (CH), 124.7 (CHarm), 126.7 (CHarm), 127.0 (CHarm), 128.2 (CHarm), 128.5 (CHarm), 129.5 (CHarm), 136.1 (Carm), 138.8 (Carm), 141.4 (Carm), 155.7 (CO carbamate), 170.1 (CO ester); IR (KBr) 3290, 1736, 1693, 1555, 1276 cm^{-1}. MS (FAB$^+$, nitrobenzyl alcohol) m/z: 326 [(M+1)$^+$, 6], [(M+Na)$^+$, 100]. $[\alpha]_D^{23}$=−115.42 (*c* 0.24 in $CHCl_3$). Determination of ee for (1*R*,2*S*)-**6**, 99% by chiral HPLC (Chiralcel OD), hexane:propan-2-ol (80%, 20 v/v) in isocratic conditions (flux 0.8 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 10.5 min for the *SR* and 11.71 min for the *RS*; *R*s, 1.53.

*3.3.8. Benzyl (1*R,*2*R)-N-*(2-acetoxyindan-1-yl)carbamate* ***8***

The previously described procedure gave 75% of (1*R*,2*R*)-**8** as a white solid, mp 103–105°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3), AB portion of ABX multiplet (δ_A 2.78, δ_B 3.53, J_{AB} 15.48), 4.41 (m, 1H, C*H*-NH), 5.14 (m, 2H, O-CH_2-Ph), 5.36 (m, 1H C*H*-OAc), 6.13 (d, 1H, N*H*), *7*.23–7.37 (m, 9Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_3), 37.2 (CH_2), 58.6 (CH), 66.8 (CH_2), 81.1 (CH), 124.9 (CHarm), 125.0 (CHarm), 127.2 (CHarm), 128.1 (CHarm), 128.5 (CHarm), 129.2 (CHarm), 136.2 (Carm), 138.4 (Carm), 140.3 (Carm), 156.0 (CO carbamate), 171.4 (CO ester); IR (KBr) 3330, 1732, 1692, 1541, 1273 cm^{-1}. MS (FAB^+, nitrobenzyl alcohol) m/z: 326 [$(M+1)^+$, 32], [$(M+Na)^+$, 48]. $[\alpha]_D^{23}$=−77.7 (*c* 0.26 in $CHCl_3$). Determination of ee for (1*R*,2*R*)-**8**, 96% by chiral HPLC (Chiralcel OD-H), *T*=40°C, hexane:ethanol (99%, 1 v/v) in isocratic conditions (flux 0.4 mL/min) and the λ was 210 nm. The retention times of the stereoisomers were 96.43 min for the *RR* and 104.29 min for the *SS*; *R*s, 1.38.

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