Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2558–2564

Chemoenzymatic preparation of optically active secondary amines: a new efficient route to enantiomerically pure indolines

Vicente Gotor-Fernández, Pedro Fernández-Torres and Vicente Gotor*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Biotecnología de Asturias, Universidad de Oviedo, 33071 Oviedo (Asturias), Spain

Received 18 August 2006; accepted 21 August 2006
Available online 22 September 2006

Abstract—An efficient chemoenzymatic route for the synthesis of optically active substituted indolines has been developed. Different lipases have been tested in the alkoxycarbonylation of these secondary amines, *Candida antarctica* lipase A (CAL-A) was found to be the best biocatalyst for 2-substituted-indolines, and *C. antarctica* lipase B (CAL-B) for 3-methylindoline. The combination of lipases with a variety of allyl carbonates and *tert*-butyl methyl ether (TBME) as solvent has allowed the isolation of the carbamate and amine derivatives with a high level of enantiopurity.

1. Introduction

Optically active secondary amines are important chiral building blocks in the preparation of pharmaceuticals and agrochemicals.[1] In addition, they possess important applications in organic asymmetric synthesis as chiral auxiliaries,[2] catalysts[3] or resolving agents.[4] For that reason, many chemical processes have been reported for the preparation of this class of compounds using chiral auxiliaries,[5] asymmetric hydrogenation,[6] reductive amination[7] or hydrosilylation conditions,[8] with the recrystallization of diastereomeric salts being the most common methodology for the isolation of the amines.[9] On the other hand, enzyme-catalyzed processes have recently shown their potential in the preparation of enantioenriched secondary amines using aminoacylases,[10] proteases[11] or amino oxidases obtained by directed evolution methods.[12]

Lipases usually accept a wide range of racemic substrates in order to catalyze their transformation into enantiomerically pure compound.[13] However until now, only a few examples of the lipase-catalyzed enzymatic kinetic resolution of secondary amines have been published in the literature.[14]

The indole and indoline cores have attracted particular attention in recent years due to their presence in a great variety of natural products, biologically active alkaloids and pharmaceuticals.[15] Unfortunately, the enzymatic resolution of optically active indolines has been limited to a couple of examples in which good enantiomeric excesses are obtained, but low conversions were achieved using subtilisin as the biocatalyst.[14b,d]

Herein, we report the development of a practical chemoenzymatic route for the preparation of optically active 2- or 3-substituted-indolines through enzymatic alkoxycarbonylation procedures. An extensive optimization study of the reaction parameters in terms of biocatalyst and solvent was carried out for the isolation of enantiomerically pure compounds.

2. Results and discussion

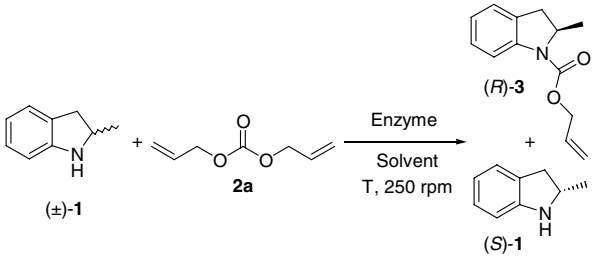
Initially the resolution by acetylation procedures of commercially available 2-methylindoline **1** was carried out using different lipases such as CAL-A, CAL-B and *Candida rugosa* lipase (CRL) with toluene as a solvent and ethyl acetate (EtOAc) as the acyl donor, achieving only low conversions in the case of CAL-B, but promising enantioselectivities. The use of different solvents, acyl donor and high temperatures did not allow the formation of the corresponding amides in appreciable yields, so at this point we

* Corresponding author. Tel./fax: +34 985 103448; e-mail: vgs@fq.uniovi.es

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.08.012

turned our attention to the study of the alkoxycarbonylation reaction of **1**, a process that has shown excellent results for the enzymatic resolution of 1-methyl-1,2,3,4-tetrahydroisoquinoline.[14g]

Diallyl carbonate was selected as the alkoxycarbonylating reagent for an initial screening of enzyme activity using dry Et_2O as a solvent (Scheme 1, Table 1). In this way at 30 °C, CAL-B and CRL did not show any activity (entries 1 and 2), while CAL-A showed a low reaction rate, but displayed complete enantioselectivity, affording 13% of the carbamate (+)-**3** (entry 3). This is not a surprising result as CAL-A has been identified as an ideal catalyst in the resolution of sterically hindered compounds.[16] *Pseudomonas cepacia* lipase (PSL-C) was also attempted but low conversions were observed (entry 4), so we decided to study the behaviour of other non-polar solvents such as toluene and *tert*-butyl methyl ether (TBME, entries 5 and 6) finding TBME to be a good candidate for the enzymatic resolution of (±)-**1**, partly because slightly higher conversions were achieved than is the case with Et_2O, and partly because its higher boiling point allows the possibility of increasing the temperature of the process. As shown in Table 1, CAL-A reached higher conversions (20–25%) at 45 °C whilst maintaining a complete enantiopreference for the (+)-enantiomer (entries 7 and 8). By comparison of the specific rotation previously described in the literature with the one obtained in the enzymatic resolution process {experimental $[\alpha]_D^{20} = -16.3$ (*c* 0.5, $CHCl_3$), literature $[\alpha]_D^{20} = -12.2$ (*c* 2.6, benzene)}, the absolute configuration of the recovered amine was assigned as (*S*),[5c] and the (*R*)-carbamate being obtained.[14b,d]



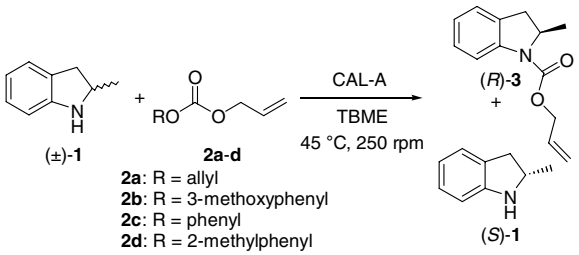
Scheme 1. Enzymatic kinetic resolution of 2-methylindoline employing diallyl carbonate.

