JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

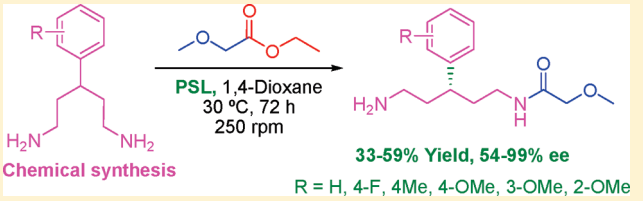
Chemoenzymatic Asymmetric Synthesis of Optically Active Pentane-1,5-diamine Fragments by Means of Lipase-Catalyzed Desymmetrization Transformations†

Nicolás Ríos-Lombardía, Eduardo Busto, Vicente Gotor-Fernández,* and Vicente Gotor*

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

Supporting Information

ABSTRACT: A novel family of prochiral pentane-1,5-diamines has been efficiently synthesized, possessing stabilities significantly higher than those of corresponding propane-1,3-diamine analogues. Diamines have been later desymmetrized using *Pseudomonas cepacia* lipase as an efficient biocatalyst for the mono- but also stereoselective protection of one of their amino groups. Reaction parameters such as type and loading of enzyme, temperature, solvent, and acyl donor have been exhaustively analyzed, searching for optimal conditions for the production of interesting optically active nitrogenated compounds. Thus, acylation and alkoxycarbonylation processes have been compared in terms of conversion and enantiomeric excess values. The best results were found in the reaction of prochiral diamines with ethyl methoxyacetate as acyl donor and 1,4-dioxane as solvent, yielding (*S*)-monoamides in 33−59% isolated yield and 54−99% ee, depending on the aromatic pattern substitution.



INTRODUCTION

Polyamines are central motifs in chemistry but also play an essential role in living systems.[1] In fact, they possess very diverse biological applications such as metabolic or plant growth regulators, DNA stabilizing agents, ion channels modulators, or cell membrane transport systems.[2,3] In addition, polyamines are adequate building blocks for the production of more complex and useful structures, e.g. polymers, semiconductors or cyclic receptors,[4,5] possessing remarkable importance when their chiral versions are considered.[6] From this vast group of nitrogenated compounds, cadaverine is one of its most important integrants because of different implications.

Also known as pentane-1,5-diamine, cadaverine is chemically produced from petrol-based raw material or alternatively through a greener decarboxylation of lysine by the action of a lysine decarboxylase.[7] Pentane-1,5-diamine possesses an unpleasant odor, and it is produced by protein hydrolysis during putrefaction of animal tissues, being very toxic when found in high concentrations. In addition to its utility as building blocks of natural products[8] or interesting biologically active compounds such as cyclic amines,[9] antitumor,[10,11] or antitubercular agents,[12] its role as enzyme inhibitor has been widely explored.[13,14] The possibility to produce chiral complexes highlights the importance of the pentane-1,5-diamine fragment because of their use as chiral shift agents,[15] ligands in organocatalysis,[16−18] chemical catalysts,[19−22] macrocycles for chiral recognition,[23−25] or with binding affinity capacities.[26]

In recent years, large efforts have been made to develop monoselective protection of polyfunctional compounds.[27] Enzymatic methods are very practical for the development of stereoselective processes, taking advantage of the chiral composition of enzymatic sources. In this sense, desymmetrization of prochiral or *meso*-compounds using biocatalysts is a challenging strategy[28,29] and in particular for lipases when diamines are involved in the process.[30]

Recently, we demonstrated the versatility of hydrolytic enzymes for the stereoselective alkoxycarbonylation of 2-substituted-propane-1,3-diamines[31−35] but also the acylation and hydrolysis of 3-arylpentane-1,5-diol fragments.[36] On the basis of our research experience in the synthesis of prochiral 1,3-diamine derivatives, we have now turned our attention toward the preparation and next lipase-catalyzed desymmetrization of a novel family of prochiral 3-arylpentane-1,5-diamines, searching for optimal synthetic methods for the production of optically active monocarbamates and monoamides.

RESULTS AND DISCUSSION

First of all, we focused on the development of an efficient and straightforward preparation for prochiral 3-phenylpentane-1,5-diamine (**4a**), an ideal model substrate for the optimization of the synthetic enzymatic study. Starting from 3-phenylpentane-1,5-diol, which is easily accessible from commercially available 3-phenyl-1,5-pentanedioic acid,[36] the chemical diactivation was carried out with mesyl chloride (MsCl) in the presence of pyridine (Scheme 1). Substitution reaction with sodium azide in DMF led to the diazide **3a** in very high yield, which was finally hydrogenated in the presence of Pd−C. Unfortunately, some uncontrolled experiments occurred, depending on the rate of methanol and hydrogen addition. In fact, in

Received: April 18, 2011
Published: May 31, 2011

Scheme 1. Chemical Synthesis of Diamine 4a

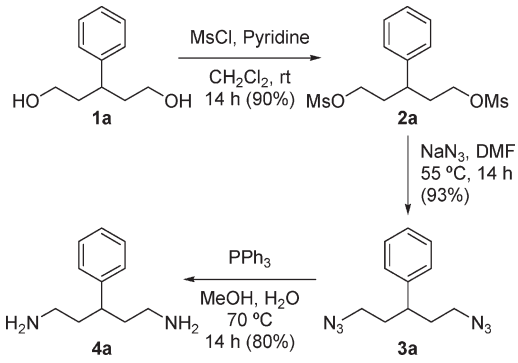


Table 1. Enzymatic Desymmetrization of Diamine 4a Using Lipases (ratio 1:1 in weight of substrate with respect to the enzyme) and Diallyl Carbonate (1 equiv) in 1,4-Dioxane (0.1 M) during 72 h at 30 °C and 250 Revolutions per Minute (rpm)

entry	enzyme	yield (%)[a]	(*S*)-**6**, ee (%)[b]
1	CAL-B	78 (100)	0
2	PSL-C I	32 (34)	88
3	PSL IM	14 (17)	30
4	PSL SD	17 (18)	0

[a] Isolated yield after flash chromatography. Conversion values in brackets measured by ^{1}H NMR of the reaction crude. [b] Enantiomeric excess of (*S*)-**6** determined by HPLC after appropriate derivatization.

one occurrence, the interaction between 3-phenylpentane-1,5-diazide, palladium, and hydrogen led to an explosion of the 50-mL round-bottom flask. At that point, we decided to replace this simple method for the synthesis of propane-1,3-diamines by a safer reaction using triphenylphosphine in MeOH, leading to the diamine **4a** in good yield. Although for safety reasons the latter method is recommended, a chromatographic separation was needed for the purification of the resulting diamine. In contrast with the extraordinary instability shown by propane-1,3-diamines, 3-phenylpentane-1,5-diamine showed excellent stability to moisture over long storage times, allowing subsequent chemical or enzymatic modification.

Because of the excellent levels of stereoselectivity shown by *Pseudomonas cepacia* lipase (PSL-C I), also currently known as *Burkholderia cepacia* lipase, in the mono- and stereoselective alkoxycarbonylation of 2-arylpropane-1,3-diamines,[31−35] we decided to use this lipase-catalyzed system for the desymmetrization of **4a**. Thus, not only PSL but also other commercially available lipases were screened toward **4a**, e.g., *Candida antarctica* lipase B (CAL-B), *Candida antarctica* lipase A (CAL-A), *Candida rugosa* lipase (CRL), porcine pancreatic lipase (PPL), lipase from *Rhizomucor miehei* (RM), or AK lipase from *Pseudomonas fluorescens* (AK). Reactions were first conducted using diallyl carbonate as carbamoylating agent, 1,4-dioxane as solvent, and at 30 °C, reaction conditions identical to those previously used in the desymmetrization of 2-substituted-propane-1,3-diamines (Table 1). Unfortunately, but according to previous experiences with propanediamines,[31] only CAL-B (entry 1) showed an excellent level of activity, leading to the racemic monocarbamate **6** in 78% isolated yield and full extension. Only PSL-C I from Amano acted with a high stereopreference in the formation of the allyl monocarbamate (*S*)-**6** although with a low grade of conversion (34%, entry 2). Note that immobilization techniques play a fundamental role in enzyme catalysis,[37−39] observing that when using PSL IM-immobilized enzyme in diatomaceous earth (entry 3) or PSL SD, a crude enzyme preparation containing dextrin as diluent (entry 4), the activity, but mainly the stereoselectivity, dramatically diminished until the recovery of the racemic product for PSL SD. However, in all cases only starting material or the final monoallyl carbamate was identified in the reaction medium, proving this enzymatic approach as an excellent possibility for the selective protection of chemically equivalent amino groups.

An extra chemical reaction was required for the determination of the enantiomeric excess, as the amino carbamate **6** was not a good candidate for chiral HPLC analysis. For that reason, chemical protection of the remaining free amino group was performed using acetyl chloride in dry dichloromethane, obtaining optically active amido carbamate (*S*)-**7** in quantitative yields from (*S*)-**6** (Scheme 2). Complementary to this approach, racemic **7** was prepared by slow and carefully addition of acetic anhydride over diamine **4a**, which led to the formation of the amino amide (±)-**8** that was subsequently protected with allyl chloroformate, finally yielding the racemic amido carbamate **7** in only 9% yield because of the appearance of homodisubstituted final products or the starting material. Although the recovered amount of racemic amido carbamate **8** was low, that was enough for our purposes in the development of adequate chiral HPLC methods for the determination of the optical purity of final products.

