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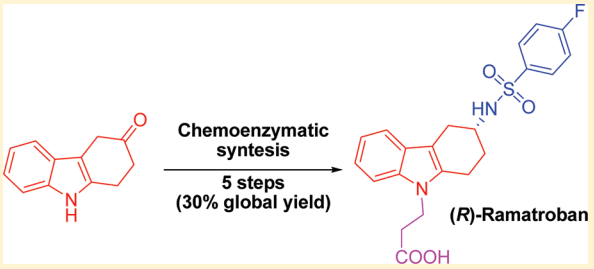
Asymmetric Chemoenzymatic Synthesis of Ramatroban Using Lipases and Oxidoreductases

Eduardo Busto, Vicente Gotor-Fernández, and Vicente Gotor*

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

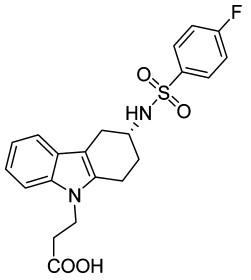
Supporting Information

ABSTRACT: A chemoenzymatic asymmetric route for the preparation of enantiopure (*R*)-ramatroban has been developed for the first time. The action of lipases and oxidoreductases has been independently studied, and both were found as excellent biocatalysts for the production of adequate chiral intermediates under very mild reaction conditions. CAL-B efficiently catalyzed the resolution of (±)-2,3,4,9-tetrahydro-1*H*-carbazol-3-ol that was acylated with high stereocontrol. On the other hand, ADH-A mediated bioreduction of 4,9-dihydro-1*H*-carbazol-3(2*H*)-one provided an alternative access to the same enantiopure alcohol previously obtained through lipase-catalyzed resolution, a useful synthetic building block in the synthesis of ramatroban. Inversion of the absolute configuration of (*S*)-2,3,4,9-tetrahydro-1*H*-carbazol-3-ol has been identified as a key point in the synthetic route, optimizing this process to avoid racemization of the azide intermediate, finally yielding (*R*)-ramatroban in enantiopure form by the formation of the corresponding amine and the convenient functionalization of both exocyclic and indole nitrogen atoms.



The necessity to produce enantioenriched compounds has been established as a highly demanded goal for the industrial sector, especially in pharmaceutical and agrochemical applications because of the different properties of drug enantiomers.[1] In this context, biocatalysis has emerged in the last years as an excellent tool for the production of organic compounds in a stereoselective fashion.[2] Biotransformations offer some clear advantages in comparison with traditional chemical processes, as they generally occur under environmentally friendly reaction conditions,[3] avoiding the use of hazardous organic reagents or extreme reaction conditions (i.e., pressure, pH, temperature, etc.), which usually lead to unwanted side reactions.[4] On the basis of these advantages, many biocatalytic processes have been adopted by the industry for the preparation of valuable goods such as cosmetics, agrochemicals, or food additives.[5] In particular, lipases and oxidoreductases have shown extraordinary properties in the preparation of a range of optically active alcohols and amines, which are interesting intermediates in the preparation of pharmaceuticals.[6]

Herein, the development of asymmetric chemoenzymatic routes for the total synthesis of ramatroban (**1**, Figure 1) has been exhaustively analyzed. Ramatroban is a pharmacologically active compound with 1-indolepropanoic acid structure,[7] which is commercialized in Japan under the trade name Baynas for the treatment of allergic rhinitis and asthma. Additionally, **1** shows potential applications for the treatment of coronary artery disease.[8] This drug acts as a thromboxane A_2 (TxA_2) antagonist and prostaglandin D_2-induced eosinophil migration inhibitor improving nasal obstruction symptoms by lowering the levels of lipid mediators such as thromboxane A_2 and leukotriene in the respiratory system.[9] Its activity mainly resides on the (*R*)-enantiomer, which is from 10 to 100 times more active than its counterpart.[10] This fact allows the administration of lower doses, minimizing the side effects and unspecific toxicities derived from the administration of the less active (*S*)-enantiomer.



(*R*)-Ramatroban (**1**)

Figure 1. Structure of ramatroban.

Until now, different chemical transformations have been used for the production of (*R*)-ramatroban such as the use of chiral auxiliaries,[10] resolution with chiral acids,[11] or more recently, the asymmetric catalytic Fischer indolization employing chiral phosphoric acids as ligands.[12] In this manuscript, an efficient chemoenzymatic asymmetric synthesis of ramatroban is reported for the first time, enzymatic sources such as lipases and oxidoreductases being used to introduce chirality in the 1-

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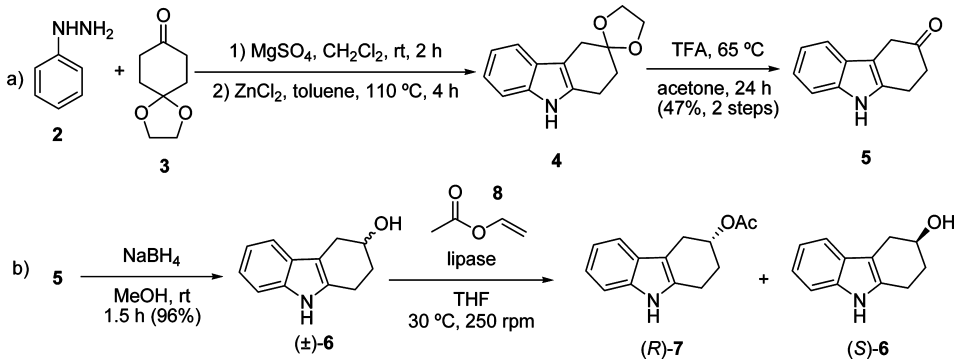
Scheme 1[a]



[a](a) Chemical synthesis of the ketone **5**. (b) Preparation of racemic alcohol **6** and its lipase-catalyzed acetylation using vinyl acetate in THF.

indolepropanoic acid moiety. Optically active intermediates achieved in this manner will be later conveniently modified achieving the straightforward synthesis of (*R*)-ramatroban in good overall yield and excellent optical purity.

In this manner, we have initially focused our attention on the preparation of adequate precursors for the total synthesis of the target compound ramatroban. With this idea in mind, commercially available phenyl hydrazine (**2**) and 1,4-cyclohexanone monoethylene ketal (**3**) were coupled in the presence of magnesium sulfate in dichloromethane at rt. Subsequent reaction with $ZnCl_2$ in refluxing toluene using a Dean–Stark apparatus led to the corresponding ketal **4**, which was next deprotected employing trifluoroacetic acid (TFA) in refluxing acetone,[13] obtaining the ketone **5** in 47% isolated yield after two steps (Scheme 1a).

