JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

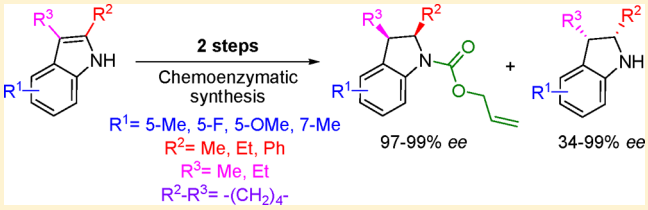
Stereoselective Synthesis of 2,3-Disubstituted Indoline Diastereoisomers by Chemoenzymatic Processes

María López-Iglesias, Eduardo Busto, Vicente Gotor, and Vicente Gotor-Fernández*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Biotecnología de Asturias, Universidad de Oviedo, 33006 Oviedo, Spain

Supporting Information

ABSTRACT: Racemic indolines including a variety of structural motifs such as C-2 and C-3 substitutions (alkyl or aryl), *cis*/*trans* relative stereochemistry and functionalization of the aromatic ring (fluoro, methyl or methoxy groups) have been efficiently prepared through Fischer indolization and subsequent diastereoselective reduction of the unprotected indoles. Combination of *Candida antarctica* lipase type A and allyl 3-methoxyphenyl carbonate has been identified as the best tandem for their kinetic resolutions, observing excellent stereodiscriminations for most of the tested indolines.



INTRODUCTION

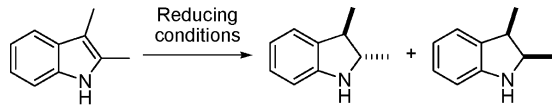
Optically active 2,3-disubstituted indolines are targeted compounds in medicinal and natural products chemistry since their structures are present in many natural occurring alkaloids (i.e., Vindoline, (−)-Strychnine, (−)-Physostigmine, etc.)[1] but also in synthetic drugs such as the antipsychotic agent WAY-163909.[2] The presence of two chiral centers in the indoline moiety leads to four possible diastereoisomers, each of them having the possibility to display very different chemical, physical and biological activities. Therefore, the development of stereoselective routes for the preparation of indoline single diastereoisomers continues to be a highly demanded goal in synthetic organic chemistry. Until now, asymmetric transformations leading to optically active 2,3-indolines have been based on different synthetic approaches such as catalytic hydrogenation[3] or hydrosilylation of the corresponding indoles,[4] nonenzymatic kinetic resolution of indolines[5] and a broad range of convergent methodologies as free radical promoted aryl aminations,[6] intramolecular shifting of sulfonyl groups,[7] asymmetric electrophilic cyclization processes[8] or palladium catalyzed coupling reactions.[9]

Although enzymes are ideal catalysts for the preparation of optically active cyclic secondary amines under very mild reaction conditions,[10] the chemoenzymatic production of 2,3-disubstituted indolines remains nowadays unexplored. In particular our research group has demonstrated the usefulness of lipases for the kinetic resolution of mono 2- and 3-substituted indolines by means of alkoxycarbonylation processes,[11] identifying lipases from *Candida antarctica* type A (CAL-A) and *Candida antarctica* type B (CAL-B) as the best catalysts. Thus, while the combination of CAL-A and allyl 3-methoxyphenyl carbonate has efficiently led to the resolution of 2-substituted derivatives, less hindered 3-methylindoline was efficiently resolved using CAL-B and diallyl carbonate. Herein, we report a general and robust approach for the synthesis of a family of *cis*-2,3-substituted indolines, studying later in depth their lipase-catalyzed kinetic resolution processes through alkoxycarbonylation reactions. In this manner, the level of structural complexity has been increased dealing with the production of indoline diasteroisomers by controlling the chirality of both stereogenic centers for the production of the carbamates and amines with *cis*-configuration in enantiopure form.

RESULTS AND DISCUSSION

To explore the possibilities of lipases in the kinetic resolution of this class of heterocyclic amines, 2,3-dimethylindoline (**2a**) was selected as the model substrate because of its easy accessibility through simple chemical reduction of 2,3-dimethyl-1*H*-indole (**1a**). Depending on the reducing agent, it is possible to drive the reaction toward the formation of the *cis*- or the *trans*-isomer (Scheme 1), so when using sodium cyanoborohydride ($NaBH_3CN$) predominately occurs the formation of the *trans*-isomer (ratio *trans*/*cis* 3:1),[5a,12] while the formation of

Scheme 1. Reduction of 2,3-Dimethyl-1*H*-indole (1a) for the Synthesis of (±)-*trans*- and (±)-*cis*-2,3-Dimethyl-indoline (2a)



Received: June 22, 2012
Published: August 22, 2012

   dx.doi.org/10.1021/jo301307q | J. Org. Chem. 2012, 77, 8049−8055

the *cis*-isomer is favored with platinum catalyzed hydrogenation (ratio *trans*/*cis* 1:6).[13]

Trying to optimize the production of a single diastereoisomer, the hydrogenation of **1a** was performed over Adams' catalyst (PtO_2), and although the analysis of the reaction crude revealed complete conversion, large amounts of the undesired *trans*-isomer were detected leading to the *cis*-indoline in 50% *de*. At this point, similar conditions to the ones reported by Wee and co-workers for 2-ethyl-3-methylindole were attempted for the production of the corresponding *cis*-indoline.[14] Then, Pd−C was used as catalyst, and a combination of a perchloric acid solution in acetic acid (5% v/v) was chosen as reaction medium. Data are summarized in Table 1. Satisfyingly, racemic *cis*-indoline **2a** was exclusively obtained as reaction product, although in moderate conversion (50%, entry 1). In our search for higher conversion values, the amount of $HClO_4$ was increased to 10% (v/v), and we observed a slight improvement of the conversion value (56%, entry 2), finding the best results with a higher loading of $HClO_4$ (30% v/v), which exclusively led to the racemic indoline *cis*-**2a** in very good isolated yield (entry 3).

Table 1. Optimization of the Diastereoselective Reduction of 2,3-Dimethyl-1*H*-indole (1a) for the Production of *cis*-2a Using 10% Pd−C in a Solution of $HClO_4$ in AcOH

entry	$HClO_4$ (%)[a]	*c* (%)[b]	*de* (%)[b]
1	5	50	>97
2	10	56	>97
3	30	>97 (85)	>97

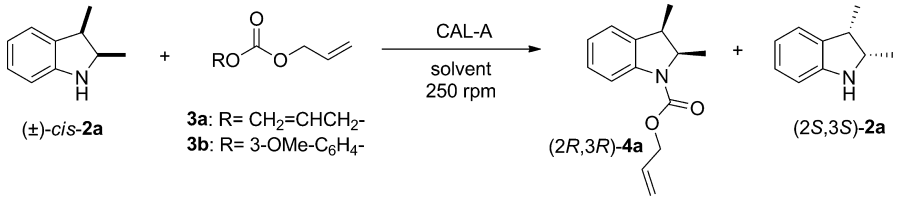
[a]Ratio in v/v. [b]Conversion and diasteromeric excess determined by ^{1}H NMR of the crude. Isolated yields in parentheses.

Once the synthesis of *cis*-(±)-**2a** was optimized, its lipase-catalyzed alkoxycarbonylation was analyzed on the basis of the excellent results previously achieved in the resolution of mono 2- or 3-substituted indolines,[11] and also indoline-2-carboxylic acid derivatives,[15] selecting CAL-A, a very active catalyst for sterically hindered indolines,[16] diallyl carbonate or allyl 3-methoxyphenyl carbonate as alkoxycarbonylating agents, and a variety of organic solvents for an exhaustive study of the enzymatic resolution of *cis*-(±)-**2a** (Table 2). Initial experiments were conducted with diallyl carbonate (**3a**), and we observed a low reaction rate but a complete enantioselectivity toward the formation of the carbamate (2*R*,3*R*)-**4a** (entry 1). This promising result in terms of stereoselectivity made us move forward to the use of a more reactive carbonate such as allyl 3-methoxyphenyl carbonate (**3b**). Satisfyingly, conversion reached 50% after 24 h, isolating both substrate (2*S*,3*S*)-**2a** and product (2*R*,3*R*)-**4a** nearly in enantiopure form (entry 2). The use of higher temperatures (45 °C) did not improve the reaction rate, and we observed a slight decrease of the optical purity for both substrate and product (entry 3). Similar results in terms of excellent enantioselectivity were achieved with other solvents such as Et_2O, THF, *n*-hexane or toluene (entries 4−7), although lower conversion values were attained. For the assignment of the absolute configuration, the optical rotation of the so-obtained enantioenriched amine *cis*-**2a** ($[\alpha]_D^{20}$= −29.0 (*c* 0.83, $CHCl_3$) in 99% *ee*) was compared with the one reported in the literature ($[\alpha]_D^{20}$= +26.6 (*c* 0.83, $CHCl_3$) for (2*R*,3*R*)-**2a** in 92% *ee*).[3b] According to this, the product configurations in the lipase-catalyzed resolution of the indoline were assigned as (2*S*,3*S*) for the amine **2a** and (2*R*,3*R*) for the carbamate **4a**.