The results from our study highlight the successful development of a synthetic strategy for the selective protection of diamines. Note also that some elegant chemical processes for the monoselective protection of diamines have recently appeared in the literature.[40,41] Once PSL-C I was chosen as the best biocatalyst for the desymmetrization of **4a**, we studied this process in depth, searching for an improvement in the selectivity and activity of our catalyst. In this sense, a screening of solvents was performed, including polar and nonpolar solvents that allowed good solubility of the starting diamine. In addition to 1,4-dioxane, other solvents such as *tert*-butyl methyl ether, diethyl ether, tetrahydrofuran, toluene, acetonitrile, and *tert*-butyl alcohol were used with a 100 mM substrate concentration. Data are summarized in Table 2; note again that only starting material or monocarbamate was identified in the reaction medium after 72 h of reaction, the highest conversion being attained with ether solvents such as TBME or Et_2O.

Although similar or lower stereoselectivities were observed (60−86% ee) compared with the biotransformation in 1,4-dioxane (88% ee), very much higher isolated yields were attained in the reactions with nonpolar ether solvents such as TBME or Et_2O (entries 2 and 3). This is a surprising result because lower solubilities are achieved for **4a** with the latter solvents, although the improved performance of immobilized lipases in nonpolar solvents compared to higher polar solvents is known.[42]

Next we took into account other parameters that have influence on the enzymatic performance such as loading of biocatalyst and temperature, again using 1,4-dioxane because of the higher enantiomeric excesses achieved and the possibility to carry out the biotransformations at higher temperatures without solvent volatility problems. In all cases, the reaction temperature correlates with isolated yields of the optically active monocarbamates (Table 3). An increase in the temperature led to higher amounts of the final products (32−45% conversion, entries 1−3) although the stereopreference shown by PSL decreases at higher temperatures (80−88% ee). To reach higher conversions in shorter reaction times, the amount of PSL was doubled, achieving a similar level of selectivities and an optimum

dx.doi.org/10.1021/jo2007972 |*J. Org. Chem.* 2011, 76, 5709–5718

Scheme 2. Enzymatic Desymmetrization of Diamine 4a Using Diallyl Carbonate Followed by Derivatization to the Amido Carbamate 7, Which Has Been Also Prepared in Racemic Form for the Measurement of Enantiomeric Excesses

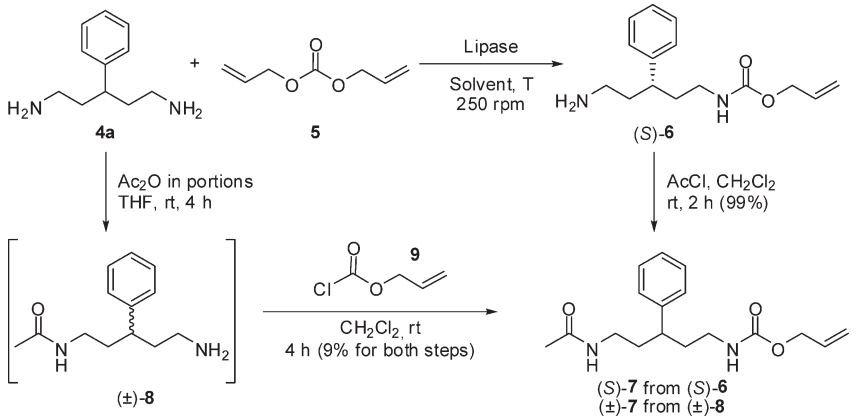


Table 2. Enzymatic Desymmetrization of 4a with PSL-C I (ratio 1:1 in weight of substrate respect to the enzyme) and Diallyl Carbonate (1 equiv) in Organic Solvent (0.1 M) during 72 h at 30 °C and 250 rpm

entry	solvent	yield (%)[a]	(*S*)-**6**, ee (%)[b]
1	1,4-dioxane	32 (34)	88
2	TBME	60 (66)	86
3	Et_2O	49 (79)	86
4	THF	37 (48)	86
5	Toluene	23 (33)	82
6	MeCN	14 (16)	60
7	^{t}BuOH	31 (38)	81

[a] Isolated yields after flash chromatography. Conversion values in brackets measured by ^{1}H NMR of the reaction crude. [b] Enantiomeric excess of (*S*)-**6** determined by HPLC after appropriate derivatization.

Table 3. Enzymatic Desymmetrization of 4a Using PSL-C I and Diallyl Carbonate (1 equiv) in 1,4-Dioxane (0.1 M) during 72 h at 250 rpm

entry	PSL-C I:**4a**[a]	*T* (°C)	yield (%)[b]	(*S*)-**6**, ee (%)[c]
1	1:1	30	32 (34)	88
2	1:1	45	35 (41)	83
3	1:1	60	45 (54)	80
4	2:1	30	29 (39)	88
5	2:1	45	63 (75)	87
6	2:1	60	41 (50)	84

[a] Ratio of weight of enzyme (PSL-C I) with respect to the substrate (diamine **4a**). [b] Isolated yield after flash chromatography. Conversion values in brackets measured by ^{1}H NMR of the reaction crude. [c] Enantiomeric excess of (*S*)-**6** determined by HPLC after appropriate derivatization.

temperature of 45 °C for the recovery of (*S*)-**6** in 63% isolated yield and 87% ee (entry 5). Finally we scaled-up the reaction, searching for an improvement in the isolation of the final product, and as expected, using 1.35 mmol instead of 0.17 mmol (entry 1 of Table 3) resulted in an increase in isolated yield from 32 to 48% and maintained the same enantiomeric excess (88%).

The acylation reaction is an alternative to the carbomoylation process for the selective modification of polyfunctional compounds. Activated esters such as vinyl acetate are used in the reaction with secondary alcohols, and nonactivated esters (e.g., ethyl acetate or ethyl methoxyacetate) are usually employed in the reaction with amino groups to avoid the chemical reaction that often occurs between amines and activated esters. Thus, PSL was also applied to the acylation of prochiral diamine **4a** using ethyl acetate (EtOAc, **10a**), finding results similar to that of alkoxycarbonylation reaction with diallyl carbonate (Scheme 3, entries 1 and 2 of Table 4). For the determination of the enantiomeric excess, the resulting (*S*)-monoamide **8** was subjected to carbamoylation with allyl chloroformate (**9**), a process that occurs at room temperature in 92% yield after 2 h. When ethyl methoxyacetate (**10b**) was used instead of ethyl acetate, an almost total conversion was achieved in the formation of (*S*)-monoamide **11a**, reaching a similar enantiomeric excess value (entry 3). Significantly, the optically active amido amine was identified as a unique product in the reaction, being isolated in 58% yield after chromatographic purification and demonstrating the usefulness of the stereoselective monoprotection with practical applications, as the diprotected product was not observed in the crude reaction product. This is not a surprising result, as ester **10b** has been successfully applied as an ideal acyl donor in lipase-catalyzed kinetic and dynamic kinetic resolution of primary amines.[43−45] To simplify the enzymatic system, reactions without an inert atmosphere were attempted, interestingly leading to results identical to those under nitrogen atmosphere.

With all these results in hand we decided to move forward toward the development of a general route for the synthesis and lipase-catalyzed desymmetrization of prochiral pentane-1,5-diamines. Probing the efficiency of the previously proposed synthetic pathway for diamine **4a**, diols **1b**−**f** obtained from their corresponding commercially available dicarboxylic acids[36] were subjected to a dimesylation, azide substitution, and reduction sequence leading to the corresponding diamines **4b**−**f** with high overall yields, ranging from a global 61% for the *o*-methoxyphenyl derivative **4f** to 75% for the *p*-methylphenyl **4c** or the *p*-methoxyphenyl **4d** (Scheme 4).

For the para-substituted compounds including the fluoro (b), methyl (c), and methoxy (d) groups, in all cases good to high selectivities were achieved (82−90%, entries 2−4 of Table 5) for

dx.doi.org/10.1021/jo2007972 |*J. Org. Chem.* 2011, 76, 5709–5718

Scheme 3. Enzymatic Desymmetrization of Prochiral Diamine 4a Using Ethyl Esters 10a,b, Followed by Chemical Synthesis of Optically Active (*R*)-Amido Carbamates 7 and 12a for ee Measurement

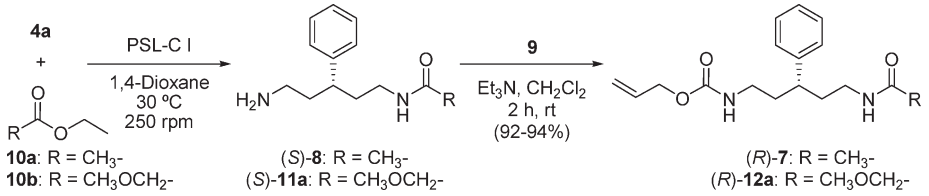


Table 4. Enzymatic Desymmetrization of 4a Using PSL-C I (ratio 1:1 of weight of substrate with respect to the enzyme) and an Ester or Carbonate (1 equiv) in 1,4-Dioxane (0.1 M) at 30 °C during 72 h at 250 rpm

entry	donor	yield (%)[a]	(*S*)-**6**, -**8**, -**11a**, ee (%)[b]
1	**5**	32 (34)	88
2	**10a**	27 (52)	90
3	**10b**	58 (100)	91

[a] Isolated yield after flash chromatography for (*S*)-**6**, (*S*)-**8**, and (*S*)-**11a**. Conversion values in brackets measured by ^{1}H NMR of the reaction crude. [b] Enantiomeric excess of (*S*)-**6**, (*S*)-**8**, and (*S*)-**11a** determined by HPLC after appropriate derivatization.