Table 1. Enzymatic kinetic resolution of 2-methylindoline using diallyl carbonate

Entry	Enzyme	Solvent	*T* (°C)	Ratio[a]	*t* (h)	ee_S (%)[b]	ee_P (%)[b]	*c* (%)[c]	*E*[d]
1	CAL-B	Et_2O	30	1:5	88	—	—	—	—
2	CRL	Et_2O	30	1:5	88	—	—	—	—
3	CAL-A	Et_2O	30	1:5	136	15	>99	13	>200
4	PSL-C	Et_2O	30	1:5	88	—	18	5	1.5
5	CAL-A	Toluene	60	1:5	87	14	>99	12	>200
6	CAL-A	TBME	30	1:5	135	18	>99	15	>200
7	CAL-A	TBME	45	1:5	135	25	>99	20	>200
8	CAL-A	TBME	45	1:10	111	33	>99	25	>200

[a] The ratio of amine/diallyl carbonate.
[b] Calculated by HPLC.
[c] $c = ee_S/(ee_S + ee_P)$.
[d] $E = \ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_S)]$.

These initial encouraging results, in terms of enantioselectivity, made us focus our attention onto the search for adequate alkoxycarbonylating reagents, which would permit us to increase the reaction conversion up to values around 50%. To this end, we synthesized three different carbonates **2b–d** following the procedures described by Breen,[14g] to compare their reactivity in the kinetic resolution of (±)-**1** using the best conditions found in previous attempts for its enzymatic resolution; TBME as a solvent, a ratio of amine versus carbonate of 1:5, a temperature of 45 °C and CAL-A as biocatalyst. However, in these cases we employed double the amount of enzyme in order to reach higher conversions (Scheme 2).



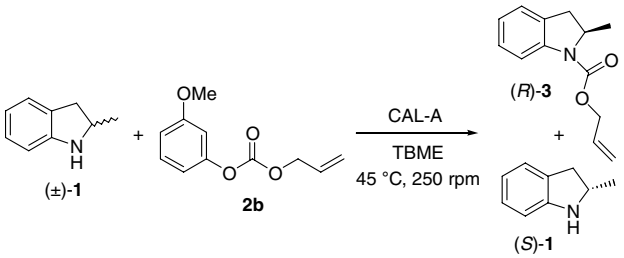
Scheme 2. Enzymatic kinetic resolution of (±)-**1** using different allyl carbonates.

Observing the results shown in Table 2, these mixed carbonates presented higher activities than the diallyl carbonate, and except for the phenyl carbonate **2c**, all of them afforded the enantiomerically pure amide (+)-**3**. It is of note that conversions close to 50% were reached using both carbonates **2b** and **2d**. However, the latter presented serious problems in the isolation of reaction products, so we decided to perform the optimization of the enzymatic resolution of (±)-**1** using the 3-methoxyphenyl allyl carbonate **2b** (Scheme 3).

Table 2. Enzymatic kinetic resolution of (±)-**1** with different carbonates in a ratio of 1:5 and CAL-A with a proportion of 2:1 in weight with respect to the amine in TBME at 45 °C

Entry	**2**	*t* (h)	ee_S (%)[a]	ee_P (%)[a]	*c* (%)[b]	*E*[c]
1	**2a**	111	33	>99	25	>200
2	**2b**	67	87	>99	47	>200
3	**2c**	66	83	82	50	27
4	**2d**	67	94	>99	49	>200

[a] Calculated by HPLC.
[b] $c = ee_S/(ee_S + ee_P)$.
[c] $E = \ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_S)]$.



Scheme 3. Enzymatic kinetic resolution of 2-methylindoline using 3-methoxyphenyl allyl carbonate.

Kinetic resolution of racemic 2-methylindoline was then attempted by varying the different reaction conditions such as the amount of biocatalyst, solvent, temperature and the amount of carbonate (Table 3). Firstly the amount of carbonate was reduced in order to both avoid any possible formation of by-products, and reduce inhibition effects at high concentrations of the reactants. However, with only 1 equiv of carbonate, the reaction stopped at 34% conversion (entry 2). Increasing the amount of **2b** to 2–2.5 equiv, conversions of around 50% are obtained with excellent enantioselectivities (entries 3 and 4). In order to design an economic process, we decided to study the recycling of the enzyme, observing non-appreciable loss of activity after two cycles (entries 5 and 6), and a slower reaction rate in the third cycle in spite of the excellent enantioselectivity obtained (entry 7).