Encouraged by the excellent results achieved for *cis*-**2a**, the influence of the relative disposition (*cis*/*trans*) of the methyl groups was explored in its enzymatic resolution. So, the kinetic resolution of the racemic amine *trans*-**2a** was attempted using a representative set of catalysts such as CAL-A, CAL-B, *Candida rugosa* lipase (CRL), pig pancreas lipase (PPL), *Thermomyces lanuginose* lipase (TLL), *Rhizomucor miehei* lipase (RM-IM) and lipase AK from *Pseudomonas fluorescens* in the presence of diallyl carbonate (**3a**) or the more reactive allyl 3-methoxyphenyl carbonate (**3b**) in dry TBME, but unfortunately, the starting materials were recovered unaltered.

At this point, and considering that CAL-A displays good catalytic activities for indolines in relative *cis*-disposition, we have considered two substitution patterns in the *cis*-indoline core to correctly expand the potential of our synthetic approach, those bearing different functionalities in the aromatic ring (methyl, methoxy or fluoro in C-5 or C-7), and alternatively varying the substituents in the C-2 and C-3 positions of the unsaturated ring (alkyl or aryl rests). Because of the lack of commercial availability for substituted indoles **1b−i**,

Table 2. Enzymatic Kinetic Resolution of Indoline *cis*-2a Using 2.5 equiv of Carbonates 3a,b in Different Organic Solvents

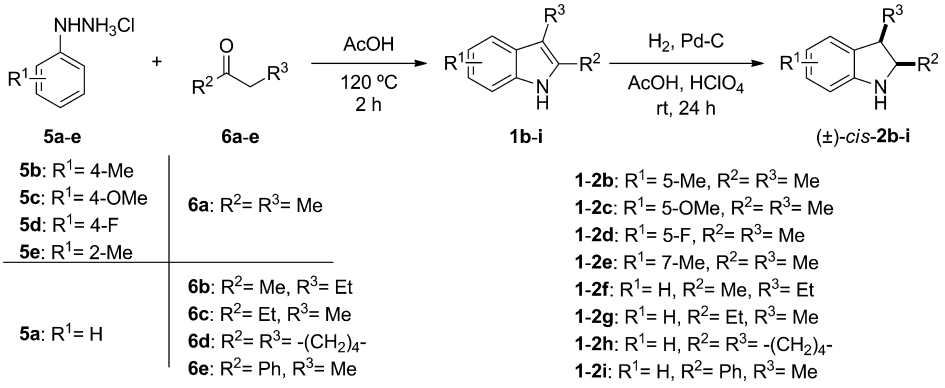


entry	carbonate	*T* (°C)	*t* (h)	solvent	ee_p (%)[a]	ee_s (%)[a]	*c* (%)[b]	*E*[c]
1	**3a**	30	167	TBME	>99	19	16	>200
2	**3b**	30	24	TBME	98 (35)	99 (30)	50	>200
3	**3b**	45	24	TBME	96	98	50	>200
4	**3b**	30	24	Et_2O	99	94	49	>200
5	**3b**	30	24	THF	99	6	6	>200
6	**3b**	30	24	*n*-hexane	99	63	39	>200
7	**3b**	30	24	toluene	99	70	41	>200

[a]Determined by HPLC. Isolated yields in parentheses calculated from the conversion value. [b]$c = ee_s/(ee_s + ee_p)$. [c]$E = \ln[(1 - c)(1 - ee_p)]/\ln[(1 - c)(1 + ee_p)]$.[17]

dx.doi.org/10.1021/jo301307q | J. Org. Chem. 2012, 77, 8049−8055

Scheme 2. Synthesis of Racemic Indolines *cis*-2b−i through Fischer Indolization and Diasteroselective Palladium Catalyzed Hydrogenation



they were prepared following a general route by means of Fischer indolization reaction of the corresponding phenyl hydrazines (**5a−e**) and a variety of ketones (**6a−e**) in refluxing acetic acid,[18] yielding indoles **1b−i** in good to high yields after 2 h (65−92%, Scheme 2).

Next, the diasteroselective catalytic hydrogenation of **1b−i** was studied using the optimized reaction conditions for **1a**. Remarkably, in all cases the racemic *cis*-indolines were isolated as the unique products without observing the formation of the *trans*-isomers after 24 h. Higher conversions were achieved for the indoles **1b**,**c** with electron-donating groups at the 5-position, isolating the *cis*-indolines in good yields (65%, Table 3, entries 1−2). On the other hand, moderate conversions were attained for the 5-F and 7-Me derivatives isolating the amines *cis*-**1d**,**e** in low to moderate yields (27−41%, entries 3−4). Full conversions were attained for the hydrogenation of indoles bearing aliphatic rests such as ethyl groups in C-2 or C-3 (**1f**,**g**) and also the carbazole derivative (**1h**), achieving the diastereomercally pure *cis*-indolines **2f−h** in moderate isolated yields (47−63%, entries 5−7). However, a very low conversion (less than 5%) was noticed for the hydrogenation of indole **1i**, with a phenyl group linked to the C-2 position (data not shown). To overcome this limitation, the catalytic hydrogenation was carried out at a higher hydrogen pressure (8 atm), allowing the complete disappearance of the starting material and the isolation of indoline *cis*-**2i** in 35% yield without observing the formation of the *trans* isomer (entry 8).

Table 3. Synthesis of Racemic Indolines 2b−i through Fischer Indolization and Subsequent Palladium Catalyzed Hydrogenation

entry	R^1	R^2	R^3	indole **1b−i** (%)[a]	H_2 (atm)	indoline **2b−i** (%)[b]
1	5-Me	Me	Me	85 (**b**)	1	65 (80)
2	5-OMe	Me	Me	85 (**c**)	1	65 (76)
3	5-F	Me	Me	91 (**d**)	1	41 (69)
4	7-Me	Me	Me	76 (**e**)	1	27 (57)
5	H	Me	Et	92 (**f**)	1	47 (>97)
6	H	Et	Me	75 (**g**)	1	46 (>97)
7	H	$-(CH_2)_4-$		65 (**h**)	1	63 (>97)
8	H	Ph	Me	82 (**i**)	8	35 (>97)

[a]Isolated yields. [b]Isolated yields. Conversion in brackets determined by ^{1}H NMR of the crude.

Finally the enzymatic resolution of racemic indolines *cis*-**2b−i** was attempted under the optimized conditions for **2a** (Table 4). Excellent enantiopreferences were observed for indolines with different groups linked to the C-5 position (entries 2−4), especially in very short span for the activating methyl and methoxy groups (entries 2−3). An opposite behavior was observed for *cis*-**2e**, with a methyl group at the 7-position, so close to the reactive point, not detecting any reaction after 111 h (entry 5).

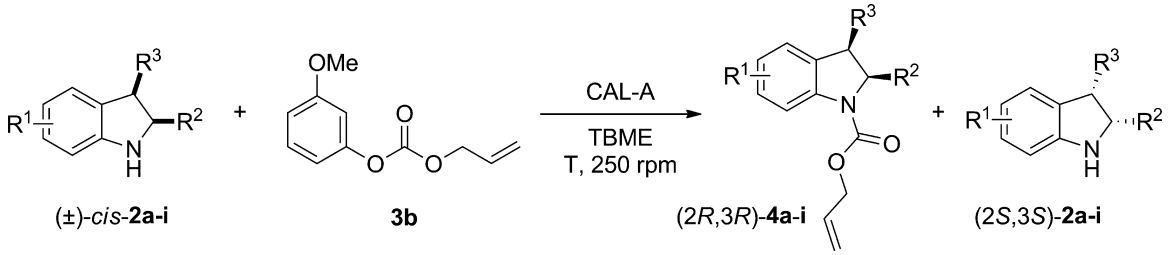
The introduction of conformationally flexible ethyl groups at C-2 or C-3 positions led to excellent stereopreferences, although moderate conversions at 30 °C obtaining 31% conversion for **2f** after 67 h (entry 6) and 20% for **2g** after 71 h (entry 8), longer reaction times without increasing these conversion values. When the use of higher temperatures (entries 7 and 9) or alternative alkoxycarbonylating agents (data not shown) were examined, neither substantially improve the conversions. On the other hand, efficient kinetic resolutions take place with indolines bearing bulky rests such as cyclohexyl (**2h**) or 2-phenyl (**2i**). Biotranformations reached 50% conversion after 34 h for the cyclohexyl derivative (**2h**) isolating substrate and product in near enantiopure form (entry 10). Similar results were obtained for the 2-phenyl derivative *cis*-**2i** isolating both (2*R*,3*S*)-amine and (2*S*,3*R*)-carbamate in excellent enantiomeric excess after 72 h (entry 11), where the C-2 carbon configuration has changed due to the higher priority of the phenyl group in the CIP rules.