Table 5. Enzymatic Desymmetrization of 4a−f Using PSL-C I (ratio 1:1 in weight of substrate with respect to the enzyme) and Ethyl Methoxyacetate (10b, 1 equiv) in 1,4-Dioxane (0.1 M) at 30 °C during 72 h at 250 rpm

entry	diamine	yield (%)[a]	(*S*)-**11a**−**f**, ee (%)[b]
1	**4a** (H)	58	91
2	**4b** (*p*-F)	58	82
3	**4c** (*p*-Me)	59	90
4	**4d** (*p*-OMe)	51	86
5	**4e** (*m*-OMe)	50	>99
6	**4f** (*o*-OMe)	33	54

[a] Isolated yield of (*S*)-**11a**−**f** after flash chromatography. [b] Enantiomeric excesses of (*S*)-**11a**−**f** determined by HPLC after adequate derivatization.

the production of (*S*)-monoamides **11b**−**d** in moderate yields (51−59%). At this point, we were interested in analyzing the influence of the substituent position inside the aromatic ring, considering prochiral diamines possessing the methoxy substitution in the phenyl ring located at the 3-position of the 1,5-diamine fragment. Excellent results were attained in terms of activity and stereoselectivity for the production of enantiopure (*S*)-monoamide **11e** (entry 5) while a lower reactivity and the lowest chiral induction was reached for **4f** (entry 6) in the PSL-catalyzed desymmetrization acylation with ethyl methoxyacetate (**10b**).

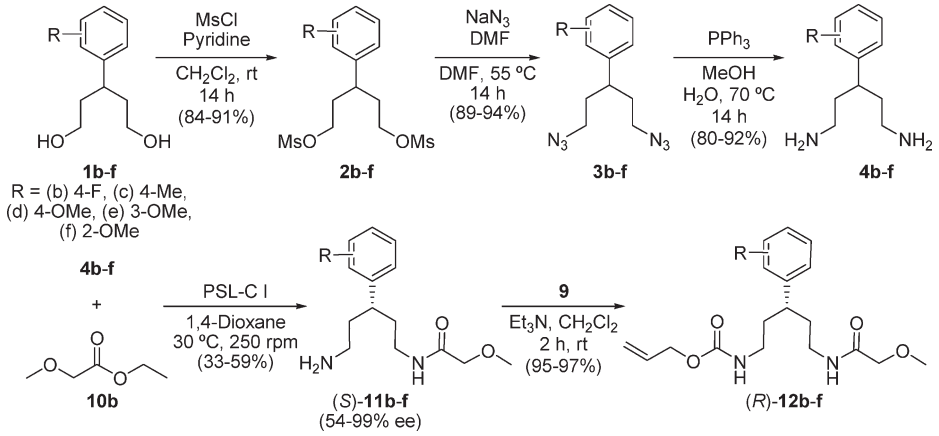
Lastly, the determination of the absolute configuration for (*S*)-**11a** obtained by chemoenzymatic methods was demonstrated, designing a synthetic route from known monoacetate (*S*)-**14**, which is easily prepared in enantiopure form through the lipase-desymmetrization of 3-phenyl-pentane-1,5-diol (**1a**) with vinyl acetate (**13**) and AK lipase (Scheme 5). In this manner, transformation of the (*S*)-**14** free hydroxyl group led to compound (*R*)-**15** with changed absolute stereochemistry because of CIP priority rules. A substitution reaction with sodium azide in hot DMF and a hydrogenation reaction with simultaneous ester hydrolysis led to the amino alcohol (*S*)-**17**. Then N-selective protection with 1 equiv of methoxyacetyl chloride (**18**) added portionwise in the absence of triethylamine led to the amido alcohol (*S*)-**19**, which was next O-activated using mesyl chloride in the presence of pyridine. Reaction with NaN_3 and hydrogenation of the corresponding product mediated by Pd−C in MeOH allowed the formation of the amido amine (*R*)-**11a**, which was reacted with allyl chloroformate (**9**) in order to finally obtain the enantiopure amido carbamate (*S*)-**12a**. In this case, the hydrogenation was preferred rather than the reduction of the azide with PPh_3, looking for an easy purification of the resulting polar compound and the avoidance of high temperatures because of possible undesired racemization in the process. Optical rotation and retention times after HPLC analysis were compared with the ones obtained by lipase-catalyzed desymmetrization of prochiral diamine, undoubtedly confirming the (*S*)-absolute stereochemistry of the final product (*S*)-**11a** from the enzymatic desymmetrization of diamine **4a**. Note that the (*R*)-allyl carbamate is obtained from the lipase-catalyzed enantioselective desymmetrization of 2-phenylpropane-1,3-diamine[31,32] while the (*S*)-allyl carbamate or (*S*)-amides are synthesized from 3-phenyl-pentane-1,5-diamine. Comparing the optical rotation values and the peak elution orders for all the 1,5-monoamido carbamates, the same (*S*)-stereopreference was assigned for the PSL action toward the panel of prochiral diamines studied in this manuscript (see also Supporting Information for more data).

CONCLUSIONS

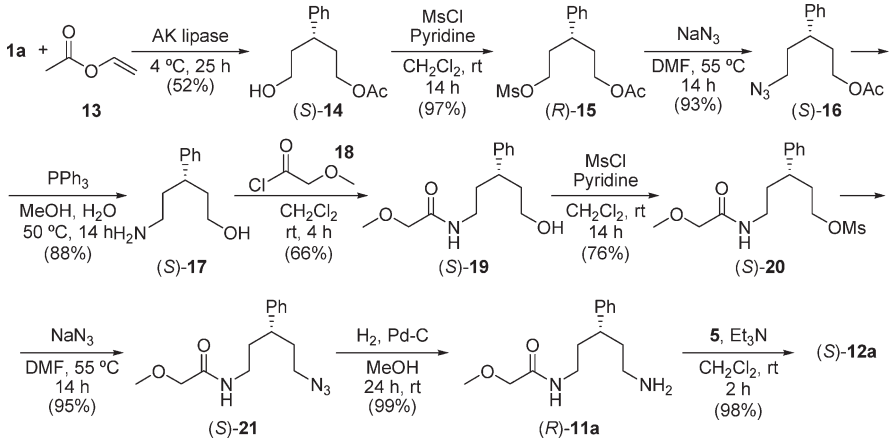
In summary, starting from commercially available dicarboxylic acids, a short and straightforward method for the production of optically active monoamides or amido carbamates derived from the pentane-1,5-diamine has been developed for the first time. Good overall yields have been achieved for the production of prochiral 3-arylpentane-1,5-diamines, finding *Pseudomonas cepacia* lipase as an optimum biocatalyst for their mono- and stereoselective protection under mild reaction conditions, especially when higher amounts of reactants are used in the biotransformation. Different enzymatic reaction parameters have been exhaustively analyzed, identifying the type of immobilized enzyme and the class of synthetic processes as fundamental issues for the development of elegant monoacylation enzymatic processes. The wide scope of the process has been demonstrated by the good to excellent results obtained in the desymmetrization of prochiral diamines. Playing an important role in the pattern substitution in the aromatic rings for the isolation of optically active amides in high enantiomeric excess, PSL gives predominantly meta-substitution. Most significant results have been summarized in Figure 1. Finally, the determinations of the absolute configurations of monoamino carbamates have been demonstrated by chemical synthetic processes.

dx.doi.org/10.1021/jo2007972 |*J. Org. Chem.* 2011, 76, 5709–5718

Scheme 4. Chemical Synthesis of Diamines 4b−f Followed by Lipase-Catalyzed Desymmetrization Processes



Scheme 5. Chemoenzymatic Synthesis of Amido Amine (*R*)-11a and Amido Carbamate (*S*)-12a from 3-Phenylpentane-1,5-diol (1a)



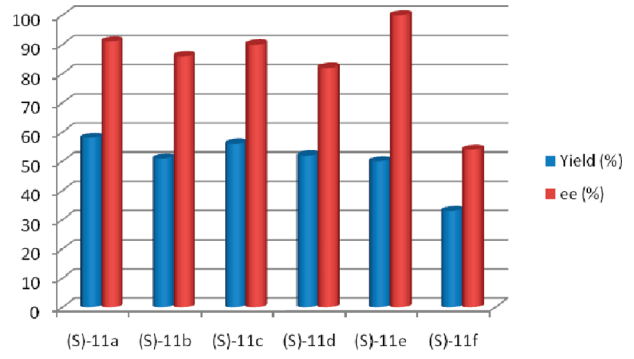


Figure 1. Summary of the best synthetic reactions for the enzymatic desymmetrization of diamines **4a**−**f** after final purification by flash chromatography.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Dimesylates 2a−f.