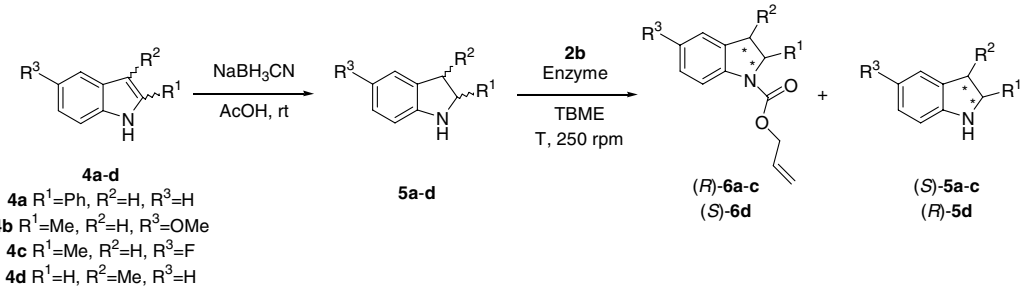
Table 3. Enzymatic kinetic resolution of 2-methylindoline using **2b** and CAL-A with a ratio of 2:1 in weight with respect to the amine in TBME at 45 °C

Entry	Ratio[a]	t (h)	ee_S (%)[b]	ee_P (%)[b]	c (%)[c]	E[d]
1	1:5	67	87	>99	47	>200
2	1:1	63	51	>99	34	>200
3	1:2	69	90	98	48	>200
4	1:2.5	66	>99 (88)[e]	>99 (90)[e]	50	>200
5[f]	1:2.5	66	97	97	50	>200
6[g]	1:2.5	66	88	99	47	>200
7[h]	1:2.5	66	73	>99	43	>200

[a] The ratio of amine/carbonate in mmol.
[b] Calculated by HPLC.
[c] $c = ee_S/(ee_S + ee_P)$.
[d] $E = \ln[(1 - c) \times (1 - ee_S)]/\ln[(1 - c) \times (1 + ee_S)]$.
[e] Isolated yields in brackets.
[f] Enzyme recovered from entry 4.
[g] Enzyme recovered from entry 5.
[h] Enzyme recovered from entry 6.

Once we had satisfactorily developed an enzymatic procedure for the resolution of an indoline derivative, we decided to extend this methodology to the chemoenzymatic synthesis of different indolines using the corresponding indoles as starting materials. These can be transformed in the chiral cyclic secondary amines with very good yields by reduction with sodium cyanoborohydride ($NaBH_3CN$) in acetic acid following a modified protocol of the type described by Gribble and Hoffman (Scheme 4).[17]

Under the same conditions as those used for the kinetic resolution of (±)-**1**, the 2-substituted-indoline with a phenyl group at the C-2-position instead of a methyl group (entry 1, Table 4), or indolines with different groups at the C-5-position (entries 2 and 3) were used, observing a complete enantiopreference in lower reaction times. It is worthy of note that the isolation of the products in the enzymatic resolution of **1** and **5a** required only a flash chromatography purification step to obtain the corresponding optically active amines and carbamates in high levels of purity. However, the fact that the R_f values of the remaining



4a-d
4a R^1=Ph, R^2=H, R^3=H
4b R^1=Me, R^2=H, R^3=OMe
4c R^1=Me, R^2=H, R^3=F
4d R^1=H, R^2=Me, R^3=H

5a-d

(*R*)-**6a-c**
(*S*)-**6d**

(*S*)-**5a-c**
(*R*)-**5d**

Scheme 4. Enzymatic kinetic resolution of different indolines using 3-methoxyphenyl allyl carbonate.

Table 4. Enzymatic kinetic resolution of 2-methylindoline using 3-methoxyphenyl allyl carbonate

Entry	Enzyme	Carbonate	R^1	R^2	R^3	T (°C)	Ratio[a]	t (h)	ee_S (%)[b]	ee_P (%)[b]	c (%)[c]	E[d]
1	CAL-A[e]	**2b**	Ph	H	H	45	1:2.5	20	97 (78)	>99 (90)	50	>200
2	CAL-A[e]	**2b**	Me	H	OMe	45	1:2.5	20	>99 (82)	95[g] (84)	51[g]	>200
3	CAL-A[e]	**2b**	Me	H	F	45	1:2.5	20	>99 (76)	>99 (81)	50	>200
4	CAL-A[e]	**2b**	H	Me	H	45	1:2.5	4	>99	23	81	6
5	CAL-A[e]	**2b**	H	Me	H	30	1:1	15	90	39	70	6
6	CAL-B[e]	**2b**	H	Me	H	45	1:2.5	16	>99	73	58	32
7	CAL-B[e]	**2b**	H	Me	H	30	1:2.5	21	>99	77	56	39
8	CAL-B[f]	**2b**	H	Me	H	30	1:2.5	9	>99	93	52	145
9	CAL-B[f]	**2a**	H	Me	H	30	1:2.5	10	>99 (88)	97 (92)	51	>200

[a] The ratio of amine/carbonate in mmol.
[b] Calculated by HPLC.
[c] $c = ee_S/(ee_S + ee_P)$.
[d] $E = \ln[(1 - c) \times (1 - ee_S)]/\ln[(1 - c) \times (1 + ee_S)]$.
[e] Using a ratio of amine/enzyme (1:2) in weight.
[f] Using a ratio of amine/enzyme (1:1) in weight.
[g] Conversion calculated by ^1H NMR of the crude and the ee_S from $ee_P = ee_S \times (1 - 1/c)$.

amines **5b** and **5c** were very similar to that of 3-methoxyphenol, by-product obtained in the enzymatic reactions caused us to develop a different purification procedure for these substrates, which included an additional extraction separation step (see Section 4).