CONCLUSIONS

The chemical syntheses of a panel of nine 2,3-disubstituted indolines have been possible by means of a sequence consisting of a Fischer indolization reaction followed by the catalytic diastereoselective hydrogenation of the resulting unprotected indoles. Lipase-catalyzed kinetic resolutions of the so-obtained indolines were later studied using different biocatalysts and alkoxycarbonylating agents searching for the generation of two chiral centers in the indoline core. This synthetic approach has allowed us to study the influence of different structural vectors such as *cis*/*trans* relative stereochemistry, functionalization in the aromatic ring (fluoro, methyl and methoxy) and different groups at the C-2 and C-3 positions (alkyl or aryl) in the enzymatic catalysis. The combination of *Candida antarctica* lipase type A and allyl 3-methoxyphenyl carbonate has been found as the best tandem, the enzymatic alkoxycarbonylations being found highly dependent on the indoline structure. Remarkably, a complete absence of reactivity was detected for *trans*-isomers or with *cis*-2,3,7-trimethylindoline, containing the substitution closer to the reactive point. However, efficient

dx.doi.org/10.1021/jo301307q | J. Org. Chem. 2012, 77, 8049−8055

Table 4. CAL-A Catalyzed Kinetic Resolution of (±)-*cis*-2a−i Using 2.5 equiv of Carbonate 3b in TBME at 250 rpm



entry	indoline	T (°C)	t (h)	ee_p (%)[a]	ee_s (%)[a]	c (%)[b]	E[c]
1	**2a**	30	24	98 (35)	99 (30)	50	>200
2	**2b**	30	6.5	97 (36)	>99 (29)	50	>200
3	**2c**	30	4	97 (38)	>99 (30)	50	>200
4	**2d**	30	24	99 (35)	99 (29)	50	>200
5	**2e**	30	111	–	–	–	–
6	**2f**	30	67	>99	45	31	>200
7	**2f**	45	67	>99	51	34	>200
8	**2g**	30	71	>99	25	20	>200
9	**2g**	45	71	>99	34	26	>200
10	**2h**	30	34	98 (39)	97 (25)	50	>200
11	**2i**	30	72	>99 (25)	96 (20)	49	>200

[a]Determined by HPLC. Isolated yields in parentheses. [b]$c = ee_s/(ee_s + ee_p)$. [c]$E = \ln[(1 - c)(1 - ee_p)]/\ln[(1 - c)(1 + ee_p)]$.[17]

kinetic resolutions were attained for *cis*-indolines bearing different groups at C-2, C-3 or C-5 positions observing in all cases excellent enantioselectivity values.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Indoles 1b−i. Phenylhydrazine hydrochloride **5a−e** (2.86 mmol) was added to a solution of the corresponding ketone **6a−e** (8.90 mmol) in AcOH (14.3 mL), and the solution was stirred at 120 °C for 2 h. After this time, EtOAc (60 mL) was added, the organic phase was washed with brine (2 × 150 mL) and with a saturated solution of $NaHCO_3$ (150 mL) and dried over Na_2SO_4, and the solvent was removed by distillation under reduced pressure affording the indoles **1b−i** (65−92%). **1b** (387 mg, 85% yield): R_f (10% EtOAc/*n*-hexane) 0.38; mp 104−106 °C (lit 98−99 °C);[19] IR (KBr) ν 3393, 2919, 2855, 2362, 1595, 1478, 1449, 1417, 1303, 1265, 791, 740 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.37 (s, 3H), 2.63 (s, 3H), 7.10 (dd, $^3J_{HH}$= 8.1, $^4J_{HH}$= 1.4 Hz, 1H), 7.17 (d, $^3J_{HH}$= 8.1 Hz, 1H), 7.35 (br s, 1H), 7.43 (d, $^4J_{HH}$= 0.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.5 (CH_3), 11.4 (CH_3), 21.6 (CH_3), 106.5 (C), 109.9 (CH), 117.8 (CH), 122.4 (CH), 128.1 (C), 129.7 (C), 131.0 (C), 133.6 (C); HRMS (ESI^-, m/z) calcd for $(C_{22}H_{25}N_2)^-$ $(2M - H)^-$ 317.2023, found 317.2008. **1c** (426 mg, 85% yield): R_f (10% EtOAc/*n*-hexane) 0.21; mp 106−109 °C (lit. 108−109 °C);[19] IR (KBr) ν 3463, 3406, 3049, 2919, 2359, 1595, 1484, 1268, 1217, 1137, 1029, 736 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.35 (s, 3H), 3.89 (s, 3H), 6.79 (d, $^3J_{HH}$= 8.6 Hz, 1H), 6.95 (s, 1H), 7.14 (d, $^3J_{HH}$= 8.6 Hz, 1H), 7.57 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.6 (CH_3), 11.7 (CH_3), 56.1 (CH_3), 100.6 (CH), 107.1 (C), 110.6 (CH), 110.8 (CH), 130.0 (C), 130.4 (C), 131.8 (C), 153.9 (C); HRMS (ESI^+, m/z) calcd for $(C_{11}H_{14}NO)^+$ $(M + H)^+$ 176.1070, found 176.1064. **1d** (425 mg, 91% yield): R_f (5% EtOAc/*n*-hexane) 0.14; mp 98−99 °C (lit. 98−99 °C);[19] IR (KBr) ν 3465, 3365, 2913, 2869, 1594, 1487, 1437, 1270 1229, 1176, 794, 734 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.36 (s, 3H), 6.85−6.92 (m, 1H), 7.13−7.17 (m, 2H), 7.64 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.6 (CH_3), 11.7 (CH_3), 103.1 (d, $^2J_{CF}$= 23.3 Hz, CH), 107.5 (d, $^4J_{CF}$= 4.5 Hz, C), 108.9 (d, $^2J_{CF}$= 26.1 Hz, CH), 110.6 (d, $^3J_{CF}$= 9.7 Hz, CH), 130.0 (d, $^3J_{CF}$= 9.5 Hz, C), 131.7 (C), 132.9 (C), 157.9 (d, $^1J_{CF}$= 233.3 Hz, C); HRMS (ESI^-, m/z) calcd for $(C_{10}H_9FN)^-$ $(M - H)^-$ 162.0725, found 162.0720. **1e** (346 mg, 76% yield): R_f (10% EtOAc/*n*-hexane) 0.38; mp 58−64 °C (lit. 64−65 °C);[19] IR (KBr) ν 3393, 2919, 2855, 2362, 1595, 1478, 1449, 1417, 1303, 1265, 791, 740 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.44 (s, 3H), 2.52 (s, 3H), 6.98−7.05 (m, 1H), 7.10 (t, $^3J_{HH}$= 7.5 Hz, 1H), 7.42 (d, $^3J_{HH}$= 7.8 Hz, 1H), 7.64 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.7 (CH_3), 11.7 (CH_3), 16.7 (CH_3), 107.7 (C), 115.8 (CH), 119.2 (C), 119.3 (CH), 121.7 (CH), 129.1 (C), 130.4 (C), 134.7 (C); HRMS (ESI^+, m/z) calcd for $(C_{22}H_{27}N_2)^+$ $(2M + H)^+$ 319.2169, found 319.2181. **1f** (419 mg, 92% yield): R_f (10% Et_2O/*n*-hexane) 0.24; IR (NaCl) ν 3406, 3055, 2964, 2930, 2869, 1612, 1461, 1338, 1299, 1265, 1235, 1011, 741, 704, 665 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.52 (t, $^3J_{HH}$= 7.3 Hz, 3H), 2.39 (s, 3H), 3.00 (q, $^3J_{HH}$= 7.3 Hz, 2H), 7.20 (br s, 1H), 7.24−7.33 (m, 1H), 7.39−7.49 (m, 2H), 7.81−7.91 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.4 (CH_3), 15.5 (CH_3), 17.5 (CH_2), 110.3 (CH), 113.9 (C), 118.1 (CH), 119.0 (CH), 120.8 (CH), 128.5 (C), 130.3 (C), 135.3 (C); HRMS (ESI^-, m/z) calcd for $(C_{11}H_{12}N)^-$ $(M - H)^-$ 158.0975, found 158.0957. **1g** (341 mg, 75% yield): R_f (10% EtOAc/*n*-hexane) 0.28; mp 57−59 °C (lit. 61−62 °C);[20] IR (KBr) ν 3464, 3410, 3054, 2971, 2922, 2873, 2305, 1618, 1589, 1464, 1383, 1318, 1265, 1153, 1010, 896, 740, 705 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 1.33 (t, $^3J_{HH}$= 7.6 Hz, 3H), 2.33 (s, 3H), 2.80 (q, $^3J_{HH}$= 7.6 Hz, 2H), 7.05−7.35 (m, 3H), 7.47−7.63 (m, 1H), 7.66 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.4 (CH_3), 14.1 (CH_3), 19.5 (CH_2), 106.2 (C), 110.3 (CH), 118.1 (CH), 119.1 (CH), 121.0 (CH), 129.6 (C), 135.2 (C), 136.7 (C); HRMS (ESI^+, m/z) calcd for $(C_{11}H_{13}N)^+$ $(M)^+$ 159.1043, found 159.1043. **1h** (318 mg, 65% yield): R_f (10% EtOAc/*n*-hexane) 0.38; mp 103−107 °C (lit. 110−115 °C);[21] IR (KBr) 3406, 3055, 2964, 2930, 2869, 1261, 1461, 1299, 1265, 1234, 1011, 741 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 1.95−2.12 (m, 4H), 2.68−2.81 (m, 2H), 2.82−2.93 (m, 2H), 7.21−7.34 (m, 3H), 7.39 (br s, 1H), 7.60−7.69 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (CH_2), 23.2 (CH_2), 23.3 (CH_2), 23.4 (CH_2), 110.0 (C), 110.5 (CH), 117.8 (CH), 119.1 (CH), 120.9 (CH), 127.8 (C), 134.2 (C), 135.7 (C); HRMS (ESI^-, m/z) calcd for $(C_{12}H_{12}N)^-$ $(M - H)^-$ 170.0975, found 170.0966. **1i** (486 mg, 82% yield): R_f (10% Et_2O/*n*-hexane) 0.28; mp 89−92 °C (lit. 87−90 °C);[19] IR (KBr) ν 3457, 3054, 2984, 2921, 2305, 1686, 1604, 1459, 1333, 1305, 1265, 740, 702 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 2.64 (s, 3H), 7.32−7.47 (m, 3H), 7.47−4.55 (m, 1H), 7.57−7.65 (m, 2H), 7.65−7.72 (m, 2H), 7.77−7.85 (m, 1H), 7.68 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.7 (CH_3), 108.6 (C), 110.8 (CH), 119.0 (CH), 119.6 (CH), 122.3 (CH), 127.3 (CH), 127.8 (2CH), 128.8 (2CH), 130.1 (C), 133.3 (C),