To a solution of the corresponding diol **1a**−**f** (9.39 mmol) in dry CH_2Cl_2 (94 mL) was added pyridine (4.54 mL, 56.33 mmol), and the mixture was cooled at 0 °C. Then methanesulfonyl chloride (MsCl, 4.08 mL, 56.33 mmol) was added and the resulting solution stirred at room temperature for 14 h after complete disappearance of the starting material. The solvent was evaporated by distillation at reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (30−50% EtOAc/hexane) to yield the corresponding dimesylate **2a,b,d**−**f** as a colorless oil and **2c** as a white solid (84−91%). **2a** (90% yield): R_f (50% EtOAc/hexane): 0.16; IR (NaCl): ν 3030, 2941, 1353, 1174, 973, 919, 734, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.90−2.03 (m, 2H), 2.04−2.19 (m, 2H), 2.86 (s, 6H), 2.87−2.99 (m, 1H), 3.86−3.97 (m, 2H), 4.00−4.12 (m, 2H), 7.10−7.18 (m, 2H), 7.19−7.25 (m, 1H), 7.26−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.3 (2C), 36.8 (2C), 37.8, 67.7 (2C), 127.0, 127.3 (2C), 128.7 (2C), 141.0; MS (ESI^+, *m*/*z*): 359 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{13}H_{20}NaO_6S_2)^+$ [$(M + Na)^+$]: 359.0594; found: 359.0597. **2b** (89% yield): R_f (50% EtOAc/hexane): 0.29; IR (NaCl): ν 3031, 2942, 1604, 1510, 1352, 1224, 1174, 974, 917, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.86−2.05 (m, 2H), 2.07−2.23 (m, 2H), 2.91 (s, 6H), 2.95−3.05 (m, 1H), 3.88−3.99 (m, 2H), 4.05−4.15 (m, 2H), 7.02 (t, $^3J_{HH}$ = 8.7 Hz, 2H), 7.10−7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.6 (2C), 37.1 (2C), 37.2, 67.4 (2C), 115.7 (d, $^2J_{CF}$ = 21 Hz, 2C), 129.0 (d, $^3J_{CF}$ = 7 Hz, 2C), 136.9, 161.7 (d, $^1J_{CF}$ = 246 Hz); MS (ESI^+, *m*/*z*): 377 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{13}H_{19}FNaO_6S_2)^+$ [$(M + Na)^+$]: 377.0499; found: 377.0508. **2c** (91% yield): R_f (50% EtOAc/hexane): 0.27; Melting point: 54−56 °C; IR (KBr): ν 3026, 2940, 1351, 1173, 973, 921, 819, 736 cm^{-1}; ^1H NMR

dx.doi.org/10.1021/jo2007972 |*J. Org. Chem.* 2011, 76, 5709–5718

($CDCl_3$, 300.13 MHz): δ 1.88−2.02 (m, 2H), 2.04−2.18 (m, 2H), 2.29 (s, 3H), 2.87 (s, 6H), 2.82−2.94 (m, 1H), 3.88−3.95 (m, 2H), 4.03−4.10 (m, 2H), AB system (δ_A = 7.03 δ_B = 7.11, $^3J_{HH}$ = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.7, 35.4 (2C), 36.8 (2C), 37.4, 67.8 (2C), 127.2 (2C), 129.4 (2C), 136.6, 137.8; MS (ESI$^+$, *m*/*z*): 373 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{14}H_{22}NaO_6S_2$)$^+$ [(M + Na)$^+$]: 373.0750; found: 373.0764. **2d** (90% yield): R_f (50% EtOAc/hexane): 0.29; IR (NaCl): ν 2941, 1514, 1353, 1250, 1174, 973, 914, 832, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.84−2.01 (m, 2H), 2.03−2.18 (m, 2H), 2.79−2.87 (m, 1H), 2.88 (s, 6H), 3.75 (s, 3H), 3.86−3.98 (m, 2H), 4.01−4.13 (m, 2H), AB system (δ_A = 6.83 δ_B = 7.06, $^3J_{HH}$ = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.5 (2C), 36.9 (2C), 37.0, 55.0, 67.7 (2C), 114.2 (2C), 128.3 (2C), 132.8, 158.5; MS (ESI$^+$, *m*/*z*): 389 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{14}H_{22}NaO_7S_2$)$^+$ [(M + Na)$^+$]: 389.0699; found: 389.0707. **2e** (85% yield): R_f (50% EtOAc/hexane): 0.27; IR (NaCl): ν 3027, 2941, 1600, 1488, 1352, 1258, 1173, 1040, 973, 918, 794, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.89−2.04 (m, 2H), 2.05−2.20 (m, 2H), 2.90 (s, 6H), 2.82−2.97 (m, 1H), 3.77 (s, 3H), 3.88−4.01 (m, 2H), 4.04−4.15 (m, 2H), 6.67−6.80 (m, 3H), 7.23 (t, $^3J_{HH}$ = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.3 (2C), 36.9 (2C), 37.9, 55.0, 67.7 (2C), 112.0, 113.4, 119.6, 129.4, 142.7, 159.8; MS (ESI$^+$, *m*/*z*): 389 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{14}H_{22}NaO_7S_2$)$^+$ [(M + Na)$^+$]: 389.0699; found: 389.0704. **2f** (84% yield): R_f (50% EtOAc/hexane): 0.30; IR (NaCl): ν 2943, 1493, 1353, 1244, 1174, 969, 916, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.01−2.23 (m, 4H), 2.86 (s, 6H), 3.24−3.37 (m, 1H), 3.79 (s, 3H), 3.92−4.12 (m, 4H), 6.83−6.95 (m, 2H), 7.10 (d, $^3J_{HH}$ = 6.2 Hz, 1H), 7.20 (t, $^3J_{HH}$ = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 32.7, 33.9 (2C), 36.8 (2C), 55.1, 68.3 (2C), 110.8, 120.8, 128.1, 128.5, 128.7, 157.4; MS (ESI$^+$, *m*/*z*): 389 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{14}H_{22}NaO_7S_2$)$^+$ [(M + Na)$^+$]: 389.0699; found: 389.0706.

General Procedure for the Synthesis of Diazides 3a−f. To a solution of the corresponding dimesylate **2a**−**f** (5.30 mmol) in dry DMF (21 mL) was added sodium azide (2.10 g, 31.79 mmol) under nitrogen atmosphere, and the resulting suspension was stirred at 55 °C during 14 h. After this time, the reaction was quenched with H_2O (25 mL) and the residue extracted with Et_2O (3 × 25 mL). The organic phases were combined and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure, affording a crude product that was purified by flash chromatography (5% EtOAc/hexane), which yielded the corresponding diazide **3a**−**f** as a colorless oil (89−94%), that were next reduced without longer storage times inclusively at low temperatures. **3a** (93% yield): R_f (5% EtOAc/hexane): 0.42; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.78−2.04 (m, 4H), 2.76−2.90 (m, 1H), 2.99−3.12 (m, 2H), 3.13−3.25 (m, 2H), 7.13−7.20 (m, 2H), 7.21−7.29 (m, 1H), 7.25−7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.3 (2C), 40.1, 49.2 (2C), 126.9, 127.5 (2C), 128.8 (2C), 142.1. **3b** (89% yield): R_f (5% EtOAc/hexane): 0.27; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.73−2.01 (m, 4H), 2.77−2.90 (m, 1H), 2.96−3.10 (m, 2H), 3.12−3.24 (m, 2H), 7.02 (t, $^3J_{HH}$ = 8.5 Hz, 2H), 7.09−7.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.6 (2C), 39.3, 49.1 (2C), 115.6 (d, $^2J_{CF}$ = 21 Hz, 2C), 128.8 (d, $^3J_{CF}$ = 8 Hz, 2C), 137.7, 161.6 (d, $^1J_{CF}$ = 245 Hz). **3c** (89% yield): R_f (5% EtOAc/hexane): 0.45; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.76−2.02 (m, 4H), 2.35 (s, 3H), 2.72−2.85 (m, 1H), 2.98−3.11 (m, 2H), 3.12−3.25 (m, 2H), AB system (δ_A = 7.06 δ_B = 7.15, $^3J_{HH}$ = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.9, 35.5 (2C), 39.6, 49.2 (2C), 127.3 (2C), 129.4 (2C), 136.4, 138.8. **3d** (94% yield): R_f (5% EtOAc/hexane): 0.27; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.70−2.02 (m, 4H), 2.69−2.85 (m, 1H), 2.97−3.10 (m, 2H), 3.11−3.27 (m, 2H), 3.79 (s, 3H), AB system (δ_A = 6.86 δ_B = 7.06, $^3J_{HH}$ = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.5 (2C), 39.1, 49.1 (2C), 54.9, 114.0 (2C), 128.2 (2C), 133.8, 158.3. **3e** (94% yield): R_f (5% EtOAc/hexane): 0.26; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.77−2.00 (m, 4H), 2.73−2.86 (m, 1H), 2.99−3.11 (m, 2H), 3.12−3.23 (m, 2H), 3.80 (s, 3H), 6.70−6.83 (m, 3H), 7.25 (t, $^3J_{HH}$ = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.4 (2C), 40.1, 49.1 (2C), 54.9, 111.7, 113.3, 119.6, 129.7, 143.7, 159.8. **3f** (89% yield): R_f (5% EtOAc/hexane): 0.45; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.84−2.07 (m, 4H), 3.03−3.23 (m, 4H), 3.24−3.38 (m, 1H), 3.84 (s, 3H), 6.90 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 6.96 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 7.13 (dd, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.24 (t, $^3J_{HH}$ = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 33.7, 34.2 (2C), 49.5 (2C), 55.1, 110.6, 120.7, 127.6, 127.9, 129.9, 157.5.