A different behaviour was observed for 3-methylindoline **5d**; the amine reacted very quickly and with a poor enantioselectivity value (entry 4). Attempts to perform the reaction under milder conditions with respect to temperature and a smaller amount of carbonate did not result in better selectivities, so we decided to study the influence of a different enzyme such as CAL-B (entries 6–8). This showed a lower reaction rate and a very good selectivity, especially at 30 °C and using a smaller ratio of biocatalyst. Due to the good selectivity presented by CAL-B and the low reactivity of the diallyl carbonate, the kinetic resolution of racemic **5d** was attempted at 30 °C in TBME, using 2.5 equiv of **2a** and CAL-B in a ratio of 1:1 in weight with respect to the amine. After 10 h, a conversion of 51% was reached, the amine was enantiomerically pure and the corresponding carbamate was isolated in 97% ee (entry 9). By comparison with the data described in the literature, the amine was assigned an (*R*)-configurations and so the amide resulted with (*S*)-configuration[6d] (Table 4).

3. Conclusions

In conclusion, we have developed an efficient chemoenzymatic route for the production of enantiomerically pure indolines, with CAL-A proving as an excellent enzyme for the kinetic resolution of 2-substituted-indolines, while CAL-B showed greater effectivity in the kinetic resolution of 3-methylindoline. Different parameters have been studied such as the alkoxycarbonylating agent, temperature, solvent and the amount of enzyme, amine and carbonate, in order to establish the optimal reaction conditions for the development of successful enzymatic resolutions for this type of secondary cyclic amines. In addition, the recycling of CAL-A in the kinetic resolution of 2-methyl-indoline has been studied, with no significant loss of activity observed after two cycles.

4. Experimental

4.1. General

Candida antarctica lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novo Nordisk Co. *C. antarctica* lipase type A (CAL-A, Chirazyme L-5, c-f, lyophilized, 1000 U/g using tributyrin) was acquired from Roche. *P. cepacia* lipase (PSL-C, 783 U/g) was obtained from Amano Pharmaceutical Co. Chemical reagents were commercialized by Aldrich, Fluka or Lancaster. The solvents were distilled over an appropriate desiccant under nitrogen. Flash chromatography was performed using silica gel 60 (230–240 mesh). High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph UV detector at 210 nm using a Daicel Chiralcel OD or OB-H column (25 cm × 4.6 mm I.D.) varying the conditions depending on the specific substrate. Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded using NaCl plates or KBr pellets in a Perkin–Elmer 1720-X F7. ^{1}H, ^{13}C NMR, DEPT, ^{1}H–^{1}H homonuclear experiments and ^{1}H–^{13}C heteronuclear experiments were obtained using AC-200 (^{1}H, 200.13 MHz and ^{13}C, 50.3 MHz), AC-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz), DPX 300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz), AV-400 (^{1}H, 400.13 MHz and ^{13}C, 100.6 MHz) or AV-600 (^{1}H, 600.15 MHz and ^{13}C, 150.9 MHz) spectrometers. Chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). ESI$^+$ using a HP1100 chromatograph mass detector, or EI with a Finigan MAT 95 spectrometer were used to record mass spectra (MS). Microanalyses were performed on a Perkin–Elmer model 2400 instrument. Measurement of the optical rotation was done in a Perkin–Elmer 241 polarimeter.

4.2. Typical experimental procedure for the reduction of indoles 4a–d to indoline derivatives 5a–d

To a solution of the corresponding indole **5a**–**d** (1.86 mmol) in AcOH (9.3 mL) was added $NaBH_3CN$ (11.16 mmol), and the resulting mixture stirred until no starting material could be detected by TLC analysis (2–8 h). Then, 25 mL of H_2O and additional NaOH pellets were added until pH >12, extracting the solution with Et_2O (3 × 25 mL). The organic phases were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure, to give a crude that was purified by flash chromatography.

4.2.1. 2-Phenylindoline 5a. 85% Isolated yield. R_f (10% EtOAc/hexane): 0.49; Mp: 42–43 °C; IR (KBr): ν 3370, 3030, 1609, 1484, 1455, 1362, 1247, 1033, 927, 849 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.91 (dd, $^2J_{HH} = 15.6$ Hz, $^3J_{HH} = 8.7$ Hz, 1H, H_3), 3.36 (dd, $^2J_{HH} = 15.6$ Hz, $^3J_{HH} = 8.7$ Hz, 1H, H_3), 3.87 (br s, 1H, H_1), 4.86 (t, $^3J_{HH} = 9.0$ Hz, 1H, H_2), 6.59 (d, $^3J_{HH} = 7.8$ Hz, 1H, H_4), 6.67 (td, $^3J_{HH} = 8.4$ Hz, $^4J_{HH} = 1.0$ Hz, 1H, H_5), 7.00 (t, $^3J_{HH} = 8.1$ Hz, 2H, H_6+H_7), 7.20 (m, 3H, $2H_{12}$+H_{13}), 7.23 (dt, $^3J_{HH} = 8.4$ Hz, $^4J_{HH} = 1.8$ Hz, 2H, $2H_{11}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 39.5 (C_3), 63.4 (C_2), 108.8 (C_4), 118.7 (C_5), 124.5 (C_7), 126.2 ($2C_{11}$), 127.3 (C_{13}), 127.4 (C_6), 128.0 (C_{10}), 128.5 ($2C_{12}$), 144.4 (C_9), 150.7 (C_8). MS (EI$^+$, m/z): 196 [(M+H)$^+$, 100%]. Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.2; H, 6.6; N, 7.1. $[\alpha]_D^{20} = +65.4$ (c 0.5, $CHCl_3$) for 97% ee of the (*S*)-enantiomer.