dx.doi.org/10.1021/jo301307q | J. Org. Chem. 2012, 77, 8049−8055

134.1 (C), 135.9 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{13}N)^+$ $(M)^+$ 207.1043, found 207.1048.

Synthesis of Racemic *trans*-2,3-Dimethylindoline (*trans*-2a). $NaBH_3CN$ (1.30 g, 20.64 mmol) was slowly added to a solution of 2,3-dimethylindole (**1a**, 1 g, 6.88 mmol) in AcOH (60 mL), and the solution was stirred for 5 h. After this time, the reaction was stopped with a saturated solution of Na_2CO_3 (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL), the organic phases were combined and dried, and the solvent was removed by distillation under reduced pressure. The crude was purified by flash chromatography (100% CH_2Cl_2) affording 385 mg of (±)-*trans*-**2a** as a colorless oil (38%): R_f (100% CH_2Cl_2) 0.37; IR (NaCl) ν 3367, 3050, 3032, 2967, 2865, 1615, 1487, 1468, 1254, 1095, cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.36 (d, $^3J_{HH}$= 6.6 Hz, 3H), 1.37 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.77−3.02 (m, 1H), 3.47−3.56 (m, 1H), 3.83 (br s, 1H), 6.66 (d, $^3J_{HH}$= 7.6 Hz, 1H), 6.75−6.87 (m, 1H), 7.03−7.18 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.3 (CH_3), 20.6 (CH_3), 44.4 (CH), 64.0 (CH), 109.2 (CH), 118.6 (CH), 123.3 (CH), 127.4 (CH), 134.3 (C), 150.6 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{10}H_{14}N)^+$ $(M + H)^+$ 148.1121, found 148.1122.