General Procedure for the Synthesis of Diamines 4a−f. To a solution of the corresponding diazide **3a**−**f** (4.91 mmol) in MeOH (49 mL) was added PPh_3 (1.44 g, 14.7 mmol), and the resulting suspension was stirred until the triphenylphosphine was completely dissolved. After this time, H_2O (264 μL, 14.7 mmol) was added to the reaction vessel and the resulting solution stirred at 70 °C for 14 h until complete disappearance of the diazide by TLC analysis. Then the solvent was evaporated by distillation at reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (100% MeOH to 10% NH_3/MeOH), affording the corresponding diamine **4a**−**f** as a yellowish oil (80−92%). **4a** (80% yield): R_f (10% NH_3/MeOH): 0.14; IR (NaCl): ν 3352, 3290, 2934, 2821, 1581, 1493, 1454, 1389, 1316, 1132, 1034, 762, 704 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 1.72−1.97 (m, 4H), 2.40−2.62 (m, 4H), 2.65−2.78 (m, 1H), 7.14−7.25 (m, 3H), 7.26−7.35 (m, 2H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 40.1 (2C), 40.7 (2C), 42.8, 128.1, 129.1 (2C), 130.2 (2C), 145.9; MS (ESI$^+$, *m*/*z*): 179 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{11}H_{19}N_2$)$^+$ [(M + H)$^+$]: 179.1543; found: 179.1548. **4b** (91% yield): R_f (10% NH_3/MeOH): 0.14; IR (NaCl): ν 3357, 3286, 2925, 2863, 1579, 1512, 1315, 837 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 1.68−1.96 (m, 4H), 2.40−2.64 (m, 4H), 2.69−2.85 (m, 1H), 7.06 (t, $^3J_{HH}$ = 8.8 Hz, 2H), 7.21−7.31 (m, 2H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 40.5 (2C), 40.7 (2C), 41.7, 116.1 (d, $^2J_{CF}$ = 21 Hz, 2C), 130.1 (d, $^3J_{CF}$ = 7 Hz, 2C), 141.8, 162.9 (d, $^1J_{CF}$ = 243 Hz); MS (ESI$^+$, *m*/*z*): 197 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{11}H_{18}FN_2$)$^+$ [(M + H)$^+$]: 197.1449; found: 197.1452. **4c** (92% yield): R_f (10% NH_3/MeOH): 0.13; IR (NaCl): ν 3354, 3289, 2925, 2862, 1580, 1513, 1469, 1317, 816 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 1.66−1.91 (m, 4H), 2.29 (s, 3H), 2.37−2.54 (m, 4H), 2.56−2.73 (m, 1H), 7.10 (brs, 4H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 21.4, 40.9 (2C), 41.0 (2C), 42.4, 128.8 (2C), 130.5 (2C), 137.3, 142.9; MS (ESI$^+$, *m*/*z*): 193 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{12}H_{21}N_2$)$^+$ [(M + H)$^+$]: 193.1699; found: 193.1706. **4d** (88% yield): R_f (10% NH_3/MeOH): 0.10; IR (NaCl): ν 3362, 3281, 2926, 2863, 1610, 1511, 1301, 1247, 1179, 1035, 830 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 1.63−1.96 (m, 4H), 2.39−2.60 (m, 4H), 2.62−2.79 (m, 1H), 3.80 (s, 3H), AB system (δ_A = 6.90 δ_B = 7.17, $^3J_{HH}$ = 8.3 Hz); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 40.8 (4C), 41.9, 56.0, 115.3 (2C), 129.8 (2C), 137.9, 160.0; MS (ESI$^+$, *m*/*z*): 209 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{12}H_{21}N_2O$)$^+$ [(M + H)$^+$]: 209.1648; found: 209.1648. **4e** (88% yield): R_f (10% NH_3/MeOH): 0.15; IR (NaCl): ν 3361, 3282, 2927, 2862, 1597, 1589, 1488, 1259, 1159, 1044, 785, 703 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 1.68−1.88 (m, 4H), 2.38−2.58 (m, 4H), 2.60−2.74 (m, 1H), 3.77 (s, 3H), 6.72−6.83 (m, 3H), 7.21 (t, $^3J_{HH}$ = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 40.9 (4C), 42.9, 55.9, 112.9, 114.7, 121.2, 130.9, 147.8, 161.7; MS (ESI$^+$, *m*/*z*): 209 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{12}H_{21}N_2O$)$^+$ [(M + H)$^+$]: 209.1648; found: 209.1650. **4f** (82% yield): R_f (10% NH_3/MeOH): 0.20; IR (NaCl): ν 3364, 3285, 2933, 2859, 1594, 1491, 1463, 1239, 1027, 756 cm^{-1}; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 1.71−1.95 (m, 4H), 2.38−2.54 (m, 4H), 3.15−3.33 (m, 1H), 3.82 (s, 3H), 6.89−6.71 (m, 2H), 7.12−7.28 (m, 2H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 34.1, 40.2 (2C), 40.9 (2C), 56.3, 112.1, 122.4, 128.6, 128.8, 133.6, 159.2; MS (ESI$^+$, *m*/*z*): 209 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for ($C_{12}H_{21}N_2O$)$^+$ [(M + H)$^+$]: 209.1648; found: 209.1647.

dx.doi.org/10.1021/jo2007972 |*J. Org. Chem.* 2011, 76, 5709–5718

Enzymatic Desymmetrization of Diamine 4a Using Diallyl Carbonate. To a suspension of diamine **4a** (100 mg, 0.56 mmol) and *Pseudomonas cepacia* lipase type I (PSL-C I, 100 mg) in dry 1,4-dioxane (5.6 mL) was added diallyl carbonate (**5**, 81 μL, 0.56 mmol) under nitrogen atmosphere, and the mixture was shaken at 30 °C and 250 rpm, following the progress of the reaction by TLC analysis. The reaction was stopped after 72 h, and the enzyme was filtered off and washed with MeOH (3 × 5 mL). The solvent was evaporated under reduced pressure and the resulting crude purified by flash chromatography (60% MeOH/EtOAc), affording 63 mg of the amino carbamate (*S*)-(+)-**6** as a colorless oil (32% isolated yield, 88% ee; see Tables 1−4). R_f (60% MeOH/EtOAc): 0.11; IR (NaCl): ν 3327, 3027, 2933, 2875, 1703, 1538, 1453, 1257, 1145, 1029, 994, 928, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.61−1.95 (m, 4H), 2.39−2.77 (m, 5H), 2.88−3.08 (m, 2H), 4.49 (d, $^3J_{HH}$ = 5.0 Hz, 2H), 4.94 (brs, 1H), 5.16 (d, $^3J_{cis}$ = 10.5 Hz, 1H), 5.23 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.77−5.95 (m, 1H), 7.08−7.21 (m, 3H), 7.22−7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.6 (2C), 39.1, 39.6, 40.9, 65.2, 117.3, 126.4, 127.3 (2C), 128.5 (2C), 132.9, 143.8, 156.1; MS (ESI$^+$, *m*/*z*): 263 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for $(C_{15}H_{23}N_2O_2)^+$ [(M + H)$^+$]: 263.1754; found: 263.1748; $[\alpha]_D^{20}$ +14.3 (*c* 0.7, EtOH) for 88% ee.

Enantiomeric Excess Measurement for Compound 6 Obtained by Lipase-Catalyzed Desymmetrization of Diamine 4a Using Diallyl Carbonate. To a solution of compound (*S*)-(+)-**6a** (20 mg, 0.08 mmol) in dry CH_2Cl_2 (0.8 mL) were successively added Et_3N (12 μL, 0.09 mmol) and acetyl chloride (6 μL, 0.09 mmol) under nitrogen atmosphere. The mixture was stirred for 2 h at room temperature, and after this time the solvent was evaporated under reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (60% EtOAc/hexane to 100% EtOAc) to afford 23 mg of the amido carbamate (*S*)-(+)-**7** as a colorless oil (99%). R_f (100% EtOAc): 0.21; IR (NaCl): ν 3056, 2932, 1710, 1655, 1541, 1453, 1369, 1266, 1140, 1038, 993, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.66−1.82 (m, 2H), 1.84−2.02 (m, 5H), 2.54−2.70 (m, 1H), 2.92−3.22 (m, 4H), 4.47 (d, $^3J_{HH}$ = 5.1 Hz, 2H), 4.78 (brs, 1H), 5.19 (d, $^3J_{cis}$ = 10.5 Hz, 1H), 5.27 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.80−5.97 (m, 2H), 7.10−7.17 (m, 2H), 7.18−7.24 (m, 1H), 7.25−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.9, 35.7, 36.8, 38.0, 39.0, 41.0, 65.4, 117.5, 126.7, 127.4 (2C), 128.8 (2C), 132.8, 143.7, 156.4, 170.4; MS (ESI$^+$, *m*/*z*): 327 [(M + Na)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for $(C_{17}H_{24}N_2NaO_3)^+$ [(M + Na)$^+$]: 327.1679; found: 327.1682. $[\alpha]_D^{20}$ +1.2 (*c* 1.0, EtOH) for 88% ee.

Synthesis of the Racemic Amido Carbamate 7. To a solution of diamine **4a** (89 mg, 0.50 mmol) in dry THF (1.0 mL) was added Ac_2O (47 μL, 0.50 mmol) in portions under nitrogen atmosphere, and the mixture was stirred for 4 h at room temperature. After this time, the solvent was evaporated under reduced pressure obtaining a crude reaction product that was passed through a plug of SiO_2 (100% MeOH to 1% NH_3/MeOH). The solvent was removed by distillation under reduced pressure, isolating a colorless oil containing the amido amine (±)-**8**, which was immediately dissolved in dry CH_2Cl_2 (1 mL) successively adding pyridine (5 μL, 0.07 mmol) and allyl chloroformate (**9**, 6 μL, 0.07 mmol). The mixture was stirred for 4 h at room temperature, and after this time, the solvent was evaporated under reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (100% EtOAc) to afford 13 mg of the amido carbamate (±)-**7** as a colorless oil (9% for both steps).