By reducing the carbonyl group of ketone **5** with sodium borohydride in methanol racemic alcohol **6** was formed, which is a suitable intermediate for the introduction of chirality in the tetrahydrocarbazole moiety by means of enzymatic acylation processes (Scheme 1b). The enzymatic acetylation of (±)-**6** was performed using different enzymatic sources such as *Pseudomonas cepacia* lipase (PSL-C I, currently known as *Burkholderia cepacia* lipase), *Candida antarctica* lipase type A (CAL-A), and *Candida antarctica* type B (CAL-B), 3 equiv of vinyl acetate as acyl donor, and THF as solvent at 30 °C and 250 rpm (Table 1). PSL-C I acted with a high reaction rate but

Table 1. Kinetic Resolution of (±)-6 with Different Lipases (Ratio 1:1 Enzyme/Substrate in Weight) Using 3 equiv of Vinyl Acetate in THF (0.1 M) at 30 °C and 250 rpm

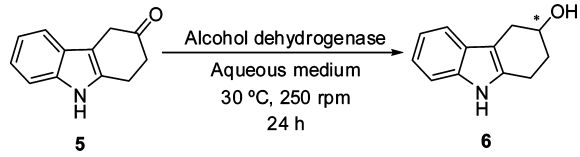
entry	enzyme	time (h)	ee_p (%)[a]	ee_s (%)[a]	*c* (%)[b]	*E*[c]
1	PSL-C I	8	75	>99	57	37
2	CAL-A	5	>99	5	5	>200
3	CAL-B	8	99 (43)	>99 (44)	50	>200

[a]Determined by HPLC. Isolated yields in parentheses. [b]$c = ee_s/(ee_s + ee_p)$. [c]$E = \ln[(1 - c)(1 - ee_p)]/\ln[(1 - c)(1 + ee_p)]$.[14]

low enantioselectivity (*E* = 37, Table 1, entry 1), even when the conversion value was below 50% (data not shown). On the other hand, CAL-A displayed excellent enantioselectivities, although very low conversions were attained (Table 1, entry 2). Satisfyingly, CAL-B was found to be an ideal biocatalyst reaching 50% conversion in a short span (8 h) and allowing the recovery of both substrate and product in enantiopure form and with good isolated yields for a classical kinetic resolution (Table 1, entry 3).

As an alternative to lipase-mediated acylation of racemic alcohol **6**, the asymmetric bioreduction of the ketone **5** was explored using other classes of enzymes, such as alcohol dehydrogenases (ADHs) in aqueous medium.[15] This approach offers clear advantages since the reduction of prochiral ketones enables 100% yield of the enantiopure product overcoming the maximum 50% yield of enantiomerically pure product obtained in kinetic resolutions. For that purpose, different ADHs were tested in a mg-scale to find optimal conditions for the bioreduction of the ketone **5** (Table 2). From the four ADHs

Table 2. Bioreduction of Ketone 5 in Aqueous Systems at 30 °C and 250 rpm



entry	ADH	*c* (%)[a]	ee_p (%)[b]	alcohol configuration
1	LK	37	92	*R*
2	Baker's yeast	63	16	*R*
3	CP	<3	>99	*S*
4	A	>97	>99	*S*
5[c]	A	>97	>99 (93)	*S*

[a]Determined by ^{1}H NMR from the reaction crude. [b]Determined by HPLC. Isolated yield in parentheses. [c]Scaled up to 200 mg of substrate.

tested, ADH-A from *Rhodoccocus ruber*, *Candida parapsilosis* (ADH-CP), *Lactobacillus kefir* (ADH-LK), and whole cells of Baker's yeast, the (*R*)-stereopreference was observed for ADH-LK and Baker's yeast, obtaining (*R*)-**6** with high enantiomeric excess (92% *ee*) and low conversion (37%) for ADH-LK (Table 2, entry 1), while moderate conversion (63%) and low enantiomeric excess (16% *ee*) were observed with Baker's yeast (Table 2, entry 2). On the other hand ADH-CP and ADH-A clearly displayed (*S*)-selectivity (Table 2, entries 3 and 4), obtaining for both enzymes (*S*)-**6** in enantiopure form, with ADH-A giving the best result since complete disappearance of the starting material was observed after 24 h (Table 2, entry 4). The synthetic application of the bioreduction with ADH-A was demonstrated when the process was scaled up to 200 mg of ketone, giving (*S*)-**6** in 93% isolated yield and enantiopure form after a simple purification step by liquid–liquid extraction (Table 2, entry 5).

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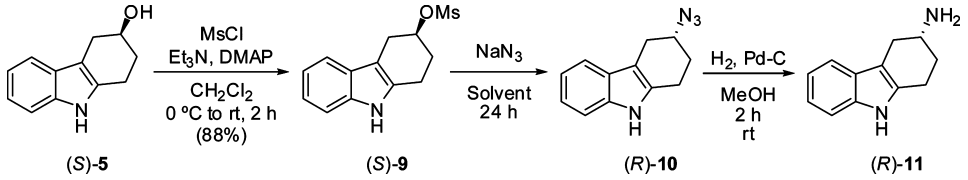
Scheme 2. Proposed Chemical Route Towards the Enantiopure Amine (*R*)-11



Because the more active isomer of ramatroban possesses the (*R*)-configuration, it was necessary to perform a stereoinversion of the chiral center of the so-obtained alcohol (*S*)-**6** to synthesize the amine (*R*)-**11**, an optimal building block for the total synthesis of ramatroban. Thus, we designed a three step route (Scheme 2), where first the alcohol was activated, forming the mesylate (*S*)-**9** in good yield and without racemization. Then, we tried to perform the S_N2 inversion using sodium azide in DMF at 70 °C as nucleophile. As previously observed by Bäckvall in the synthesis of neonicotinoide,[16] appreciable racemization in the stereoinversion was observed because of the competing S_N1 pathway (Table 3, entry 1). For that reason, the reaction temperature

Table 3. Optimization of the Mesylate 9 S_N2 Substitution with Different Solvents and Temperatures after 24 h

entry	solvent	*t* (°C)	*c* (%)[a]	*ee* (%)[b]
1	DMF	70	>97	87
2	DMF	35	55	92
3	THF	63	<3	n.d.[c]
4	DMSO	20	>97	93

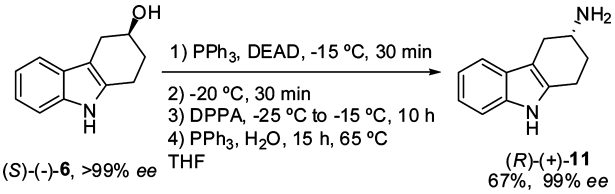
[a]Determined by ^{1}H NMR from the reaction crude. [b]Determined by HPLC. [c]Not determined.

was decreased to 35 °C, affording an improvement in the azide enantiomeric excess, although the reaction did not reach complete conversion at this temperature (Table 3, entry 2). With the aim of suppressing the S_N1 pathway, a less ionizating solvent such as THF was tested; unfortunately, the process did not proceed (Table 3, entry 3). The best results were finally obtained with DMSO as solvent, where the reaction occurred very fast even at 20 °C (Table 3, entry 4); however, (*R*)-**10** was isolated in only 93% *ee*, impeding the total synthesis of enantiopure (*R*)-ramatroban.