General Procedure for the Synthesis of Racemic *cis*-Indolines 2a−h. To a suspension containing the corresponding indole **1a−g** (0.94 mmol) and Pd−C 10% (34 mg) in a 100 mL round-bottom flask was connected a H_2 balloon. Then, AcOH (3.0 mL) and $HClO_4$ (1 mL) were carefully added. The resulting suspension was stirred at room temperature during 24 h, and after this time, the reaction was stopped, filtering the mixture through diatomaceous earth. The crude was basified with NaOH 4 N (100 mL), extracted with CH_2Cl_2 (3 × 30 mL), and dried, and the solvent was removed under reduced pressure, affording a reaction crude that was purified by flash chromatography (Et_2O/*n*-hexane mixtures) affording the *cis* indolines **2a−h** as colorless oils (27−85%). *cis*-**2a** (118 mg, 85% yield): R_f (10% EtOAc/*n*-hexane) 0.27; IR (NaCl) ν 3367, 3049, 3032, 2966, 2919, 2870, 1610, 1484, 1463, 1250, 1092, 1011, 922, 742 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.17 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.22 (d, $^3J_{HH}$= 7.2 Hz, 3H), 3.30 (q, $^3J_{HH}$= 7.3 Hz, 1H), 3.47 (br s, 1H), 3.91−4.03 (m, 1H), 6.65 (d, $^3J_{HH}$= 7.7 Hz, 1H), 6.77 (dt, $^3J_{HH}$= 7.7 Hz; $^4J_{HH}$= 0.9 Hz, 1H), 6.97−7.18 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7 (CH_3), 16.4 (CH_3), 39.5 (CH), 58.4 (CH), 109.4 (CH), 118.8 (CH), 123.9 (CH), 127.3 (CH), 134.4 (C), 150.2 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{10}H_{14}N)^+$ $(M + H)^+$ 148.1121, found 148.1118. $[\alpha]_D^{20}$= −29.0 (*c* 0.83, $CHCl_3$) [for (2*S*,3*S*)-**2a** in 99% *ee*] [lit. $[\alpha]_D^{20}$= +26.6 (*c* 0.83, $CHCl_3$) for (2*R*,3*R*)-**2a** in 92% *ee*].[3b] *cis*-**2b** (99 mg, 65% yield): R_f (10% Et_2O/*n*-hexane) 0.16; IR (NaCl) ν 3362, 3010, 2965, 2918, 2866, 1618, 1494, 1448, 1378, 1249, 1115, 1095, 925, 807 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.15 (d, $^3J_{HH}$= 6.6 Hz, 3H), 1.18 (d, $^3J_{HH}$= 7.2 Hz, 3H), 2.28 (s, 3H), 3.00−3.47 (m, 1H), 3.87−4.03 (m, 1H), 6.55 (d, $^3J_{HH}$= 7.8 Hz, 1H), 6.84 (d, $^3J_{HH}$= 7.8 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8 (CH_3), 16.4 (CH_3), 21.0 (CH_3), 39.7 (CH), 58.7 (CH), 109.5 (CH), 124.7 (CH), 127.7 (CH), 128.2 (C), 134.8 (C), 147.9 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{11}H_{16}N)^+$ $(M + H)^+$ 162.1277, found 162.1268. $[\alpha]_D^{20}$= −28.4 (*c* 1, CH_2Cl_2) [for (2*S*,3*S*)-**2b** in >99% *ee*]. *cis*-**2c** (108 mg, 65% yield): R_f (20% EtOAc/*n*-hexane) 0.16; IR (NaCl) ν 3358, 2964, 2933, 2831, 1598, 1491, 1434, 1379, 1286, 1232, 1203, 1150, 1041, 908, 866, 806, 717 cm^{-1}; ^{1}H NMR (400.13 MHz, CD_3CN) δ 1.05 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.08 (d, $^3J_{HH}$= 7.2 Hz, 3H), 2.28 (br s, 1H), 3.12 (q, $^3J_{HH}$= 7.3 Hz, 1H), 3.67 (s, 3H), 3.77−3.84 (m, 1H), 6.44 (d, $^3J_{HH}$= 8.3 Hz, 1H), 6.52 (dd, $^3J_{HH}$= 8.3 Hz; $^4J_{HH}$= 2.4 Hz, 2H), 6.68 (d, $^3J_{HH}$= 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3CN) δ 13.9 (CH_3), 16.2 (CH_3), 40.8 (CH), 56.3 (CH), 59.5 (CH_3), 110.1 (CH), 111.7 (CH), 112.7 (CH), 137.0 (C), 145.7 (C), 154.1 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{11}H_{16}NO)^+$ $(M + H)^+$ 178.1226, found 178.1217. $[\alpha]^{20}{}_D$ −29.0 (*c* 0.5, CH_2Cl_2) [for (2*S*,3*S*)-**2c** in >99% *ee*]. *cis*-**2d** (64 mg, 41% yield): R_f (40% CH_2Cl_2/*n*-hexane) 0.21; IR (NaCl) ν 3372, 2969, 2924, 2873, 1606, 1484, 1436, 1201, 798; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.14 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.17 (d, $^3J_{HH}$= 7.2 Hz, 3H), 3.19−3.32 (m, 1H), 3.33 (br s, 1H), 3.86−4.07 (m, 1H), 6.48−6.54 (m, 1H), 6.65−6.76 (m, 1H), 6.76−6.84 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6 (CH_3), 16.3 (CH_3), 39.9 (CH), 59.1 (CH), 109.6 (d, $^3J_{CF}$= 8.2 Hz, CH), 111.3 (d, $^2J_{CF}$= 23.6 Hz, CH), 113.1 (d, $^2J_{CF}$= 23.2 Hz, CH), 136.2 (d, $^3J_{CF}$= 7.5 Hz, C), 146.1 (C), 157.3 (d, $^1J_{CF}$= 234.8 Hz, C); HRMS (ESI$^+$, m/z) calcd for $(C_{10}H_{13}FN)^+$ $(M + H)^+$ 166.1027, found 166.1046. $[\alpha]_D^{20}$= −24.6 (*c* 0.5, CH_2Cl_2) [for (2*S*,3*S*)-**2d** in 99% *ee*]. *cis*-**2e** (41 mg, 27% yield): R_f (40% CH_2Cl_2/*n*-hexane) 0.24; IR (NaCl) ν 3365, 3050, 3022, 2965, 2928, 2870, 1888, 1836, 1602, 1465, 1378, 1351, 1318, 1257, 1228, 1203, 1093, 1058, 924, 771, 747 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.20 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.22 (d, $^3J_{HH}$= 7.1 Hz, 3H), 2.17 (s, 3H), 3.15−3.43 (m, 1H), 3.30 (br s, 1H), 3.92−4.06 (m, 1H), 6.73 (t, $^3J_{HH}$= 7.2 Hz, 1H), 6.91 (d, $^3J_{HH}$= 7.2 Hz, 1H), 6.98 (d, $^3J_{HH}$= 7.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9 (CH_3), 16.6 (CH_3), 16.8 (CH_3), 39.8 (CH), 58.3 (CH), 118.7 (C), 119.0 (CH), 121.4 (CH), 128.3 (CH), 133.8 (C), 148.7 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{11}H_{16}N)^+$ $(M + H)^+$ 162.1277, found 162.1281. *cis*-**2f** (71 mg, 47% yield): R_f (10% Et_2O/*n*-hexane) 0.15; IR (NaCl) ν 3353, 3056, 2942, 2488, 1682, 1570, 1539, 1455, 1429, 1325, 1251, 996, 789, 670 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.13 (t, $^3J_{HH}$= 7.4 Hz, 3H), 1.23 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.61−1.89 (m, 2H), 3.11 (q, $^3J_{HH}$= 7.5 Hz, 1H), 3.64 (br s, 1H), 4.05 (dq, $^3J_{HH}$= 13.2, 6.5 Hz, 1H), 6.71 (d, $^3J_{HH}$= 7.7 Hz, 1H), 6.82 (dt, $^3J_{HH}$= 7.4 Hz; $^4J_{HH}$= 0.9 Hz, 1H), 7.13 (t, $^3J_{HH}$= 7.6 Hz, 1H), 7.20 (d, $^3J_{HH}$= 7.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.5 (CH_3), 15.9 (CH_3), 20.8 (CH_2), 46.7 (CH), 58.4 (CH), 109.5 (CH), 118.4 (CH), 124.4 (CH), 127.3 (CH), 132.7 (C), 150.6 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{11}H_{16}N)^+$ $(M + H)^+$ 162.1277, found 162.1269. $[\alpha]_D^{20}$= −2.4 (*c* 1.35, $CHCl_3$) [for (2*S*,3*S*)-**2f** in 54% *ee*] and $[\alpha]_D^{20}$= +6.8 (*c* 1, $CHCl_3$) [for (2*R*,3*R*)-**2f** in >99% *ee* obtained from (2*R*,3*R*)-**4f**][22] [lit. $[\alpha]_D^{20}$= +4.3 (*c* 1.34, $CHCl_3$) for (2*R*,3*R*)-**2f** in 93% *ee*].[4] *cis*-**2g** (70 mg, 46% yield): R_f (20% EtOAc/*n*-hexane) 0.44; IR (NaCl) ν 3365, 3050, 3030, 2962, 2932, 2874, 1609, 1483, 1462, 1380, 1242, 1097, 1020, 741 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.08 (t, $^3J_{HH}$= 7.4 Hz, 3H), 1.22 (d, $^3J_{HH}$= 7.2 Hz, 3H), 1.53−1.79 (m, 2H), 3.33 (q, $^3J_{HH}$= 7.3 Hz, 1H), 3.74 (td, $^3J_{HH}$= 8.1, 5.9 Hz, 1H), 3.96 (br s, 1H), 6.70 (d, $^3J_{HH}$= 7.7 Hz, 1H), 6.82 (dt, $^3J_{HH}$= 7.4 Hz; $^4J_{HH}$= 0.9 Hz, 1H), 7.08−7.14 (m, 1H), 7.17 (d, $^3J_{HH}$= 7.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.5 (CH_3), 14.3 (CH_3), 23.2 (CH_2), 38.9 (CH), 64.9 (CH), 109.3 (CH), 118.7 (CH), 123.8 (CH), 127.3 (CH), 135.3 (C), 150.1 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{11}H_{16}N)^+$ $(M + H)^+$ 162.1277, found 162.1282. $[\alpha]_D^{20}$= +0.55 (*c* 0.91, $CHCl_3$) [for (2*S*,3*S*)-**2g** in 34% *ee*] and $[\alpha]_D^{20}$= −4.0 (*c* 0.25, $CHCl_3$) [for (2*R*,3*R*)-**2g** in >99% *ee* obtained from (2*R*,3*R*)-**4g**][22] [lit. $[\alpha]_D^{20}$= +2.5 (*c* 0.90, $CHCl_3$) for (2*S*,3*S*)-**2g** in 90% *ee*].[4] *cis*-**2h** (102 mg, 63% yield): R_f (20% Et_2O/*n*-hexane) 0.29; IR (NaCl) ν 3362, 3048, 3030, 2928, 2854, 1763, 1610, 1477, 1460, 1249, 1151, 1017, 974, 749 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.31−1.46 (m, 3H), 1.69−1.52 (m, 3H), 1.73−1.82 (m, 2H), 3.11 (q, $^3J_{HH}$= 6.6 Hz, 1H), 3.65 (br s, 1H), 3.70−3.79 (m, 1H), 6.69 (d, $^3J_{HH}$= 7.7 Hz, 1H), 6.75 (t, $^3J_{HH}$= 7.3 Hz, 1H), 7.04 (t, $^3J_{HH}$= 7.7 Hz, 1H), 7.10 (d, $^3J_{HH}$= 7.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8 (CH_2), 22.7 (CH_2), 27.1 (CH_2), 29.3 (CH_2), 41.1 (CH), 59.8 (CH), 110.3 (CH), 118.9 (CH), 123.3 (CH), 127.1 (CH), 133.7 (C), 150.9 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{12}H_{16}N)^+$ $(M + H)^+$ 174.1277, found 174.1290. $[\alpha]_D^{20}$= −32.4 (*c* 0.33, $CHCl_3$) [for (2*S*,3*S*)-**2h** in 97% *ee*]. [lit. $[\alpha]_D^{20}$= +23.4 (*c* 1.2, $CHCl_3$) for (2*R*,3*R*)-**2h** in 91% *ee*].[3b]