Enzymatic Desymmetrization of Diamine 4a Using Ethyl Acetate. To a suspension of diamine **4a** (100 mg, 0.56 mmol) in dry 1,4-dioxane (5.6 mL) were successively added *Pseudomonas cepacia* lipase type I (PSL-C I, 100 mg) and ethyl acetate (**10a**, 55 μL, 0.56 mmol), and the mixture was shaken at 30 °C and 250 rpm. The progress of the reaction was followed by TLC analysis during 72 h. Then the enzyme was filtered off and washed with MeOH (3 × 5 mL), the solvent evaporated under reduced pressure, and the resulting crude product purified by flash chromatography (60% MeOH/EtOAc to 100% MeOH), affording 41 mg of the amide (*S*)-(+)-**8** as a colorless oil (27% isolated yield, 90% ee; see Table 4). R_f (80% MeOH/EtOAc): 0.16; IR (NaCl): ν 3285, 3082, 2932, 2871, 1647, 1560, 1450, 1371, 1298, 1135, 1035, 762, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.64−2.01 (m, 9H), 2.48−2.62 (m, 2H), 2.62−2.77 (m, 1H), 2.95−3.11 (m, 1H), 3.11−3.27 (m, 1H), 5.47 (brs, 1H), 7.08−7.23 (m, 3H), 7.24−7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.1, 36.4, 38.1, 39.8, 40.0, 41.4, 126.5, 127.4 (2C), 128.6 (2C), 144.2, 169.9; MS (ESI$^+$, *m*/*z*): 221 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for $(C_{13}H_{21}N_2O)^+$ [(M + H)$^+$]: 221.1648; found: 221.1649; $[\alpha]_D^{20}$ = +8.9 (*c* 0.7, EtOH) for 90% ee.

Enantiomeric Excess Measurement of Compound 8 Obtained by Lipase-Catalyzed Desymmetrization of Diamine 4a Using Ethyl Acetate. To a solution of compound (*S*)-(+)-**8** (11 mg, 0.05 mmol) in dry CH_2Cl_2 (0.5 mL) were successively added Et_3N (9 μL, 0.07 mmol) and allyl chloroformate (**9**, 8 μL, 0.07 mmol) under nitrogen atmosphere. The mixture was stirred for 2 h at room temperature, and after this time, the solvent was evaporated under reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (60% EtOAc/hexane to 100% EtOAc) to afford 14 mg of the amido carbamate (*R*)-(−)-**7** as a colorless oil (92%). $[\alpha]_D^{20}$ −0.9 (*c* 1.0, EtOH) for 90% ee.

Enzymatic Desymmetrization of Diamines 4a−f Using Ethyl Methoxyacetate. To a suspension of the corresponding diamine **4a−f** (0.56 mmol) in dry 1,4-dioxane (5.6 mL) *Pseudomonas cepacia* were successively added lipase type I (PSL-C I, 100 mg) and ethyl methoxyacetate (**10b**, 66 μL, 0.56 mmol), and the mixture was shaken at 30 °C and 250 rpm following the progress of the reaction by TLC analysis. The progress of the reaction was followed by TLC analysis during 72 h. Then the enzyme was filtered off and washed with MeOH (3 × 5 mL). The solvent was evaporated under reduced pressure and the resulting crude product purified by flash chromatography (60% MeOH/EtOAc to 100% MeOH), affording the corresponding amide (*S*)-(+)-**11a−f** as a colorless oil (33−59% isolated yield, 54−99% ee; see Tables 4 and 5). (*S*)-(+)-**11a** (58% yield, 91% ee): R_f (80% MeOH/EtOAc): 0.14; IR (NaCl): ν 3413, 2935, 1665, 1539, 1494, 1453, 1267, 1199, 1117, 735, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.40 (brs, 2H), 1.67−1.99 (m, 4H), 2.54 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 2.62−2.75 (m, 1H), 3.03−3.28 (m, 2H), 3.53 (s, 3H), 3.81 (s, 2H), 6.39 (brs, 1H), 7.09−7.23 (m, 3H), 7.24−7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.4, 37.2, 40.0, 40.6, 41.4, 59.0, 71.9, 126.4, 127.4 (2C), 128.6 (2C), 143.9, 169.2; MS (ESI$^+$, *m*/*z*): 251 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for $(C_{14}H_{23}N_2O_2)^+$ [(M + H)$^+$]: 251.1754; found: 251.1760; $[\alpha]_D^{20}$ +5.8 (*c* 1.0, EtOH) for 91% ee. (*S*)-(+)-**11b** (58% yield, 82% ee): R_f (80% MeOH/EtOAc): 0.18; IR (NaCl): ν 3414, 3300, 3050, 2935, 1664, 1603, 1539, 1509, 1222, 1118, 837, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.58−1.93 (m, 4H), 2.49 (brs, 2H), 2.56−2.73 (m, 1H), 2.94−3.25 (m, 4H), 3.31 (s, 3H), 3.75 (s, 2H), 6.48 (brs, 1H), 6.93 (t, $^3J_{HH}$ = 8.5 Hz, 2H), 7.01−7.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.4, 36.9, 38.3, 39.4, 40.4, 58.8, 71.6, 115.3 (d, $^2J_{CF}$ = 21 Hz, 2C), 128.6 (d, $^3J_{CF}$ = 7 Hz, 2C), 139.4, 161.3 (d, $^1J_{CF}$ = 244 Hz), 169.3; MS (ESI$^+$, *m*/*z*): 269 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for $(C_{14}H_{22}FN_2O_2)^+$ [(M + H)$^+$]: 269.1660; found: 269.1668; $[\alpha]_D^{20}$ +3.3 (*c* 1.0, EtOH) for 82% ee. (*S*)-(+)-**11c** (59% yield, 90% ee): R_f (80% MeOH/EtOAc): 0.19; IR (NaCl): ν 3300, 2929, 1664, 1538, 1451, 1198, 1117, 818 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.59−1.94 (m, 4H), 2.16 (brs, 2H), 2.28 (s, 3H), 2.32−2.44 (m, 1H), 2.46−2.70 (m, 2H), 2.96−3.24 (m, 2H), 3.31 (s, 3H), 3.76 (s, 2H), 6.41 (brs, 1H), AB system (δ_A = 7.00 δ_B = 7.06, $^3J_{HH}$ = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.8, 36.4, 37.1, 39.7, 39.9, 40.8, 58.9, 71.7, 127.1 (2C), 129.2 (2C), 135.7, 140.7, 169.2; MS (ESI$^+$, *m*/*z*): 265 [(M + H)$^+$, 100%]; HRMS (ESI$^+$, *m*/*z*) calcd for $(C_{15}H_{25}N_2O_2)^+$ [(M + H)$^+$]: 265.1911; found: 265.1914; $[\alpha]_D^{20}$ +4.1 (*c* 1.0, EtOH)

dx.doi.org/10.1021/jo2007972 |*J. Org. Chem.* 2011, 76, 5709–5718

for 90% ee. (*S*)-(+)-**11d** (51% yield, 86% ee): R_f (80% MeOH/EtOAc): 0.16; IR (NaCl): ν 3411, 2935, 1661, 1611, 1539, 1513, 1248, 1179, 1117, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.52−1.96 (m, 4H), 2.41−2.67 (m, 3H), 2.91−3.21 (m, 2H), 3.31 (s, 3H), 3.73 (s, 3H), 3.75 (s, 2H), 5.01 (brs, 2H), 6.58 (brs, 1H), AB system (δ_A = 6.77 δ_B = 7.03, $^3J_{HH}$ = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.3, 37.0 (2C), 38.8, 40.1, 55.0, 58.9, 71.6, 113.9 (2C), 128.2 (2C), 135.2, 158.0, 169.3; MS (ESI^+, *m*/*z*): 281 [$(M + H)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{15}H_{25}N_2O_3)^+$ [$(M + H)^+$]: 281.1860; found: 281.1861; $[\alpha]_D^{20}$ +8.9 (*c* 1.0, EtOH) for 86% ee. (*S*)-(+)-**11e** (50% yield, >99% ee): R_f (80% MeOH/EtOAc): 0.14; IR (NaCl): ν 3409, 3306, 2936, 1663, 1597, 1541, 1487, 1261, 1117, 735, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.39 (brs, 2H), 1.63−1.96 (m, 4H), 2.42−2.70 (m, 3H), 3.01−3.26 (m, 2H), 3.34 (s, 3H), 3.77 (s, 3H), 3.78 (s, 2H), 6.38 (brs, 1H), 6.66−6.77 (m, 3H), 7.19 (t, $^3J_{HH}$ = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.3, 37.2, 39.9, 40.5, 41.5, 55.0, 58.9, 71.8, 111.3, 113.3, 119.8, 129.5, 145.7, 159.8, 169.2; MS (ESI^+, *m*/*z*): 281 [$(M + H)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{15}H_{25}N_2O_3)^+$ [$(M + H)^+$]: 281.1860; found: 281.1863; $[\alpha]_D^{20}$ +5.6 (*c* 1.0, EtOH) for >99% ee. (*S*)-(+)-**11f** (33% yield, 54% ee): R_f (80% MeOH/EtOAc): 0.15; IR (NaCl): ν 3410, 3307, 2939, 1660, 1593, 1540, 1490, 1263, 1117, 735, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.45 (brs, 2H), 1.59−1.90 (m, 4H), 2.38−2.53 (m, 2H), 2.76−2.90 (m, 1H), 3.15−3.32 (m, 2H), 3.34 (s, 3H), 3.77 (s, 5H), 6.69 (brs, 1H), 6.81 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 6.89 (t, $^3J_{HH}$ = 7.3 Hz, 1H), 7.06−7.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 31.7, 35.9, 36.6, 39.6, 39.9, 55.2, 58.8, 71.8, 110.3, 120.9, 126.9, 127.1, 131.6, 157.1, 168.9; MS (ESI^+, *m*/*z*): 281 [$(M + H)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{15}H_{25}N_2O_3)^+$ [$(M + H)^+$]: 281.1860; found: 281.1858; $[\alpha]_D^{20}$ +9.2 (*c* 1.0, EtOH) for 54% ee.