In view of this limitation, we decided to investigate alternative procedures for the preparation of enantiopure (*R*)-**11**, such as the combination of the Mitsunobu and Staudinger reactions, which is known to be a very useful approach for the one-pot transformation of optically active alcohols into optically active amines of opposite absolute configuration, without loss of the optical activity.[17] Thus, triphenylphosphine, diethyl azodicarboxylate (DEAD), and diphenylphosphoryl azide (DPPA) were reacted with (*S*)-**6** in dry THF at low temperature. The use of a safe source of azide such as (DPPA) as nucleophile in the Mitsunobu reaction removes the formation of hazardous hydrazoic acid in the course of the S_N2 reaction, while the careful control of the temperature,[18] avoids racemization in the inversion step. The subsequent Staudinger reduction of the azide **10** with PPh_3 led to the formation of the enantiopure (*R*)-amine in good isolated yield (Scheme 3).

Once we developed an efficient route for the preparation of the amine, the lipase-catalyzed enzymatic acetylation of (±)-**11** was explored as an alternative method to introduce chirality

Scheme 3. One-Pot Chemical Synthesis of the Enantiopure Amine (*R*)-11 from Alcohol (*S*)-6



into the tetrahydrocarbazole core. First of all, (±)-**11** was prepared using the same conditions previously used for the preparation of the enantiopure amine. The kinetic resolution was performed using CAL-B as catalyst, which is known to be a powerful catalyst for the resolution of amines,[19] and particularly for 1-heteroarylpropan-2-amines with a very similar structural motif to the amine (±)-**11**.[20] THF was selected as solvent because of the solubility of the amine, while methoxyacetic acid esters were used as acylating donors, since they lead to excellent results in terms of selectivity and reactivity in aminolysis reactions (Scheme 4).[21] Aliquots were regularly taken from the reaction flask, converting the nonreacted amine into the carbamate **14** in situ to provide a reliable method to measure the enantiomeric excess of the remaining amine (see the Experimental Section).

First of all, the CAL-B catalyzed acetylation (1:1 in weight of substrate with respect of the enzyme) of (±)-**11** using 5 equiv of ethyl methoxyacetate (**12a**) as acylating agent at 30 °C was studied. As occurred in the acylation of the alcohol, CAL-B stereoselectively acylated the (*R*)-enantiomer, recovering (*R*)-**13** in enantiopure form and the remaining (*S*)-amine in 32% *ee* after 3 h; however, longer reaction times did not improve the *ee* of the amine. Reactions with higher enzyme loading (ratio 1:2 substrate/enzyme in weight) or higher amounts of acyl donor (10 equiv) led to similar values, suggesting a possible inhibition effect of CAL-B by the reaction product. An increase in the reaction temperature to 60 °C led to the formation of enantiopure (*R*)-**13** and a slight improvement on the *ee* value of (*S*)-**11** (40%) after 1 h. Unfortunately, as occurred at 30 °C, the reaction did not proceed further with longer reaction times. The same inhibition effect was observed using isopropyl methoxyacetate (**12b**) as acyl donor; however, in this case, a lower *ee* value (14%) was detected for (*S*)-**11** after 3 h at 30 °C.

Although good selectivities were attained in the lipase-catalyzed resolution of (±)-**11** ($E > 200$), low conversions were reached in the formation of the (*R*)-amides, hampering the development of a straightforward route to (*R*)-ramatroban. Therefore, the previous route where amine (*R*)-**11** was obtained from alcohol (*S*)-**6** was selected as the optimal choice to continue the synthetic access to (*R*)-**1**. So finally, a three-step route from the enantiopure amine (*R*)-**11** was followed (Scheme 5). First, the sulfonylation of the amino group was carried with 4-fluorobenzenesulfonyl chloride (**15**) in the presence of triethylamine, obtaining (*R*)-**16** in 91% isolated

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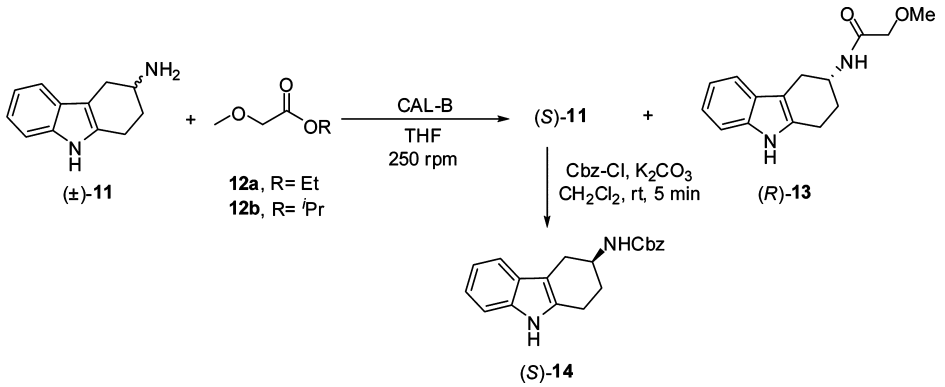
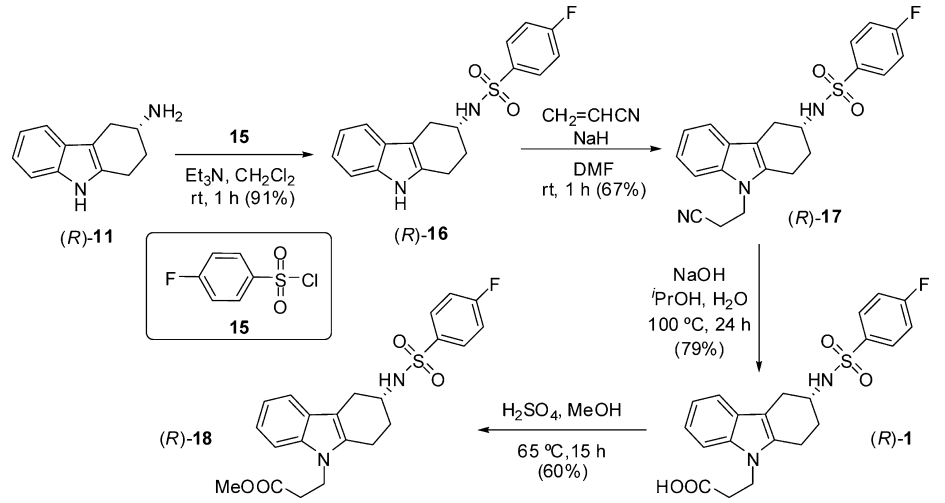
Scheme 4. CAL-B Catalyzed Kinetic Resolution of (±)-11 Using Methoxyacetic Acid Esters As Acyl Donors in THF at 250 rpm