4.2.2. 2-Methyl-5-methoxyindoline 5b. 83% Isolated yield. R_f (50% EtOAc/hexane): 0.48; Mp: 50–51 °C; IR (KBr): ν 3344, 2954, 2857, 2361, 1596, 1489, 1455, 1434, 1302, 1240, 1225, 1136, 1032, 944, 880, 858, 794 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.30 (d, $^3J_{HH} = 6.2$ Hz, 3H, H_{10}), 2.63 (dd, $^2J_{HH} = 15.6$ Hz, $^3J_{HH} = 7.8$ Hz, 1H, H_3), 3.13 (dd, $^2J_{HH} = 15.6$ Hz, $^3J_{HH} = 8.4$ Hz, 1H, H_3), 3.64 (br s, 1H, NH), 3.75 (s, 3H, H_{11}), 3.99 (m, 1H, H_2), 6.59 (m, 2H, H_4+H_6), 6.73 (t, $J_{HH} = 1.26$ Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.0 (C_{10}), 38.2 (C_3), 55.8 (C_2), 55.9 (C_{11}), 109.9 (C_4), 111.6 (C_7), 112.0 (C_6),

130.7 (C_5), 144.5 (C_9), 153.5 (C_8). MS (EI^+, *m/z*): 164 [$(M+H)^+$, 100%]. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.6; H, 8.0; N, 8.6. $[\alpha]_D^{20} = -14.2$ (*c* 0.5, $CHCl_3$) for 99% ee of the (*S*)-enantiomer.

4.2.3. 5-Fluoro-2-methylindoline 5c. 79% Isolated yield. R_f (20% EtOAc/hexane): 0.31; IR (NaCl): *v* 3375, 3038, 2964, 2927, 0360, 1609, 1487, 1446, 1379, 1235, 1215, 1125, 937, 860, 806 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.29 (d, $^3J_{HH} = 6.3$ Hz, 3H, H_{10}), 2.63 (dd, $^2J_{HH} = 15.7$ Hz, $^3J_{HH} = 8.0$ Hz, 1H, H_3), 3.12 (dd, $^2J_{HH} = 15.8$ Hz, $^3J_{HH} = 8.6$ Hz, 1H, H_3), 3.43 (br s, 1H, NH), 4.00 (m, 1H, H_2), 6.50 (dd, $J_{HH} = 8.4$ Hz, 4.5 Hz, 1H, H_4), 6.71 (m, 1H, H_7), 6.82 (dd, $J_{HH} = 2.5$ Hz, 1.2 Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.7 (C_{10}), 37.6 (C_3), 55.5 (C_2), 109.0 (C_4, $J_{CF} = 8.0$ Hz), 111.6 (C_6, $J_{CF} = 24$ Hz), 112.7 (C_7, $J_{CF} = 23$ Hz), 130.3 (C_9, $J_{CF} = 8.0$ Hz), 146.4 (C_8), 156.7 (C_5, $J_{CF} = 233$ Hz). MS (EI^+, *m/z*): 230 [$(2M)^+$, 100%], 152 [$(M+H)^+$, 20%], 151 [$(M)^+$, 12%]. Anal. Calcd for $C_9H_{10}NF$: C, 71.50; H, 6.67; N, 9.26. Found: C, 71.6; H, 6.7; N, 9.2. $[\alpha]_D^{20} = -10.1$ (*c* 0.5, $CHCl_3$) for 99% ee of the (*S*)-enantiomer.

4.2.4. 3-Methylindoline 5d. 73% Isolated yield. R_f (20% EtOAc/hexane): 0.57; IR (NaCl): *v* 3379, 3050, 2960, 2924, 2869, 1609, 1487, 1464, 1240, 1109, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.35 (d, $^3J_{HH} = 6.5$ Hz, 3H, H_{10}), 3.13 (t, $^3J_{HH} = 8.7$ Hz, 1H, H_2), 3.39 (m, 1H, H_3), 3.72 (t, $^3J_{HH} = 8.5$ Hz, 1H, H_2), 6.67 (d, $^3J_{HH} = 7.8$ Hz, 1H, H_4), 6.77 (dt, $J_{HH} = 8.4$ Hz, 6.2 Hz, 1H, H_5), 7.04 (dt, $J_{HH} = 8.4$ Hz, 7.5 Hz, 1H, H_6), 7.07 (d, $^3J_{HH} = 6.5$ Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.5 (C_{10}), 36.5 (C_3), 55.3 (C_2), 109.4 (C_4), 118.6 (C_5), 123.3 (C_7), 127.2 (C_6), 134.2 (C_9), 151.1 (C_8). MS (EI^+, *m/z*): 134 [$(M+H)^+$, 100%]. Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.1; H, 8.2; N, 10.5. $[\alpha]_D^{20} = -30.2$ (*c* 0.25, $CHCl_3$) for 99% ee of the (*R*)-enantiomer.

4.3. Typical experimental procedure for the preparation of racemic allyl carbamates 3 and 6a–d

To a solution of the corresponding indoline (0.31 mmol) in dry CH_2Cl_2 under nitrogen atmosphere and at 0 °C were added pyridine (28 μL, 0.34 mmol) and allyl chloroformate (37 μL, 0.34 mmol). The reaction was stirred at room temperature for 3 h until complete consumption of the starting material, then the solvent was evaporated and the crude purified by flash chromatography.