General Procedure for the Measurement of the Enantiomeric Excess of Compounds 11a−f Obtained by Lipase-Catalyzed Desymmetrization of Diamines 4a−f. To a solution of the corresponding monoamide (*S*)-(+)-**11a−f** (0.08 mmol) in dry CH_2Cl_2 (0.8 mL) were successively added Et_3N (12 μL, 0.09 mmol) and allyl chloroformate (**9**, 10 μL, 0.09 mmol) under nitrogen atmosphere. The mixture was stirred for 2 h at room temperature, and after this time, the solvent was evaporated under reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (60% EtOAc/hexane-100% EtOAc) to afford the corresponding amido carbamate (*R*)-**12a−f** as a colorless oil (94−97%). (*R*)-(−)-**12a** (94% yield, 91% ee): R_f (100% EtOAc): 0.19; IR (NaCl): ν 3321, 2935, 1712, 1663, 1538, 1453, 1256, 1117, 736, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.66−2.01 (m, 4H), 2.55−2.71 (m, 1H), 2.92−3.07 (m, 2H), 3.35 (s, 3H), 3.81 (s, 2H), 4.52 (s, 2H), 4.69 (brs, 1H), 5.19 (d, $^3J_{cis}$ = 10.4 Hz, 1H), 5.27 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.80−5.97 (m, 1H), 6.39 (brs, 1H), 7.08−7.24 (m, 3H), 7.25−7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.2, 36.6, 37.0, 39.1, 41.3, 59.0, 65.3, 71.8, 117.4, 126.7, 127.4 (2C), 128.8 (2C), 132.9, 143.4, 156.1, 169.4; MS (ESI^+, *m*/*z*): 357 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{18}H_{26}N_2NaO_4)^+$ [$(M + Na)^+$]: 357.1785; found: 357.1788; $[\alpha]_D^{20}$ −2.7 (*c* 1.0, EtOH) for 91% ee. (*R*)-(−)-**12b** (95% yield, 82% ee): R_f (100% EtOAc): 0.36; IR (NaCl): ν 3413, 3330, 2935, 1709, 1667, 1537, 1509, 1254, 1224, 1118, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.64−1.82 (m, 2H), 1.83−2.01 (m, 2H), 2.51−2.68 (m, 1H), 2.91−3.06 (m, 2H), 3.07−3.24 (m, 2H), 3.36 (s, 3H), 3.81 (s, 2H), 4.52 (d, $^3J_{HH}$ = 5.4 Hz, 2H), 4.73 (brs, 1H), 5.18 (d, $^3J_{cis}$ = 10.5 Hz, 1H), 5.26 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.80−5.96 (m, 1H), 6.40 (brs, 1H), 6.99 (t, $^3J_{HH}$ = 8.7 Hz, 2H), 7.06−7.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.4, 36.6, 37.0, 39.0, 40.5, 59.0, 65.4, 71.8, 115.5 (d, $^2J_{CF}$ = 21 Hz, 2C), 117.5, 128.6 (d, $^3J_{CF}$ = 7 Hz, 2C), 132.9, 139.1, 156.1, 161.5 (d, $^1J_{CF}$ = 244 Hz), 169.5; MS (ESI^+, *m*/*z*): 375 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{18}H_{25}FN_2NaO_4)^+$ [$(M + Na)^+$]: 375.1691; found: 375.1695; $[\alpha]_D^{20}$ −5.1 (*c* 1.0, EtOH) for 82% ee. (*R*)-(−)-**12c** (96% yield, 90% ee): R_f (100% EtOAc): 0.47; IR (NaCl): ν 3330, 2934, 1697, 1673, 1537, 1452, 1250, 1200, 1117, 922, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.63−2.01 (m, 4H), 2.30 (s, 3H), 2.43−2.64 (m, 1H), 2.92−3.25 (m, 4H), 3.34 (s, 3H), 3.80 (s, 2H), 4.52 (s, 2H), 4.70 (brs, 1H), 5.17 (d, $^3J_{cis}$ = 10.5 Hz, 1H), 5.26 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.79−5.99 (m, 1H), 6.37 (brs, 1H), AB system (δ_A = 7.02 δ_B = 7.10, $^3J_{HH}$ = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.8, 36.3, 36.6, 37.0, 39.1, 40.8, 58.9, 65.3, 71.8, 117.3, 127.1 (2C), 129.3 (2C), 132.9, 136.1, 140.2, 156.1, 169.3; MS (ESI^+, *m*/*z*): 371 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{19}H_{28}N_2NaO_4)^+$ [$(M + Na)^+$]: 371.1941; found: 371.1943; $[\alpha]_D^{20}$ −2.0 (*c* 1.0, EtOH) for 90% ee. (*R*)-(−)-**12d** (97% yield, 86% ee): R_f (100% EtOAc): 0.38; IR (NaCl): ν 3411, 3328, 2963, 1714, 1667, 1536, 1512, 1454, 1248, 1178, 1117, 1035, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.63−1.79 (m, 2H), 1.80−1.96 (m, 2H), 2.50−2.66 (m, 1H), 2.87−3.05 (m, 2H), 3.06−3.21 (m, 2H), 3.35 (s, 3H), 3.77 (s, 3H), 3.80 (s, 2H), 4.51 (d, $^3J_{HH}$ = 5.5 Hz, 2H), 4.72 (brs, 1H), 5.18 (d, $^3J_{cis}$ = 10.5 Hz, 1H), 5.26 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.82−5.97 (m, 1H), 6.39 (brs, 1H), AB system (δ_A = 6.83 δ_B = 7.05, $^3J_{HH}$ = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.4, 36.7, 37.1, 39.1, 40.3, 55.1, 58.9, 65.3, 71.8, 114.0 (2C), 117.4, 128.2 (2C), 132.9, 135.2, 156.1, 158.2, 169.3; MS (ESI^+, *m*/*z*): 387 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{19}H_{28}N_2NaO_5)^+$ [$(M + Na)^+$]: 387.1890; found: 387.1890; $[\alpha]_D^{20}$ −4.1 (*c* 1.0, EtOH) for 86% ee. (*R*)-(−)-**12e** (97% yield, >99% ee): R_f (100% EtOAc): 0.40; IR (NaCl): ν 3327, 2936, 1713, 1665, 1537, 1258, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.61−1.83 (m, 2H), 1.84−1.98 (m, 2H), 2.53−2.66 (m, 1H), 2.95−3.08 (m, 2H), 3.10−3.23 (m, 2H), 3.36 (s, 3H), 3.79 (s, 3H), 3.81 (s, 2H), 4.52 (d, $^3J_{HH}$ = 5.5 Hz, 2H), 4.68 (brs, 1H), 5.19 (d, $^3J_{cis}$ = 10.5 Hz, 1H), 5.25 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.82−5.96 (m, 1H), 6.39 (brs, 1H), 6.67−6.78 (m, 3H), 7.22 (t, $^3J_{HH}$ = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.2, 36.5, 37.0, 39.1, 41.3, 55.1, 59.0, 65.3, 71.8, 111.6, 113.3, 117.4, 119.7, 129.8, 132.9, 145.1, 156.1, 159.9, 169.4; MS (ESI^+, *m*/*z*): 387 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{19}H_{28}N_2NaO_5)^+$ [$(M + Na)^+$]: 387.1890; found: 387.1894; $[\alpha]_D^{20}$ −3.0 (*c* 1.0, EtOH) for >99% ee. (*R*)-(+)-**12f** (97% yield, 54% ee): R_f (100% EtOAc): 0.43; IR (NaCl): ν 3328, 2938, 1711, 1667, 1539, 1256, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.64−1.94 (m, 4H), 2.78−2.96 (m, 2H), 3.03−3.17 (m, 1H), 3.18−3.36 (m, 2H), 3.39 (s, 3H), 3.83 (s, 5H), 4.51 (d, $^3J_{HH}$ = 5.5 Hz, 2H), 4.85 (brs, 1H), 5.18 (d, $^3J_{cis}$ = 10.5 Hz, 1H), 5.25 (d, $^3J_{trans}$ = 17.1 Hz, 1H), 5.82−5.96 (m, 1H), 6.64 (brs, 1H), 6.86 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 6.94 (td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.0 Hz, 1H), 7.09−7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 32.0, 35.7, 35.8, 36.7, 39.1, 55.3, 59.0, 65.2, 71.9, 110.6, 117.3, 121.3, 127.1, 127.4, 131.0, 133.0, 156.1, 157.2, 169.2; MS (ESI^+, *m*/*z*): 387 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{19}H_{28}N_2NaO_5)^+$ [$(M + Na)^+$]: 387.1890; found: 387.1891; $[\alpha]_D^{20}$ +14.0 (*c* 1.0, EtOH) for 54% ee.