Scheme 5. Total Synthesis of Enantiopure Ramatroban from Enantiopure Amine (*R*)-11 and Final Esterification for Enantiomeric Excess Measurement



yield. Next, the alkylation of the indole was performed with sodium hydride and acrylonitrile, affording (*R*)-**17** in 67% isolated yield after 1 h at room temperature. Finally, the hydrolysis of the nitrile function was conducted with sodium hydroxide in a refluxing mixture of H_2O−^{i}PrOH, isolating enantiopure (*R*)-ramatroban (**1**) in 79% isolated yield. The identity of (*R*)-**1** was confirmed with 2D-NMR experiments (see the Supporting Information for details).

To confirm that no racemization had occurred in any step of the total synthesis, racemic ramatroban was also prepared. Since we were not able to find suitable HPLC conditions for the separation of **1** enantiomers because of the presence of the free carboxylic acid, both racemic and enantiopure ramatroban were converted to the corresponding methyl ester **18**. HPLC analysis clearly demonstrates that no racemization occurred during the synthesis of ramatroban (see chromatograms in the Supporting Information).

In summary, a straightforward chemoenzymatic strategy has been developed for the production of enantiopure (*R*)-ramatroban, with chirality being introduced by the action of lipases and oxidoreductases. Both kinetic resolution of racemic 2,3,4,9-tetrahydro-1*H*-carbazol-3-ol with *Candida antarctica* lipase B (CAL-B) and the bioreduction of 4,9-dihydro-1*H*-carbazol-3(2*H*)-one with ADH-A from *Rhodococcus ruber* have provided an efficient access to enantiopure (*S*)-2,3,4,9-tetrahydro-1*H*-carbazol-3-ol. The inversion of the (*S*)-alcohol to yield enantiopure (*R*)-2,3,4,9-tetrahydro-1*H*-carbazol-3-amine has been optimized, avoiding racemization of the azide intermediate, identifying a consecutive one-pot Mitsunobu−Staudinger reaction as the ideal method for the complete inversion of the chiral center. Finally, the (*R*)-amine has been employed as an adequate starting material for the total synthesis of enantiopure (*R*)-ramatroban.

EXPERIMENTAL SECTION

Synthesis of 4,9-Dihydro-1*H*-carbazol-3(2*H*)-one (5). To a solution of phenyl hydrazine (**1**, 970 μL, 10 mmol) and 1,4-cyclohexanone monoethylene ketal (**2**, 1.54 g, 10 mmol) in dry CH_2Cl_2 (40 mL) was added $MgSO_4$ (6 g, 50 mmol), and the resulting suspension was stirred for 2 h at rt. After this time, the magnesium sulfate was filtered off, and the solvent evaporated under reduced pressure. The resulting brownish oil was dissolved in dry toluene (30 mL), and $ZnCl_2$ (1.24 g, 9.2 mmol) was added, and the mixture was heated at 110 °C with a Dean−Stark water separator for 4 h. Then, toluene was removed under reduced pressure, and aqueous NaOH 4 M (40 mL) was added to the crude. The suspension was extracted with EtOAc (3 × 40 mL), organic phases were combined and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The reaction crude containing ketal **4** was redissolved in acetone (40 mL), trifluoroacetic acid (TFA, 1.65 mL, 21.4 mmol) was added, and the solution stirred at 65 °C for 24 h. After this time, the solvent was evaporated under reduced pressure, and the crude purified by flash chromatography (100% CH_2Cl_2) affording 872 mg of **5** as a white solid (47%): R_f (100% CH_2Cl_2) 0.29; mp 154−156 °C (lit. 156 °C);[22] IR (KBr) ν 3399, 1708, 1438, 1250 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz) δ 2.73 (t, $^3J_{HH}$ = 7.0 Hz, 2H), 3.10 (t, $^3J_{HH}$ = 6.9 Hz, 2H), 3.51

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(s, 2H), 6.96−7.10 (m, 2H), 7.27−7.33 (m, 2H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 23.7 (CH_2), 37.6 (CH_2), 39.9 (CH_2), 107.2 (C), 112.1 (CH), 118.5 (CH), 120.2 (CH), 122.5 (CH), 128.7 (C), 133.7 (C), 138.8 (C), 213.6 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{12}H_{12}NO)^+$ (M + H)$^+$ 186.0913, found 186.0906.

Synthesis of (±)-2,3,4,9-Tetrahydro-1*H*-carbazol-3-ol (6). To a solution of 4,9-dihydro-1*H*-carbazol-3(2*H*)-one (**5**, 350 mg, 1.89 mmol) in anhydrous MeOH (7.0 mL) was added $NaBH_4$ (35 mg, 0.91 mmol) under a nitrogen atmosphere at 0 °C. The solution was stirred at rt for 1.5 h, and after this time, the reaction was quenched with H_2O (10 mL). Then MeOH was removed by distillation under reduced pressure, and the aqueous residue extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (1% MeOH/CH_2Cl_2) affording 341 mg of **6** as a white solid (96%): R_f (1% MeOH/CH_2Cl_2) 0.27; mp 155−157 °C (lit. 149−150 °C);[23] IR (KBr) ν 3401, 2929, 1725, 1468, 1366, 1251 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz) δ 1.87−2.12 (m, 2H), 2.56−2.64 (m, 1H), 2.73−2.91 (m, 2H), 2.91−3.07 (m, 1H), 4.09−4.17 (m, 1H), 6.92−7.04 (m, 2H), 7.23 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.34 (d, $^3J_{HH}$ = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 22.2 (CH_2), 31.4 (CH_2), 32.8 (CH_2), 69.1 (CH), 107.8 (C), 111.5 (CH), 118.4 (CH), 119.7 (CH), 121.8 (CH), 129.3 (C), 134.6 (C), 138.5 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{12}H_{13}NNaO)^+$ (M + Na)$^+$ 210.0889, found 210.0889; Analytical separation (HPLC) Chiralcel OJ-H *n*-hexane/2-propanol (80:20), 0.8 mL/min, 40 °C, t_R (*S*) = 23.1 min, t_R (*R*) = 27.2 min.