4.3.1. 2-Methylindoline allyl carbamate 3. 98% Isolated yield. R_f (5% EtOAc/hexane): 0.30; IR (NaCl): *v* 2974, 1705, 1603, 1486, 1463, 1400, 1322, 1282, 1226, 1173, 1140, 1104, 1048, 995, 935 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.30 (d, $^3J_{HH} = 6.5$ Hz, 3H, H_{10}), 2.65 (dd, $^2J_{HH} = 16.0$ Hz, $^3J_{HH} = 2.2$ Hz, 1H, H_3), 3.38 (dd, $^2J_{HH} = 16.0$ Hz, $^3J_{HH} = 9.6$ Hz 1H, H_3), 4.60 (m, 1H, H_2), 4.76 (d, $^3J_{HH} = 5.0$ Hz, 2H, H_{12}), 5.26 (dd, $^2J_{HH} = 10.6$ Hz, $^3J_{HH} = 2.6$ Hz, 1H, H_{14}), 5.39 (dd, $^2J_{HH} = 17.2$ Hz, $^3J_{HH} = 1.5$ Hz, 1H, H_{14}), 6.05 (m, 1H, H_{13}), 6.98 (t, $^3J_{HH} = 7.4$ Hz, 1H, H_6), 7.17 (d, $^3J_{HH} = 6.6$ Hz, 1H, H_4), 7.21 (d, $^3J_{HH} = 7.7$ Hz, 1H, H_5), 7.84 (br s, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.3 (C_{10}), 35.9 (C_3), 55.4 (C_2), 65.9 (C_{12}), 115.5 (C_7), 117.9 (C_{14}), 122.8 (C_6), 125.1 (C_4), 127.5 (C_5), 130.0 (C_8), 132.7 (C_{13}), 141.6 (C_9), 152.8 (C_{11}). MS (EI^+, *m/z*): 218 [$(M+H)^+$, 100%], 240 [$(M+Na)^+$, 8%]. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.9; H, 6.9; N, 6.5. $[\alpha]_D^{20} = -47.4$ (*c* 0.5, $CHCl_3$) for 97% ee of the (*R*)-enantiomer.

4.3.2. 2-Phenylindoline allyl carbamate 6a. 97% Isolated yield. R_f (5% EtOAc/hexane): 0.22; Mp = 68–69 °C. IR(KBr): *v* 2476, 3414, 3031, 2950, 2361, 1702, 1599, 1485, 1403, 1315, 1272, 1144, 1046, 997, 950, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 3.04 (dd, $^2J_{HH} = 16.5$ Hz, $^3J_{HH} = 3.0$ Hz, 1H, H_3), 3.76 (dd, $^2J_{HH} = 16.3$ Hz, $^3J_{HH} = 10.5$ Hz 1H, H_3), 4.65 (br s, 2H, H_{15}), 5.15 (br s, 2H, H_{17}), 5.52 (dd, $J_{HH} = 10.2$, 2.4 Hz, 1H, H_2), 5.80 (br s, 1H, H_{16}), 7.06 (t, $J_{HH} = 7.2$ Hz, 1H, H_6), 7.25 (m, 7H, $H_4+H_5+2H_{11}+2H_{12}+H_{13}$), 7.95 (br s, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 37.9 (C_3), 62.5 (C_2), 66.0 (C_{15}), 115.0 (C_7), 117.5 (C_{17}), 123.1 (C_6), 124.9 (C_4), 125.4 ($2C_{11}$), 127.4, 127.8 (C_5+C_{13}), 128.7 ($2C_{12}$), 129.5 (C_{10}), 132.4 (C_{16}), 142.7 (C_8), 143.9 (C_9), 153.0 (C_{14}). MS (EI^+, *m/z*): 302 [$(M+Na)^+$, 100%], 280 [$(M+H)^+$, 20%]. Anal. Calcd for $C_{18}H_{17}NO_2F$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.5; H, 6.2; N, 5.0. $[\alpha]_D^{20} = -93.0$ (*c* 0.5, $CHCl_3$) for 99% ee of the (*R*)-enantiomer.

4.3.3. 2-Methyl-5-methoxyindoline allyl carbamate 6b. 98% Isolated yield. R_f (15% EtOAc/hexane): 0.31; IR (NaCl): *v* 2952, 2834, 1703, 1599, 1492, 1456, 1401, 1324, 1275, 1207, 1134, 1051, 1033, 995, 918, 810, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.30 (d, $^3J_{HH} = 6.2$ Hz, 3H, H_{10}), 2.60 (dd, $^2J_{HH} = 16.2$ Hz, $^3J_{HH} = 1.6$ Hz, 1H, H_3), 3.35 (dd, $^2J_{HH} = 16.2$ Hz, $^3J_{HH} = 9.7$ Hz 1H, H_3), 3.77 (s, 3H, H_{11}), 4.58 (m, 1H, H_2), 4.73 (d, $^3J_{HH} = 4.4$ Hz, 2H, H_{13}), 5.26 (dd, $^2J_{HH} = 10.6$ Hz, $^3J_{HH} = 1.3$ Hz, 1H, H_{15}), 5.37 (dd, $^2J_{HH} = 17.2$ Hz, $^3J_{HH} = 1.6$ Hz, 1H, H_{15}), 6.01 (m, 1H, H_{14}), 6.73 (m, 2H, H_4+H_6), 7.75 (br s, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.2 (C_{10}), 36.1 (C_3), 55.7 ($C_{11}+C_2$), 65.8 (C_{13}), 111.4 (C_4), 112.1 (C_6), 115.9 (C_7), 117.7 (C_{15}), 131.4 (C_5), 132.9 (C_{14}), 135.0 (C_9), 152.6 (C_{12}), 155.9 (C_8). MS (EI^+, *m/z*): 270 [$(M+Na)^+$, 100%], 248 [$(M+H)^+$, 20%]. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.1; H, 6.8; N, 5.6. $[\alpha]_D^{20} = -54.6$ (*c* 0.5, $CHCl_3$) for 95% ee of the (*R*)-enantiomer.