Synthesis of *cis*-3-Methyl-2-phenylindoline (*cis*-2i). 3-Methyl-2-phenyl-1*H*-indole (**1i**, 750 mg, 3.62 mmol), Pd−C (133 mg), AcOH (13.4 mL) and $HClO_4$ (4 mL) were put together in the reaction vessel of a Parr hydrogenator. Then, the air was evacuated, and H_2 (8 atm of pressure) was introduced into the system. The suspension was stirred for 24 h at room temperature, and after this time, the reaction was stopped, filtering the mixture through diatomaceous earth. The crude was basified with a saturated solution of $NaHCO_3$ (150 mL), extracted with CH_2Cl_2 (3 × 30 mL), and dried, and the solvent was removed under reduced pressure, affording a reaction crude that was purified by flash chromatography (5−10% Et_2O/*n*-hexane) affording *cis*-**1i** as a colorless oil (265 mg, 35%). R_f (20% Et_2O/*n*-hexane) 0.48; IR (NaCl) ν 3370, 3030, 2966, 2925, 2869, 1609, 1484, 1454, 1398, 1358, 1324, 1089, 1027, 806, 740, 702 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.86 (d, $^3J_{HH}$= 7.2 Hz, 3H), 3.53−3.68 (m, 1H), 4.09 (br s, 1H), 5.03 (d, $^3J_{HH}$= 8.7 Hz, 1H), 6.57−6.87 (m, 2H), 6.98−7.17 (m, 2H), 7.21−7.42 (m, 5H).^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.9 (CH_3), 41.3

dx.doi.org/10.1021/jo301307q | J. Org. Chem. 2012, 77, 8049−8055

(CH), 67.4 (CH), 108.9 (CH), 119.0 (CH), 124.2 (CH), 127.3 (2CH), 127.4 (CH), 127.6 (CH), 128.3 (2CH), 133.9 (C), 140.9 (C), 150.6 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{16}N)^+$ (M + H)$^+$ 210.1277, found 210.1265. $[\alpha]_D^{20}$= +176.4 (c 0.5, CH_2Cl_2) [for (2*R*,3*S*)-**2i** in 96% *ee*].