Synthesis of (±)-2,3,4,9-Tetrahydro-1*H*-carbazol-3-yl acetate (7). To a solution of racemic 2,3,4,9-tetrahydro-1*H*-carbazol-3-ol (**6**, 35 mg, 0.18 mmol) in CH_2Cl_2 (2 mL), triethylamine (75 μL, 0.54 mmol), DMAP (7 mg, 0.06 mmol), and acetic anhydride (23 μL, 0.25 mmol) were successively added under a nitrogen atmosphere. The reaction was stirred for 1.5 h at rt; after this time, the solvent was removed under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (100% CH_2Cl_2) affording 35 mg of racemic **7** as a white solid (85%): R_f (100% CH_2Cl_2) 0.34; mp 78−80 °C; IR (KBr) ν 3401, 2929, 1725, 1468, 1366, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 2.14 (s, 3H), 2.13−2.26 (m, 2H), 2.83−2.93 (m, 3H), 3.08−3.21 (m, 1H), 5.35−5.42 (m, 1H), 7.14−7.23 (m, 2H), 7.30 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 7.51 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 7.86 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.4 (CH_2), 21.5 (CH_2), 27.1 (CH_2), 27.8 (CH_3), 70.2 (CH), 106.9 (C), 110.7 (CH), 117.7 (CH), 119.3 (CH), 121.4 (CH), 132.7 (C), 136.3 (C), 171.0 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{14}H_{15}NNaO_2)^+$ (M + Na)$^+$ 252.0995, found 252.0993; Analytical separation (HPLC) Chiralpak IA *n*-hexane/2-propanol (80:20), 0.8 mL/min, 30 °C, t_R (*S*) = 6.9 min, t_R (*R*) = 16.4 min.

Enzymatic Kinetic Resolution of 2,3,4,9-Tetrahydro-1*H*-carbazol-3-ol (6). To a suspension of racemic alcohol **6** (420 mg, 2.21 mmol) and CAL-B (420 mg) in dry THF (22 mL), vinyl acetate (**8**, 609 μL, 6.61 mmol) was added under a nitrogen atmosphere. The reaction was shaken at 30 °C and 250 rpm, and regular aliquots were taken and analyzed by HPLC until around 50% was reached (8 h). The reaction was then stopped, and the enzyme filtered and washed with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated, and the crude of the reaction purified by flash chromatography on silica gel (0−1% MeOH/CH_2Cl_2), affording (*R*)-(+)-**7** [43% isolated yield and 99% *ee*, $[\alpha]_D^{20}$= +13.2 (*c* 1.8, MeOH)] and (*S*)-(−)-**6** [44% isolated yield and 99% *ee*, $[\alpha]_D^{20}$= −48.5 (*c* 0.65, MeOH)].

Bioreduction of 4,9-Dihydro-1*H*-carbazol-3(2*H*)-one (5) with ADH-LK. In an eppendorf tube containing ketone **5** (2.3 mg, 0.012 mmol) in TRIS-HCl 50 mM pH 7.5 buffer (450 μL), glucose-6-phosphate (20 μL), glucose 6-phosphate dehydrogenase (3 U, 10 μL), NADPH 10 mM solution in TRIS-HCl buffer (50 μL), and ADH-LK (3 U, 2 mg) were successively added. Reaction was shaken at 250 rpm and 30 °C for 24 h. Then, the mixture was extracted with EtOAc (2 × 500 μL) and dried over Na_2SO_4, and the reaction crude was analyzed by NMR (conversion) and HPLC (enantiomeric excess).

Bioreduction of 4,9-Dihydro-1*H*-carbazol-3(2*H*)-one (5) with Baker's Yeast. Baker's yeast (1.3 g) was added to a solution of glucose (165 mg) in H_2O (11 mL), and the resulting suspension was stirred for 15 min at 30 °C and 250 rpm. After this time, the corresponding ketone **5** (32 mg, 0.17 mmol) was added, and the suspension was stirred at 30 °C and 250 rpm. Then the reaction was centrifuged, and the supernatant extracted with EtOAc (3 × 20 mL). Organic phases were combined, dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The reaction crude was analyzed by NMR (conversion) and HPLC (enantiomeric excess).

Bioreduction of 4,9-Dihydro-1*H*-carbazol-3(2*H*)-one (5) with ADH-CP. In an eppendorf tube containing ketone **5** (2.3 mg, 0.012 mmol) in TRIS-HCl 50 mM pH 7.5 buffer (425 μL), isopropyl alcohol (25 μL), NADH 10 mM solution in TRIS-HCl buffer (50 μL) and ADH-CP (3U, 7.5 μL) were successively added. Reaction was shaken at 250 rpm and 30 °C for 24 h. Then, the mixture was extracted with EtOAc (2 × 500 μL) and dried over Na_2SO_4. The reaction crude was analyzed by NMR (conversion) and HPLC (enantiomeric excess).

Bioreduction of 4,9-Dihydro-1*H*-carbazol-3(2*H*)-one (5) with ADH-A. *Escherichia coli*/ADH-A cells (15 mg) were rehydrated in TRIS-HCl 50 mM pH 7.5 buffer (500 μL) inside an eppendorf tube. The mixture was shaken at 250 rpm for 30 min. Then, the ketone **5** (2.3 mg, 0.012 mmol), isopropyl alcohol (30 μL), and NADH 10 mM solution (60 μL) were added. The reaction was shaken at 250 rpm and 30 °C for 24 h. The reaction crude was analyzed by NMR (conversion) and HPLC (enantiomeric excess).

Scale up of Bioreduction of 4,9-Dihydro-1*H*-carbazol-3(2*H*)-one (5) with ADH-A. To a solution containing rehydrated *E. coli*/ADH-A cells (225 mg) in TRIS-HCl 50 mM pH 7.5 buffer (26 mL), isopropyl alcohol (1.7 mL), NADH (13 mg), and the ketone **5** (200 mg, 1.10 mmol) were successively added. The reaction was shaken until no starting material was detected by TLC analysis (24 h). Then, the mixture was extracted with EtOAc (3 × 50 mL), organic layers were combined, dried over Na_2SO_4, and filtered, and the solvent was removed under reduce pressure, affording 190 mg of (*S*)-**6** in as a white solid (93%): $[\alpha]_D^{20}$= −48.5 (*c* 0.65, MeOH)].