4.3.4. 5-Fluoro-2-methylindoline allyl carbamate 6c. 85% Isolated yield. R_f (5% EtOAc/hexane): 0.29; Mp = 41–42 °C; IR: *v* 3557, 3415, 2968, 2933, 1701, 1612, 1488, 1398, 1297, 1275, 1127, 1050, 997, 934, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.31 (d, $^3J_{HH} = 6.5$ Hz, 3H, H_{10}), 2.62 (dd, $^2J_{HH} = 16.2$ Hz, $^3J_{HH} = 1.6$ Hz, 1H, H_3), 3.36 (dd, $^2J_{HH} = 16.2$ Hz, $^3J_{HH} = 9.4$ Hz 1H, H_3), 4.60 (m, 1H, H_2), 4.74 (d, $^3J_{HH} = 5.0$ Hz, 2H, H_{12}), 5.27

(dd, $^2J_{HH} = 10.3$ Hz, $^3J_{HH} = 1.3$ Hz, 1H, H_{14}), 5.37 (dd, $^2J_{HH} = 17.2$ Hz, $^3J_{HH} = 1.6$ Hz, 1H, H_{14}), 6.01 (m, 1H, H_{13}), 6.86 (m, 2H, H_4+H_6), 7.75 (br s, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.2 (C_{10}), 35.9 (C_3), 55.8 (C_2), 66.0 (C_{12}), 112.3 (C_4, $J_{CF} = 24$ Hz), 113.7 (C_6, $J_{CF} = 23$ Hz), 116.0 (C_7, $J_{CF} = 8.0$ Hz), 118.0 (C_{14}), 131.7 (C_9, $J_{CF} = 8.0$ Hz), 132.6 (C_{13}), 137.5 (C_8), 152.7 (C_{11}), 159.0 (C_5, $J_{CF} = 241$ Hz). MS (EI^+, m/z): 493 [$(2M+Na)^+$, 100%], 236 [$(M+H)^+$, 10%]. Anal. Calcd for $C_{13}H_{14}NO_2F$: C, 66.37; H, 6.00; N, 5.95. Found: C, 66.4; H, 6.1; N, 6.0. $[\alpha]_D^{20} = -37.3$ (c 0.5, $CHCl_3$) for 99% ee of the (*R*)-enantiomer.

4.3.5. 3-Methylindoline allyl carbamate 6d. 87% Isolated yield. R_f (5% EtOAc/hexane): 0.27; IR (NaCl): ν 2962, 2887, 1710, 1602, 1487, 1404, 1317, 1146, 1049, 1021, 932 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.34 (d, $^3J_{HH} = 6.9$ Hz, 3H, H_{10}), 3.44 (c, $^3J_{HH} = 7.1$ Hz, 1H, H_3), 3.59 (dd, $^2J_{HH} = 10.7$ Hz, $^3J_{HH} = 6.8$ Hz, 1H, H_2), 4.23 (t, $^3J_{HH} = 9.6$ Hz, 1H, H_2), 4.74 (br s, 2H, H_{12}), 5.28 (d, $^2J_{HH} = 10.4$ Hz, 1H, H_{14}), 5.39 (dd, $^2J_{HH} = 17.0$ Hz, $^3J_{HH} = 10.0$ Hz, 1H, H_{14}), 6.02 (m, 1H, H_{13}), 6.99 (dt, $^3J_{HH} = 7.4$ Hz, $^4J_{HH} = 1.0$ Hz, 1H, H_6), 7.16 (d, $^3J_{HH} = 7.6$ Hz, 1H, H_4), 7.22 (d, $^3J_{HH} = 7.6$ Hz, 1H, H_5), 7.88 (br s, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.1 (C_{10}), 34.2 (C_3), 55.3 (C_2), 66.7 (C_{12}), 114.6 (C_7), 117.6 (C_{14}), 122.6 (C_6), 123.4 (C_4), 127.6 (C_5), 132.6 (C_{13}), 135.9 (C_9), 142.0 (C_8), 152.7 (C_{11}). MS (EI^+, m/z): 218 [$(M+H)^+$, 100%]. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.8; H, 7.0; N, 6.5. $[\alpha]_D^{20} = +21.2$ (c 0.5, $CHCl_3$) for 97% ee of the (*S*)-enantiomer.

4.4. Typical experimental procedure for the enzymatic kinetic resolution of racemic indolines 1 and 5a

A suspension under a nitrogen atmosphere of the corresponding indoline (0.19 mmol), carbonate **2b** (90 mg, 0.47 mmol) and CAL-A (1:2 in weight with respect to the amine) in dry TBME (1.27 mL) was shaken at 45 °C and 250 rpm for the necessary time to achieve a good kinetic resolution. The reaction was followed by TLC and HPLC analysis and after this time, the enzyme was filtered off and the solvent evaporated under reduced pressure, to obtain a crude that was purified by flash chromatography.