General Procedure for the Synthesis of Racemic Carbamates *trans*-4a and *cis*-4a−i. To a solution of racemic *trans*-**2a** or *cis*-**2a**-**i** (0.25 mmol) in dry CH_2Cl_2 (0.9 mL) were successively added pyridine (19 μL, 0.27 mmol) and allyl chloroformate (29 μL, 0.27 mmol). The reaction was stirred at room temperature for 3 h, and after this time, the solvent was removed by distillation under reduced pressure. The crude was purified by flash chromatography (EtOAc/*n*-hexane mixtures) affording the corresponding carbamates *trans*-**4a** and *cis*-**4a**-**h** as colorless oils and *cis*-**4i** as a white solid (72−95%). *trans*-**4a** (55 mg, 95% yield): R_f (5% EtOAc/*n*-hexane) 0.16; IR (NaCl) ν 3047, 2979, 2877, 1705, 1607, 1483, 1280, 1149, 1068, 1021 cm^{-1}; ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$, 50 °C) δ 1.14 (d, $^3J_{HH}$= 7.0 Hz, 3H), 1.20 (d, $^3J_{HH}$= 6.3 Hz, 3H), 2.81−2.92 (m, 1H), 4.86−4.52 (m, 2H), 5.25 (d, $^3J_{HH}$= 10.5 Hz, 1H), 5.33 (dd, $^3J_{HH}$= 17.2 Hz, $^2J_{HH}$= 1.0 Hz, 1H), 5.92−6.07 (m, 1H), 6.99 (t, $^3J_{HH}$= 7.4 Hz, 1H), 7.18 (t, $^3J_{HH}$= 7.7 Hz, 1H), 7.23 (d, $^3J_{HH}$= 7.3 Hz, 3H), 7.60 (br s, 1H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$, 50 °C) δ 21.5 (CH_3), 22.8 (CH_3), 43.7 (CH), 64.5 (CH), 66.9 (CH_2), 116.0 (CH), 119.1 (CH_2), 124.4 (CH), 126.0 (CH), 128.9 (CH), 134.2 (CH), 137.2 (C), 141.3 (C), 153.9 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{14}H_{17}NNaO_2)^+$ (M + Na)$^+$ 254.1151, found 254.1149. *cis*-**4a** (45 mg, 78% yield): R_f (10% EtOAc/*n*-hexane) 0.40; IR (NaCl) ν 3047, 2979, 2940, 2875, 1707, 1603, 1483, 1402, 1277, 1149, 1068, 1024, 932, 752 cm^{-1}; ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$, 100 °C) δ 1.13 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.32 (d, $^3J_{HH}$= 7.1 Hz, 3H), 3.59 (q, $^3J_{HH}$= 7.4 Hz, 1H), 4.57−4.64 (m, 1H), 4.76 (d, $^3J_{HH}$= 5.4 Hz, 2H), 5.30 (d, $^3J_{HH}$= 10.5 Hz, 1H), 5.42 (d, $^3J_{HH}$= 17.3 Hz, 1H), 6.08 (ddt, $^3J_{HH}$= 16.2, 10.5, 5.4 Hz, 1H), 7.03 (t, $^3J_{HH}$= 7.4 Hz, 1H), 7.18−7.22 (m, 2H), 7.64 (d, $^3J_{HH}$= 7.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$, 100 °C) δ 12.2 (CH_3), 14.0 (CH_3), 37.7 (CH), 59.9 (CH), 65.7 (CH_2), 115.0 (CH), 117.9 (CH_2), 123.1 (CH), 123.7 (CH), 127.6 (CH), 133.5 (CH), 135.8 (C), 141.0 (C), 152.4 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{14}H_{17}NNaO_2)^+$ (M + Na)$^+$ 254.1151, found 254.1146. $[\alpha]_D^{20}$= −42.6 (c 1, CH_2Cl_2) [for (2*R*,3*R*)-**4a** in 98% *ee*]. *cis*-**4b** (47 mg, 77% yield): R_f (20% Et_2O/*n*-hexane) 0.48; IR (NaCl) ν 2977, 2940, 2872, 1707, 1490, 1397, 1275, 1141, 1071, 818, 760 cm^{-1}; ^{1}H NMR (400.13 MHz, CD_3CN, 70 °C) δ 1.13 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.32 (d, $^3J_{HH}$= 7.1 Hz, 3H), 2.33 (s, 3H), 3.47−3.60 (m, 1H), 4.53−4.65 (m, 1H), 4.74 (d, $^3J_{HH}$= 4.8 Hz, 2H), 5.28 (d, $^3J_{HH}$= 10.5 Hz, 1H), 5.41 (d, $^3J_{HH}$= 17.3 Hz, 1H), 6.01−6.14 (m, 1H), 6.96−7.04 (m, 2H), 7.55 (d, $^3J_{HH}$= 7.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3CN, 70 °C) δ 12.7 (CH_3), 14.6 (CH_3), 21.4 (CH_3), 39.1 (CH), 61.5 (CH), 66.9 (CH_2), 116.1 (CH), 118.2 (CH_2), 125.5 (CH), 129.0 (CH), 133.8 (C), 134.8 (CH), 137.3 (C), 140.2 (C), 153.9 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{19}NNaO_2)^+$ (M + Na)$^+$ 268.1308, found 268.1314. $[\alpha]_D^{20}$= −39.2 (c 1, CH_2Cl_2) [for (2*R*,3*R*)-**4b** in 97% *ee*]. *cis*-**4c** (48 mg, 73% yield): R_f (10% EtOAc/*n*-hexane) 0.26; IR (NaCl) ν 3052, 2985, 1692, 1490, 1401, 1260, 1068, 735 cm^{-1}; ^{1}H NMR (400.13 MHz, CD_3CN, 70 °C) δ 1.08 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.26 (d, $^3J_{HH}$= 7.1 Hz, 3H), 3.43−3.56 (m, 1H), 3.74 (s, 3H), 4.48−4.57 (m, 1H), 4.68 (d, $^3J_{HH}$= 5.2 Hz, 2H), 5.22 (d, $^3J_{HH}$= 10.4 Hz, 1H), 5.34 (d, $^3J_{HH}$= 17.2 Hz, 1H), 5.94−6.08 (m, 1H), 6.70 (d, $^3J_{HH}$= 8.4 Hz, 1H), 6.74 (s, 1H), 7.51 (d, $^3J_{HH}$= 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3CN, 70 °C) δ 12.6 (CH_3), 14.6 (CH_3), 39.3 (CH), 56.8 (CH), 61.5 (CH_3), 66.8 (CH_2), 111.6 (CH), 113.4 (CH), 116.9 (CH), 118.2 (CH_2), 134.8 (CH), 136.1 (C), 138.8 (C), 153.8 (C), 157.8 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{19}NNaO_3)^+$ (M + Na)$^+$ 284.1257, found 284.1251. $[\alpha]_D^{20}$= −19.1 (c 1, CH_2Cl_2) [for (2*R*,3*R*)-**4c** in 97% *ee*]. *cis*-**4d** (45 mg, 72% yield): R_f (10% EtOAc/*n*-hexane) 0.4; IR (NaCl) ν 3374, 3036, 2968, 2929, 2871, 1611, 1487, 1440, 1381, 1276, 1245, 1224, 1186, 1131, 918, 865, 808 cm^{-1}; ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$, 75 °C) δ 1.12 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.30 (d, $^3J_{HH}$= 7.1 Hz, 3H), 3.50−3.68 (m, 1H), 4.57−4.67 (m, 1H), 4.74 (d, $^3J_{HH}$= 4.1 Hz, 2H), 5.30 (d, $^3J_{HH}$= 10.4 Hz, 1H), 5.41 (d, $^3J_{HH}$= 17.3 Hz, 1H), 6.06 (ddt, $^3J_{HH}$= 16.0, 10.5, 5.4 Hz, 1H), 6.95−7.03 (m, 1H), 7.04−7.10 (m, 1H), 7.54−7.66 (m, 1H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$, 75 °C) δ 12.1 (CH_3), 14.2 (CH_3), 38.0 (CH), 60.4 (CH), 66.0 (CH_2), 111.5 (d, $^2J_{CF}$= 24.2 Hz, CH), 113.8 (d, $^2J_{CF}$= 23.1 Hz, CH), 115.9 (d, $^3J_{CF}$= 8.3 Hz CH), 118.2 (CH_2), 133.6 (CH), 137.4 (C), 138.5 (d, $^3J_{CF}$= 7.9 Hz, C), 152.4 (C), 159.2 (d, $^2J_{CF}$= 238.7 Hz, C); HRMS (ESI$^+$, m/z) calcd for $(C_{14}H_{16}FNNaO_2)^+$ (M + Na)$^+$ 272.1057, found 272.1051. $[\alpha]_D^{20}$= −38.8 (c 1, CH_2Cl_2) [for (2*R*,3*R*)-**4d** in 99% *ee*]. *cis*-**4e** (48 mg, 78% yield): R_f (10% EtOAc/*n*-hexane) 0.33; IR (NaCl) ν 3047, 3017, 2970, 2934, 2874, 1713, 1597, 1464, 1390, 1338, 1296, 1261, 1064, 1028, 996, 931, 763 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.09 (d, $^3J_{HH}$= 6.5 Hz, 3H), 1.24 (d, $^3J_{HH}$= 7.1 Hz, 3H), 2.29 (s, 3H), 3.55−3.65 (m, 1H), 4.70−4.82 (m, 3H), 5.24−5.44 (m, 2H), 5.95−6.08 (m, 1H), 6.95−7.02 (m, 2H), 7.03−7.10 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.1 (CH_3), 14.6 (CH_3), 20.1 (CH_3), 39.1 (CH), 63.0 (CH), 66.3 (CH_2), 117.9 (CH_2), 120.5 (CH), 124.8 (CH), 128.1 (C), 130.0 (CH), 132.9 (CH), 138.2 (C), 139.9 (C), 153.8 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{20}NO_2)^+$ (M + H)$^+$ 246.1489, found 246.1485. *cis*-**4f** (54 mg, 88% yield): R_f (10% Et_2O/*n*-hexane) 0.15; IR (NaCl) ν 3081, 3048, 2963, 2936, 2877, 1707, 1649, 1603, 1484, 1462, 1401, 1325, 1279, 1149, 1074, 1454, 933, 752 cm^{-1}; ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$, 75 °C) δ 1.04−1.17 (m, 6H), 1.51−1.67 (m, 1H), 1.92−2.13 (m, 1H), 3.30−3.41 (m, 1H), 4.55−4.68 (m, 1H), 4.70−4.81 (m, 2H), 5.30 (d, $^3J_{HH}$= 10.4 Hz, 1H), 5.42 (d, $^3J_{HH}$= 17.2 Hz, 1H), 5.99−6.15 (m, 1H), 7.02 (t, $^3J_{HH}$= 7.4 Hz, 1H), 7.30−7.14 (m, 2H), 7.65 (d, $^3J_{HH}$= 7.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$, 75 °C) δ 13.1 (CH_3), 13.6 (CH_3), 20.0 (CH_2), 45.5 (CH), 59.3 (CH), 65.9 (CH_2), 115.2 (CH), 118.1 (CH_2), 123.2 (CH), 124.0 (CH), 127.8 (CH), 133.7 (CH), 134.8 (C), 141.3 (C), 152.4 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{19}NNaO_2)^+$ (M + Na)$^+$ 268.1308, found 268.1301. $[\alpha]_D^{20}$= −37.0 (c 0.1, CH_2Cl_2) [for (2*R*,3*R*)-**4f** in >99% *ee*]. *cis*-**4g** (48 mg, 79% yield): R_f (20% EtOAc/*n*-hexane) 0.48; IR (NaCl) ν 3082, 3049, 2963, 2877, 1707, 1649, 1603, 1484, 1401, 1279, 1149, 1074, 1054, 933, 752, 709 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.87 (t, $^3J_{HH}$= 7.5 Hz, 3H), 1.38 (d, $^3J_{HH}$= 7.2 Hz, 3H), 1.44−1.59 (m, 1H), 1.70−1.84 (m, 1H), 3.56−3.66 (m, 1H), 4.51−4.58 (m, 1H), 4.77 (d, $^3J_{HH}$= 5.6 Hz, 2H), 5.28 (dd, $^3J_{HH}$= 10.4 Hz; $^4J_{HH}$= 1.2 Hz, 1H), 5.40 (dd, $^3J_{HH}$= 17.2 Hz; $^4J_{HH}$= 1.4 Hz, 1H), 5.98−6.11 (m, 1H), 7.00−7.29 (m, 3H), 7.69 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.5 (CH_3), 11.8 (CH_3), 22.4 (CH_2), 38.3 (CH), 64.9 (CH), 66.1 (CH_2), 115.7 (CH), 117.9 (CH_2), 122.6 (CH), 123.1 (CH), 127.4 (CH), 132.8 (CH), 136.5 (C), 141.7 (C), 153.3 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{19}NNaO_2)^+$ (M + Na)$^+$ 268.1308, found 268.1318. $[\alpha]_D^{20}$= −38.4 (c 0.5, CH_2Cl_2) [for (2*R*,3*R*)-**4g** in >99% *ee*]. *cis*-**4h** (60 mg, 94% yield): R_f (10% EtOAc/*n*-hexane) 0.35; IR (NaCl) ν 3356, 3049, 2932, 2859, 1707, 1604, 1480, 1402, 1323, 1276, 1254, 1141, 1089, 933, 754 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.09−1.41 (m, 3H), 1.52−1.70 (m, 2H), 1.74−1.97 (m, 1H), 2.28 (ad, $^3J_{HH}$= 14.2 Hz, 1H), 3.42−3.58 (m, 1H), 4.36−4.63 (m, 1H), 4.76 (d, $^3J_{HH}$= 5.2 Hz, 2H), 5.28 (d, $^3J_{HH}$= 10.4 Hz, 1H), 5.39 (d, $^3J_{HH}$= 17.2 Hz, 1H), 5.95−6.13 (m, 1H), 7.03 (t, $^3J_{HH}$= 7.4 Hz, 1H), 7.10−7.40 (m, 2H), 7.76 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (CH_2), 22.4 (CH_2), 24.1 (CH_2), 27.3 (CH_2), 39.5 (CH), 60.6 (CH), 66.0 (CH_2), 115.7 (CH), 117.9 (CH_2), 122.8 (CH), 122.9 (CH), 127.5 (CH), 132.9 (CH), 133.8 (C), 141.9 (C), 152.8 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{16}H_{19}NNaO_2)^+$ (M + Na)$^+$ 280.1308, found 280.1299. $[\alpha]_D^{20}$= −43.2 (c 1, CH_2Cl_2) [for (2*R*,3*R*)-**4h** in 98% *ee*]. *cis*-**4i** (60 mg, 82% yield): R_f (20% EtOAc/*n*-hexane) 0.51; mp 50−52 °C; IR (KBr) ν 3033, 2969, 2934, 2876, 1707, 1652, 1602, 1484, 1456, 1321, 1268, 1143, 1076, 1041, 933, 822, 739, 701 cm^{-1}; ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$, 75 °C) δ 0.90 (d, $^3J_{HH}$= 7.1 Hz, 3H), 3.86−3.99 (m, 1H), 4.43−4.66 (m, 2H), 4.98−5.22 (m, 2H), 5.58 (d, $^3J_{HH}$= 9.8 Hz, 1H), 5.70−5.90 (m, 1H), 7.02−7.12 (m, 3H), 7.21 (d, $^3J_{HH}$= 7.3 Hz, 1H), 7.25−7.34 (m, 4H), 7.82 (d, $^3J_{HH}$= 7.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$, 75 °C) δ 14.4 (CH_3), 39.1 (CH), 65.7 (CH_2), 67.6 (CH), 114.2 (CH), 117.3 (CH_2), 123.6 (CH), 124.2 (CH), 126.9 (CH), 127.8 (CH), 128.1 (CH), 128.6 (CH), 133.3 (CH), 135.5 (C), 139.6 (C), 143.0 (C), 152.6 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{19}H_{19}NNaO_2)^+$ (M + Na)$^+$ 316.1308, found 316.1323. $[\alpha]_D^{20}$= −115.0 (c 1, CH_2Cl_2) [for (2*S*,3*R*)-**4i** in >99% *ee*].