Synthesis of (*S*)-2,3,4,9-Tetrahydro-1*H*-carbazol-3-yl methanesulfonate (9). To a solution of the alcohol (*S*)-**6** (100 mg, 0.52 mmol) in CH_2Cl_2 (5 mL), Et_3N (149 μL, 1.04 mmol), DMAP (7 mg, 0.052 mmol), and methanesulfonyl chloride (84 μL, 1.04 mmol) were successively added under a nitrogen atmosphere. The reaction was stirred for 2 h at rt, and then the solvent evaporated under reduced pressure. The resulting crude was purified by flash chromatography (20% EtOAc/hexane), affording 120 mg of (*S*)-**9** as a white solid (88%): R_f (25% EtOAc/hexane) 0.18; mp 121−123 °C (dec.); IR (KBr) ν 3403, 2935, 1726, 1471, 1368, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 2.19−2.41 (m, 2H), 2.78−3.09 (m, 3H), 3.05 (s, 3H), 3.18−3.29 (m, 1H), 5.20−5.32 (m, 1H), 7.10−7.20 (m, 2H), 7.29 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 7.44 (d, $^3J_{HH}$ = 7.1 Hz, 1H), 7.82 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 20.4 (CH_2), 28.6 (CH_2), 29.3 (CH_2), 39.2 (CH), 106.1 (C), 111.1 (CH), 118.0 (CH), 119.9 (CH), 122.1 (CH), 127.6 (C), 132.6 (C), 136.7 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{13}H_{15}NNaO_3S)^+$ (M + Na)$^+$ 288.0665, found 288.0648; $[\alpha]_D^{20}$= −8.5 (*c* 1, MeOH) for >99% *ee*; Analytical separation (HPLC) Chiralpak OD *n*-hexane/2-propanol (80:20), 0.8 mL/min, 40 °C, t_R (*S*) = 21.7 min, t_R (*R*) = 25.5 min.

Synthesis of (*R*)-3-Azido-2,3,4,9-tetrahydro-1*H*-carbazole (10). To a solution of the mesylate (*S*)-**9** (26 mg, 0.10 mmol) in the corresponding solvent (1 mL) was added sodium azide (33 mg, 0.50 mmol). The suspension was stirred at the corresponding temperature (see Table 3) for 24 h. After this time, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL), the organic phases combined and dried over Na_2SO_4, and the solvent evaporated under reduced pressure. At this point, the conversion was measured by ^{1}H NMR of the enantiomeric excess calculated by HPLC from the reaction crude: R_f (15% EtOAc/hexane) 0.29; mp 138−140 °C; IR (KBr) ν 3400, 3252, 2922, 1468, 1327, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 2.07−2.32 (m, 2H), 2.71−2.95 (m, 3H), 3.11−3.23 (m, 1H), 3.99−4.09 (m, 1H), 7.13−7.33 (m, 3H), 7.51 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 7.72 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 21.1 (CH_2), 26.9 (CH_2), 28.1 (CH_2), 57.4 (CH), 107.0 (C), 110.6

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(CH), 117.8 (CH), 119.5 (CH), 121.6 (CH), 127.4 (C), 132.5 (C), 136.2 (C); HRMS (ESI$^-$, m/z) calcd for $(C_{12}H_{11}N_4)^-$ $(M - H)^-$ 211.0989, found 211.0947; Analytical separation (HPLC) Chiralpak OD *n*-hexane/2-propanol (80:20), 0.8 mL/min, 30 °C, t_R (*S*) = 15.9 min, t_R (*R*) = 18.9 min.

Synthesis of (*R*)-2,3,4,9-Tetrahydro-1*H*-carbazol-3-amine (11). A solution of PPh_3 (440 mg, 1.68 mmol) in dry THF (4.6 mL) was cooled to −15 °C under a nitrogen atmosphere. Diethylazodicarboxylate (DEAD, 134 μL, 0.84 mmol) was added to the reaction dropwise, and the reaction was stirred at −15 °C for 30 min. Then, the reaction was cooled to −20 °C, and the alcohol (*S*)-**6** (110 mg, 0.60 mmol) was added to the reaction mixture, which was stirred for additional 30 min. After this time, the reaction was cooled to −25 °C, and DPPA (196 μL, 0.90 mmol) added dropwise. The mixture was stirred between −25 °C and −15 °C until complete disappearance of the starting material (10 h). Next, additional PPh_3 (221 mg, 0.90 mmol) and H_2O (16 μL, 0.90 mmol) were added, and the reaction stirred at 65 °C for 15 h. The solvent was removed under reduced pressure, and the crude purified by flash chromatography (100% MeOH−3% NH_3/MeOH) affording 73 mg of (*R*)-**11** as a white solid (67%): R_f (1% NH_3/MeOH) 0.20; mp 174−176 °C (lit. 176−177).[24] IR (KBr) ν 3396, 2920, 1640, 1595, 1153 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz) δ 1.68−1.81 (m, 1H), 2.07−2.11 (m, 1H), 2.37−2.45 (m, 1H), 2.77−2.83 (m, 2H), 2.95−3.05 (m, 1H), 3.12−3.20 (m, 1H), 6.94−7.05 (m, 2H), 7.24 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.35 (d, $^3J_{HH}$ = 7.9 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 22.6 (CH_2), 31.3 (CH_2), 33.1 (CH_2), 49.3 (CH), 108.2 (C), 111.5 (CH), 118.1 (CH), 119.3 (CH), 121.5 (CH), 129.0 (C), 134.4 (C), 138.1 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{12}H_{15}N_2)^+$ $(M + H)^+$ 187.1230, found 187.1221; $[\alpha]_D^{20}$= +62.8 (*c* 2.0, MeOH) for 99% *ee*.

Synthesis of (±)-2-Methoxy-*N*-(2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)acetamide (13). To a solution of the racemic amine **11** (25 mg, 0.13 mmol) in dry CH_2Cl_2 (1 mL), Et_3N (22 μL, 0.16 mmol), and methoxyacetyl chloride (15 μL, 0.16 mmol) were successively added under a nitrogen atmosphere, and the solution stirred for 1 h. After this time, the solvent was removed under reduced pressure, and the crude purified under flash chromatography (100% EtOAc), affording 23 mg of the racemic amide **13** as a white solid (68%): R_f (100% EtOAc) 0.24; mp 168−170 °C; IR (KBr) ν 3384, 2948, 2840, 1647, 1423, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.96−2.17 (m, 2H), 2.63−2.71 (m, 1H), 2.82−2.92 (m, 2H), 3.10−3.17 (m, 1H), 3.41 (s, 3H), 3.93 (s, 2H), 4.43−4.54 (m, 1H), 6.69 (br s, 1H), 7.09−7.19 (m, 2H), 7.31 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 7.50 (d, $^3J_{HH}$ = 7.0 Hz, 1H), 8.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 21.1 (CH_2), 28.1 (CH_2), 28.7 (CH_2), 45.1 (CH_3), 59.5 (CH), 72.5 (CH_2), 107.7 (C), 111.0 (CH), 118.1 (CH), 119.7 (CH), 121.8 (CH), 128.0 (C), 133.2 (C), 136.6 (C), 169.6 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{15}H_{18}N_2NaO_2)^+$ $(M + Na)^+$ 281.1260, found 281.1265; Analytical separation (HPLC) Chiralpak IA *n*-hexane/2-propanol (80:20), 0.8 mL/min, 40 °C, t_R (*S*) = 9.4 min, t_R (*R*) = 18.7 min.