4.5. Typical experimental procedure for the enzymatic kinetic resolution of racemic indolines 5b,c

A suspension under a nitrogen atmosphere of the corresponding indoline (0.19 mmol), carbonate **2b** (90 mg, 0.47 mmol) and CAL-A (1:2 in weight with respect to the amine) in dry TBME (1.27 mL) was shaken at 45 °C and 250 rpm for the necessary time to achieve a good kinetic resolution. The reaction was followed by TLC and HPLC analysis and after this time, the enzyme was filtered off and the solvent evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and washed four times with NaOH 1M (5 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure, to give a crude that was purified by flash chromatography.

4.6. Enzymatic kinetic resolution of racemic 5d

A suspension under a nitrogen atmosphere of indoline **5d** (40 mg, 0.30 mmol), carbonate **2a** (108 μL, 0.74 mmol) and CAL-B (40 mg) in dry TBME (2 mL) was shaken at 30 °C and 250 rpm during 10 h. After this time, the enzyme was filtered off and the solvent evaporated under reduced pressure, to give a crude that was purified by flash chromatography (gradient eluent 5–20% EtOAc/hexane).

Acknowledgements

We thank Novo Nordisk for the generous gift of CAL-B. Financial support of this work by the European Project EU-04-LSHB-2003-503017 is gratefully acknowledged. V.G.-F. thanks Ministerio de Educación y Ciencia for a personal grant (Juan de la Cierva Program).

References

1. Berger, M.; Albrecht, B.; Berces, A.; Ettmayer, P.; Neruda, W.; Woisetschläger, M. *J. Med. Chem.* **2001**, *44*, 3031–3038.
2. Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Chem. Commun.* **2000**, 479–480.
3. Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317–8318.
4. Nieuwenhuijzen, J. W.; Grimbergen, R. F. P.; Koopman, C.; Kellogg, R. M.; Vries, T. R.; van Echten, E.; Kaptein, B.; Hulshof, L. A.; Broxterman, Q. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4281–4286.
5. (a) Guerrier, L.; Royer, J.; Grierson, D.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754–7755; (b) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399–5400; (c) Krasnov, V. P.; Levit, G. L.; Bukrina, I. M.; Andreeva, I. N.; Sadretdinova, L. S.; Korolyova, M. A.; Codees, M. I.; Charushin, V. N.; Chupakhin, O. N. *Tetrahedron: Asymmetry* **2003**, *14*, 1985–1988.
6. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562–7564; (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952–8965; (c) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537; (d) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213–2215; (e) Xu, L.; Lam, K. H.; Ji, J.; Fan, Q.-H.; Lo, W.-H.; Chan, A. S. C. *Chem. Commun.* **2005**, 1390–1392.
7. Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227–4230.
8. Verdauer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784–6785.
9. (a) Sheldon, R. A. *J. Chem. Technol. Biotechnol.* **1996**, *67*, 1–14; (b) Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2349–2354.
10. Youshko, M. I.; van Langen, L. M.; Sheldon, R. A.; Švedas, V. K. *Tetrahedron: Asymmetry* **2004**, *15*, 1933–1936.
11. Hu, S.; Tat, D.; Martinez, C. A.; Yazbeck, D. R.; Tao, J. *Org. Lett.* **2005**, *7*, 4329–4331.
12. (a) Carr, R.; Alexeeva, M.; Enright, A.; Eve, T. S. C.; Dawson, M. J.; Turner, N. J. *Angew. Chem.* **2003**, *42*, 4807–4810; (b) Carr, R.; Alexeeva, M.; Dawson, M. J.; Gotor-Fernández, V.; Humphrey, C. E.; Turner, N. J. *ChemBioChem* **2005**, *6*, 637–639.

13. (a) Straathof, A. J. J.; Panke, S.; Schmid, A. *Curr. Opin. Biotechnol.* **2002**, *13*, 548–556; (b) Bornscheuer, U. T.; Kazlauskas, R. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6032–6040; (c) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331–3351; (d) Wiktelius, D. *Synlett* **2005**, 2113–2114; (e) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354.
14. (a) Asensio, G.; Andreu, C.; Marco, J. A. *Tetrahedron Lett.* **1991**, *32*, 4197–4198; (b) Orsat, B.; Alper, P. B.; Moree, W.; Mak, C.-P.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 712–713; (c) Chiou, T.-W.; Chang, C.-C.; Lai, C.-T.; Tai, D.-F. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 433–436; (d) Wong, C.-H.; Orsat, B.; Moree, W. J.; Takayama, S. US-5981267; (e) Morgan, B.; Zaks, A.; Dodds, D. R.; Liu, J.; Jain, R.; Megati, S.; Njoroge, F. G.; Girijavallabhan, V. M. *J. Org. Chem.* **2000**, *65*, 5451–5459; (f) Liljeblad, A.; Lindborg, J.; Kanerva, A.; Katajisto, J.; Kanerva, L. T. *Tetrahedron Lett.* **2002**, *43*, 2471–2474; (g) Breen, G. F. *Tetrahedron: Asymmetry* **2004**, *15*, 1427–1430.
15. (a) Borschberg, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1465–1492; (b) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777; (c) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777–4779; (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920; (e) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521–535; (f) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058–1059; (g) Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1060–1061; (h) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131; (i) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653–2655; (j) Palimkar, S. S.; Kumar, P. H.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2006**, *62*, 5109–5115.
16. Domínguez de María, P.; Carboni-Oerlemans, C.; Tuin, B.; Bargeman, G.; Van de Meer, A.; Van Gemert, R. *J. Mol. Catal. B: Enzym.* **2005**, *37*, 36–46.
17. Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859–860.