dx.doi.org/10.1021/jo301307q | J. Org. Chem. 2012, 77, 8049−8055

General Procedure for the Enzymatic Kinetic Resolution of Racemic Indolines *cis*-2a–i. A suspension containing the corresponding indoline **2a–i** (0.48 mmol), allyl 3-methoxyphenyl carbonate (**3b**, 252 mg, 1.21 mmol) and CAL-A (ratio 1:2 in weight amine/enzyme) in dry TBME (3.2 mL) was shaken at 30 °C and 250 rpm for the necessary time to achieve a good kinetic resolution (see Tables 2 and 4 in the article). The reaction was followed by HPLC analysis, and after this time, the enzyme was filtered off and the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods, experimental procedures, characterization data for new compounds and copies of ^{1}H, ^{13}C and DEPT NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vicgotfer@uniovi.es. Phone: +34 98 5103454. Fax: +34 98 5103448.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Novo Nordisk Co. for the generous gift of the CAL-B (Novozyme 435). Financial support of this work by the Spanish Ministerio de Ciencia e Innovación (MICINN) through the CTQ-2007-61126 and CTQ-2011-24237 projects is gratefully acknowledged. V.G.-F. thanks MICINN for a postdoctoral grant (Ramón y Cajal Program). M.L.-I. thanks FICYT for a predoctoral fellowship.

■ REFERENCES

(1) (a) Fattorusso, E.; Taglialatela-Scafati, O., Eds.; *Modern Alkaloids*; Wiley-VCH: Weinheim, Germany, 2008. (b) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975–3984. (c) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447–457.

(2) Marquis, K. L.; Sabb, A. L.; Sheree, F. L.; Brennan, J. A.; Piesla, M. J.; Comery, T. A.; Grauer, S. M.; Ashby, C. R., Jr.; Nguyen, H. Q.; Dawson, L. A.; Barret, J. E.; Stack, G.; Meltzer, H. Y.; Harrison, B. L.; Rosenzweig-Lipson, S. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 486–496.

(3) (a) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653–2655. (b) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909–8911. (c) Chen, M.-W.; Yu, C.-B.; Duan, Y.; Jiang, G.-F. *Chem. Sci.* **2011**, *2*, 803–806. (d) Duan, Y.; Chen, M.-W.; Ye, Z.-S.; Wang, D.-S.; Chen, Q.-A.; Zhou, Y.-G. *Chem.—Eur. J.* **2011**, *17*, 7193–7197. (e) Duan, Y.; Chen, M.-W.; Chen, Q.-A.; Yu, C.-B.; Zhou, Y.-G. *Org. Biomol. Chem.* **2012**, *10*, 1235–1238. (f) Yu, Z.; Jin, W.; Jiang, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 6060–6072.

(4) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661–10664.

(5) (a) Arp, O. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264–14265. (b) Hou, X. L.; Zheng, B. H. *Org. Lett.* **2009**, *11*, 1789–1791.

(6) Viswanathan, R.; Smith, C. R.; Prabhakaran, E. N.; Johnston, J. N. *J. Org. Chem.* **2008**, *73*, 3040–3046.

(7) (a) García-Ruano, J. L.; Alemán, J.; Catalán, S.; Marcos, V.; Parra, A.; del Pozo, C.; Fustero, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7941–7944. (b) García-Ruano, J. L.; Parra, A.; Marcos, V.; del Pozo, C.; Catalán, S.; Monteagudo, S.; Fustero, S.; Poveda, A. *J. Am. Chem. Soc.* **2009**, *131*, 9432–9441.

(8) Kang, K. H.; Do, J.; Park, Y. S. *J. Org. Chem.* **2012**, *77*, 808–812.

(9) Katayev, D.; Nakanishi, M.; Bürgi, T.; Kündig, E. T. *Chem. Sci.* **2012**, *3*, 1422–1425.

(10) Busto, E.; Gotor-Fernández, V.; Gotor, V. *Chem. Rev.* **2011**, *111*, 3998–4035.

(11) Gotor-Fernández, V.; Fernández-Torres, P.; Gotor, V. *Tetrahedron: Asymmetry* **2006**, *17*, 2558–2564.

(12) (a) Gribble, A. W.; Hoffman, J. H. *Synthesis* **1977**, 859–860. (b) Yamada, F.; Kawanishi, A.; Tomita, A.; Somei, M. *ARKIVOC* **2003**, *viii*, 102–111.

(13) Kulkarni, A.; Zhou, W.; Török, B. *Org. Lett.* **2011**, *13*, 5124–5127.

(14) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404–4414.

(15) Alatorre-Santamaría, S.; Rodríguez-Mata, M.; Gotor-Fernández, V.; de Mattos, M. C.; Sayago, F.; Jiménez, A. I.; Cativiela, C.; Gotor, V. *Tetrahedron: Asymmetry* **2008**, *19*, 1714–1719.

(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) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *102*, 7294–7299.

(18) Takemoto, M.; Iwakiri, Y.; Tanaka, K. *Heterocycles* **2007**, *72*, 373.

(19) Tursky, M.; Lorentz-Petersen, L .L.; Olsen, L. B.; Madesen, R. *Org. Biomol. Chem.* **2010**, *8*, 5576–5583.

(20) Jin, Z.; Guo, S.-X.; Qiu, L.-L.; Wu, G.-P.; Fang, J. X. *Appl. Organomet. Chem.* **2011**, *25*, 502–507.

(21) Banwell, G. M.; Kelly, D. B.; Okanya, J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497–2500.

(22) General procedure for the deprotection of enantiopure carbamates (*R*,*R*)-**4f**,**g**. To a solution of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol) and 1,3-dimethylbarbituric acid (43 mg, 0.27 mmol) in dry CH_2Cl_2 (1.3 mL) was added the corresponding enantiopure carbamate (*R*,*R*)-**4f**,**g** (25 mg, 0.10 mmol) under a nitrogen atmosphere. The mixture was stirred for 4 h at 35 °C; after this time the reaction was diluted with CH_2Cl_2 (10 mL), and the organic layer was washed with H_2O (10 mL). The organic layer was dried with Na_2SO_4 and filtered, and the solvent was removed by distillation under reduced pressure affording a reaction crude that was purified by flash chromatography (10% Et_2O/*n*-hexane), yielding (*R*,*R*)-**2f** (15 mg, 92%) and (*R*,*R*)-**2g** (5 mg, 31%), respectively.