Synthesis of (±)-Benzyl 2,3,4,9-tetrahydro-1*H*-carbazol-3-ylcarbamate (14). To a solution of the racemic amine (**11**, 25 mg, 0.13 mmol) in dry CH_2Cl_2 (1 mL), Et_3N (22 μL, 0.16 mmol) and benzyl chloroformate (23 μL, 0.16 mmol) were successively added under a nitrogen atmosphere. The solution was stirred for 2 h at rt, then the solvent removed by distillation under reduced pressure, and the crude purified by flash chromatography (30% EtOAc/hexane), affording 28 mg of the carbamate **14** as a white solid (67%): R_f (30% EtOAc/hexane) 0.20; mp 157−159 °C; IR (KBr) ν 3357, 3307, 3051, 1666, 1545, 1453, 1265 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300.13 MHz) δ 1.71−1.84 (m, 1H), 1.99−2.07 (m, 1H), 2.51−2.72 (m, 1H), 2.75−2.85 (m, 2H), 2.91−2.98 (m, 1H), 3.72−3.91 (m, 1H), 5.06 (s, 2H), 6.89−7.01 (m, 2H), 7.22−7.46 (m, 7H), 10.60 (s, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) 22.3 (CH_2), 28.4 (CH_2), 30.0 (CH_2), 48.3 (CH), 66.0 (CH_2), 107.3 (C), 111.4 (CH), 117.9 (CH), 118.9 (CH), 121.1 (CH), 128.0 (C), 128.6 (2CH), 129.2 (3CH), 134.3 (C), 137.0 (C), 138.1 (C), 156.5 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{20}H_{20}N_2NaO_2)^+$ $(M + Na)^+$ 343.1417, found 343.1420; Analytical separation (HPLC) Chiralpak IA *n*-hexane/2-propanol (80:20), 0.8 mL/min, 40 °C, t_R (*S*) = 11.1 min, t_R (*R*) = 20.1 min.

Enzymatic Kinetic Resolution of 2,3,4,9-Tetrahydro-1*H*-carbazol-3-amine (11). To a suspension of racemic amine (**11**, 19 mg, 0.19 mmol) and CAL-B (19 mg) in dry THF (1.9 mL), the corresponding methoxyacetyl ester (0.50 mmol) was added under a nitrogen atmosphere. The reaction was shaken at the corresponding temperature and 250 rpm, and regular aliquots (15 μL) were regularly taken. The aliquots were dissolved in CH_2Cl_2 (0.5 mL), and K_2CO_3 (20 mg) and benzyl chloroformate (1 drop) were successively added. The suspension was shaken at rt for 5 min and dried over Na_2SO_4, and the solvent removed with a nitrogen flow. The crude was redissolved in hexane/2-propanol 90:10 (1 mL), filtered, and injected in the HPLC for *ee* measurement.

Synthesis of (*R*)-4-Fluoro-*N*-(2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)benzenesulfonamide (16). To a solution of (*R*)-**11** (73 mg, 0.40 mmol) in CH_2Cl_2 (4 mL), Et_3N (65 μL, 0.48 mmol) and 4-fluorobenzenesulfonyl chloride (**15**, 91 mg, 0.48 mmol) were successively added. The solution was stirred at rt for 1 h, and then the solvent removed by distillation at reduced pressure. The reaction crude was purified by flash chromatography (30% EtOAc/hexane), affording 126 mg of (*R*)-**16** as a white solid (91%): R_f (30% EtOAc/hexane) 0.15; mp 138−140 °C; IR (KBr) ν 3396, 3286, 2931, 1735, 1592, 1494, 1241, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.96−2.03 (m, 2H), 2.49−2.54 (m, 1H), 2.72−2.92 (m, 3H), 3.75−3.83 (m, 1H), 4.96 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 7.06−7.18 (m, 4H), 7.27 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 7.32 (d, $^3J_{HH}$ = 5.9 Hz, 1H), 7.79 (br s, 1H), 7.87−7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 20.2 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 49.5 (CH), 106.5 (C), 110.6 (CH), 116.3 (d, $^2J_{CF}$= 16.6 Hz, 2CH), 117.6 (CH), 119.5 (CH), 121.7 (CH), 127.3 (C), 129.7 (d, $^3J_{CF}$= 6.8 Hz, 2CH), 132.5 (C), 136.1 (C), 137.1 (C), 165.0 (d, $^1J_{CF}$= 191.0 Hz, C); HRMS (ESI$^-$, m/z) calcd for $(C_{18}H_{16}FN_2O_2S)^-$ $(M - H)^-$ 343.0922, found 343.0911; $[\alpha]_D^{20}$= +43.3 (*c* 0.25, $CHCl_3$) for 99% *ee* [lit. $[\alpha]_D^{20}$= −35.2 (*c* 0.25, $CHCl_3$) for (*S*)-**16** in 86% *ee*];[12] Analytical separation (HPLC) Chiralpak IC *n*-hexane/2-propanol (80:20), 0.8 mL/min, 20 °C, t_R (*S*) = 12.5 min, t_R (*R*) = 13.6 min.

Synthesis of (*R*)-*N*-[9-(2-Cyanoethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]-4-fluorobenzenesulfonamide (17). To a solution of (*R*)-**16** (58 mg, 0.17 mmol) in dry DMF (2 mL) was added dry NaH (4.5 mg, 0.19 mmol), and the solution was stirred for 5 min at rt. After this time, acrylonitrile (22 μL, 0.34 mmol) was added to the reaction vessel, and the reaction stirred until disappearance of the starting material (1 h). Then, the reaction was quenched with EtOAc (10 mL) and extracted with H_2O (3 × 10 mL). The organic phase was dried over Na_2SO_4, the solvent removed under reduced pressure, and the crude purified by flash chromatography (40% EtOAc/hexane) affording 45 mg of (*R*)-**17** as a colorless viscous oil (67%): R_f (40% EtOAc/hexane) 0.26; IR (NaCl) ν 3277, 2926, 2251, 1592, 1494, 1466, 1359, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.96−2.10 (m, 2H), 2.52−2.59 (m, 1H), 2.72−2.90 (m, 5H), 3.75−3.91 (m, 1H), 4.32 (t, $^3J_{HH}$ = 6.6 Hz, 2H), 5.10 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.09−7.22 (m, 5H), 7.33 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.86−7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.0 (CH_2), 19.4 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 39.1 (CH_2), 49.5 (CH), 107.6 (C), 108.8 (CH), 116.8 (d, $^2J_{CF}$= 21.9 Hz, 2CH), 117.8 (C), 118.6 (CH), 120.3 (CH), 122.3 (CH), 127.9 (C), 130.0 (d, $^3J_{CF}$= 9.1 Hz, 2CH), 133.6 (C), 136.3 (C), 137.6 (C), 165,4 (d, $^1J_{CF}$= 255.1 Hz, C); HRMS (ESI$^+$, m/z) calcd for $(C_{21}H_{21}FN_3O_2S)^+$ $(M + H)^+$ 398.1333, found 398.1314; $[\alpha]_D^{20}$= +38.0 (*c* 1.7, CH_2Cl_2) for 99% *ee*; Analytical separation (HPLC) Chiralcel OJ-H *n*-hexane/2-propanol (65:35), 0.8 mL/min, 40 °C, t_R (*S*) = 32.6 min, t_R (*R*) = 37.9 min.

Synthesis of (*R*)-3-[3-(4-Fluorophenylsulfonamido)-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl Propanoic Acid, Ramatroban (1). To a solution of (*R*)-**17** (40 mg, 0.10 mmol) in 2-propanol (0.50 mL) was added a 10% aqueous NaOH solution (1 mL), and the solution was stirred at 100 °C for 24 h. After this time, the solution was cooled, diluted with water (5 mL), and extracted with CH_2Cl_2 (2× 5 mL) to remove neutral impurities. Then, the aqueous phase was acidified with HCl 1 N (5 mL) and extracted with CH_2Cl_2 (5 × 5 mL). Organic layers were collected, dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure affording 33 mg of (*R*)-**1**

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(79%) as a white solid: R_f (1% AcOH/40% EtOAc/hexane) 0.23; mp 135−137 °C; IR (KBr) ν 3276, 2926, 1712, 1591, 1494, 1467, 1153 cm^{-1}; ^1H NMR (CD_3OD, 300.13 MHz) δ 1.87−2.09 (m, $2H_{14}$), 2.47−2.54 (m, $1H_{11}$), 2.67 (t, $^3J_{HH}$ = 6.7 Hz, $2H_2$), 2.75−2.91 (m, $2H_{13}$+$1H_{11}$), 3.61−3.71 (m, $1H_{12}$), 4.30 (t, $^3J_{HH}$ = 6.7 Hz, $2H_3$), 6.96 (t, $^3J_{HH}$ = 6.9 Hz, $1H_7$), 7.08 (t, $^3J_{HH}$ = 7.1 Hz, $1H_6$), 7.21−7.31 (m, $2H_{18}$+H_5+H_7), 7.93−7.98 (m, $2H_{17}$); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 21.2 (C_{14}), 29.7 (C_{11}), 31.1 (C_{13}), 35.8 (C_2), 40.0 (C_3), 51.5 (C_{12}), 108.0 (C_{10}), 110.2 (C_5), 117.4 (d, $^2J_{CF}$= 23.3 Hz, $2C_{18}$), 118.7 (C_8), 120.2 (C_7), 122.4 (C_6), 128.9 (C_{19}), 131.0 (d, $^3J_{CF}$= 9.7 Hz, $2C_{17}$), 135.3 (C_{15}), 138.0 (C_4), 139.8 (d, $^4J_{CF}$= 3.5 Hz, C_{16}), 166.6 (d, $^1J_{CF}$= 251.4 Hz, C_{19}), 175.2 (C_1); HRMS (ESI$^+$, m/z) calcd for $(C_{21}H_{22}FN_2O_4S)^+$ $(M + H)^+$ 417.1279, found 417.1273; $[\alpha]_D^{20}$= +64.4 (c 1, MeOH) for 99% *ee*.

Synthesis of (*R*)-Methyl 3-[3-(4-Fluorophenylsulfonamido)-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl]propanoate (18). To a solution of (*R*)-ramatroban (**1**, 50 mg, 0.12 mmol) in MeOH (1 mL) were added two drops of concentrated aqueous H_2SO_4 solution. The mixture was stirred at 65 °C for 15 h, and after this time, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$. MeOH was removed by distillation under reduced pressure, and the aqueous phase extracted with (3 × 5 mL) CH_2Cl_2. The organic phases were combine and dried over Na_2SO_4, and the solvent evaporated under reduced pressure affording 31 mg of (*R*)-**18** as a white solid (60%): R_f (40% EtOAc/hexane) 0.34; mp 41−43 °C; IR (KBr) 3281, 2926, 1736, 1692, 1586, 1487, and 1167 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 1.93−2.11 (m, 2H), 2.53−2.60 (m, 1H), 2.75 (t, $^3J_{HH}$ = 7.3 Hz, 2H), 2.80−2.95 (m, 3H), 3.68 (s, 3H), 3.81 (br s, 1H), 4.33 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 5.03 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.09 (t, $^3J_{HH}$ = 7.3 Hz, 1H), 7.15−7.35 (m, 4H), 7.88−7.93 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2 (CH_2), 28.6 (CH_2), 29.1 (CH_2), 34.4 (CH_2), 38.6 (CH_2), 49.3 (CH), 52.0 (CH_3), 106.1 (C), 108.9 (CH), 116.3 (d, $^2J_{CF}$= 22.6 Hz, 2CH), 117.8 (CH), 119.4 (CH), 121.5 (CH), 127.1 (C), 129.6 (d, $^3J_{CF}$= 9.8 Hz, 2CH), 133.5 (C), 136.2 (C), 137.2 (C), 165.0 (d, $^1J_{CF}$= 254.5 Hz, C), 171.6 (C); HRMS (ESI$^+$, m/z) calcd for $(C_{22}H_{24}FN_2O_4S)^+$ $(M + H)^+$ 431.1435, found 431.1430; $[\alpha]_D^{20}$= +68.8 (c 1, MeOH) for 99% *ee*.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC methods, copies of ^1H NMR, ^{13}C NMR, DEPT spectra for all novel organic compounds, and copies of 2D-NMR spectra for ramatroban. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

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