General Procedure for the Synthesis of the Racemic Amido Carbamates 12a−f. To a solution of the corresponding diamine **4a−f** (0.50 mmol) in H_2O (50 μL) was added diallyl carbonate (**5**, 72 μL, 0.50 mmol), and the mixture was stirred for 14 h at room temperature. After this time, the solvent was evaporated under reduced pressure, obtaining a crude reaction product that was passed through a plug of SiO_2 (80% MeOH/EtOAc). The solvent was removed by distillation under reduced pressure, isolating a colorless oil that contained the corresponding racemic allyl monocarbamate **6a−f**, which was immediately dissolved in dry CH_2Cl_2 (1 mL), successively adding Et_3N (6 μL, 0.05 mmol) and methoxyacetyl chloride (**18**, 5 μL, 0.05 mmol) under nitrogen atmosphere. The mixture was stirred for 4 h at room temperature, and after this time, the solvent was evaporated under reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (100% EtOAc) to afford the corresponding amido carbamate (±)-**12a−f** as a colorless oil (7−10% for both steps).

Synthesis of (*R*)-5-[(Methysulfonyl)oxy]-3-phenylpentyl Acetate (15). To a solution of (*S*)-5-hydroxy-3-phenylpentyl acetate (**14**, 600 mg, 2.70 mmol) in dry CH_2Cl_2 (27 mL) was added pyridine (292 μL, 4.05 mmol), and the mixture was cooled at 0 °C. Then methanesulfonyl chloride (MsCl, 325 μL, 4.05 mmol) was added and

dx.doi.org/10.1021/jo2007972 |*J. Org. Chem.* 2011, 76, 5709–5718

the resulting solution stirred at room temperature for 14 h after complete disappearance of the starting material. The solvent was evaporated by distillation at reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (30−50% EtOAc/hexane) to yield 786 mg of (*R*)-(−)-**15** as a colorless oil (97%). R_f (50% EtOAc/hexane): 0.47; IR (NaCl): ν 3028, 2941, 1736, 1356, 1245, 1174, 1038, 971, 960, 735, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.84−2.08 (m, 6H), 2.09−2.22 (m, 1H), 2.81−2.94 (m, 4H), 3.78−3.88 (m, 1H), 3.89−4.02 (m, 2H), 4.05−4.14 (m, 1H), 7.11−7.18 (m, 2H), 7.19−7.26 (m, 1H), 7.27−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.8, 35.1, 35.6, 37.0, 38.7, 62.2, 67.9, 126.9, 127.4 (2C), 128.8 (2C), 141.9, 170.8; MS (ESI^+, *m*/*z*): 323 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{14}H_{20}NaO_5S)^+$ [$(M + Na)^+$]: 323.0924; found: 323.0924. $[\alpha]_D^{20}$ −3.6 (*c* 1.0, EtOH) for >99% ee.

Synthesis of (*S*)-5-Azido-3-phenylpentyl Acetate (16). To a solution of compound (*R*)-(−)-**15** (766 mg, 2.55 mmol) in dry DMF (10 mL) was added sodium azide (252 mg, 3.83 mmol) under nitrogen atmosphere, and the resulting suspension stirred at 55 °C during 14 h. After this time, the reaction was quenched with H_2O (25 mL) and the residue extracted with Et_2O (3 × 25 mL). The organic phases were combined and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure, affording a crude reaction product that was purified by flash chromatography (10% EtOAc/hexane) to yield 585 mg of (*S*)-(−)-**16** as a colorless oil (93%). R_f (10% EtOAc/hexane): 0.34; IR (NaCl): ν 2938, 2098, 1738, 1454, 1368, 1243, 1042, 762, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.74−2.07 (m, 7H), 2.74−2.87 (m, 1H), 2.97−3.09 (m, 1H), 3.10−3.21 (m, 1H), 3.80−3.91 (m, 1H), 3.92−4.02 (m, 1H), 7.11−7.18 (m, 2H), 7.18−7.26 (m, 1H), 7.26−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.7, 35.1, 35.5, 39.6, 49.1, 62.3, 126.7, 127.4 (2C), 128.6 (2C), 142.2, 170.8; MS (ESI^+, *m*/*z*): 270 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{13}H_{17}N_3NaO_2)^+$ [$(M + Na)^+$]: 270.1213; found: 270.1215. $[\alpha]_D^{20}$ −5.8 (*c* 1.0, EtOH) for >99% ee.

Synthesis of (*S*)-5-Amino-3-phenylpentan-1-ol (17). To a solution of azide (*S*)-(−)-**16** (565 mg, 2.29 mmol) in MeOH (23 mL) was added PPh_3 (336 mg, 3.43 mmol), and the resulting suspension was stirred until the triphenylphosphine was completely dissolved. After this time, H_2O (61 μL, 3.43 mmol) was added to the reaction vessel and the resulting solution stirred at 50 °C for 14 h, until complete disappearance of the starting material by TLC analysis. Then the solvent was evaporated by distillation at reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (100% MeOH to 10% NH_3/MeOH) to yield 362 mg of (*S*)-(+)-**17** as a colorless oil (88%). R_f (2% NH_3/MeOH): 0.27; IR (NaCl): ν 3357, 3290, 2930, 2869, 1597, 1490, 1451, 1051, 761, 735, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.58−1.90 (m, 4H), 2.48 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 2.63 (brs, 3H), 2.70−2.83 (m, 1H), 3.29−3.48 (m, 2H), 7.05−7.18 (m, 3H), 7.19−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 39.5 (4C), 59.6, 126.0, 127.3 (2C), 128.2 (2C), 144.6; MS (ESI^+, *m*/*z*): 180 [$(M + H)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{11}H_{18}NO)^+$ [$(M + H)^+$]: 180.1383; found: 180.1381. $[\alpha]_D^{20}$ +6.5 (*c* 1.0, EtOH) for >99% ee.

Synthesis of *N*-[(*S*)-5-Hydroxy-3-phenylpentyl]-2-methoxyacetamide (19). To a solution of compound (*S*)-(+)-**17** (100 mg, 0.56 mmol) in dry CH_2Cl_2 (6.0 mL) was added methoxyacetyl chloride (**18**, 50 μL, 0.55 mmol) in small portions at 10 min intervals under nitrogen atmosphere. The mixture was stirred for 4 h at room temperature and then the solvent evaporated under reduced pressure obtaining a crude reaction product that was purified by flash chromatography on silica gel (100% EtOAc), affording 92 mg of the amino amide (*S*)-(+)-**19** as a yellowish oil (66%). R_f (100% EtOAc): 0.27; IR (NaCl): ν 3404, 3336, 2933, 1660, 1541, 1451, 1117, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.67−1.99 (m, 4H), 2.56−2.87 (m, 2H), 3.00−3.24 (m, 2H), 3.31 (s, 3H), 3.33−3.54 (m, 2H), 3.75 (s, 2H), 6.48 (br s, 1H), 7.09−7.20 (m, 3H), 7.21−7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 36.8, 37.1, 39.2, 39.8, 58.8, 60.0, 71,6, 126.2, 127.3 (2C), 128.4 (2C), 143.8, 169.4; MS (ESI^+, *m*/*z*): 274 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{14}H_{21}NNaO_3)^+$ [$(M + Na)^+$]: 274.1414; found: 274.1412; $[\alpha]_D^{20}$ +1.2 (*c* 0.5, EtOH) for >99% ee.

Synthesis of (*S*)-[(5-Methoxyacetyl)amino]-3-phenylpentyl Methanesulfonate (20). To a solution of (*S*)-**19** (57 mg, 0.23 mmol) in dry CH_2Cl_2 (2.3 mL) was added pyridine (25 μL, 0.34 mmol) and the mixture was cooled at 0 °C. Then methanesulfonyl chloride (27 μL, 0.34 mmol) was added and the resulting solution was stirred at room temperature for 14 h after complete disappearance of the starting material. The solvent was evaporated by distillation at reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (100% EtOAc) to yield 57 mg of (*S*)-(+)-**20** as a colorless oil (76%). R_f (100% EtOAc): 0.35; IR (NaCl): ν 3407, 2936, 1670, 1535, 1352, 1173, 1116, 968, 735, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.73−2.05 (m, 3H), 2.06−2.23 (m, 1H), 2.70−2.84 (m, 1H), 2.87 (s, 3H), 3.01−3.26 (m, 2H), 3.34 (s, 3H), 3.78 (s, 2H), 3.87−3.99 (m, 1H), 4.02−4.14 (m, 1H), 6.43 (brs, 1H), 7.10−7.25 (m, $3H_1$), 7.26−7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.6, 35.9, 36.8, 36.9, 39.7, 58.9, 67.8, 71.7, 126.9, 127.3 (2C), 128.7 (2C), 142.1, 169.2; MS (ESI^+, *m*/*z*): 352 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{15}H_{23}NNaO_5S)^+$ [$(M + Na)^+$]: 352.1189; found: 352.1193; $[\alpha]_D^{20}$ +8.8 (*c* 0.5, EtOH) for >99% ee.

Synthesis of *N*-[(*S*)-5-Azido-3-phenylpentyl]-2-methoxyacetamide (21). To a solution of compound (*S*)-(+)-**20** (45 mg, 0.14 mmol) in dry DMF (1.5 mL) was added sodium azide (14 mg, 0.21 mmol) under nitrogen atmosphere, and the resulting suspension was stirred at 55 °C during 14 h. After this time, the reaction was quenched with H_2O (25 mL) and the residue extracted with Et_2O (3 × 25 mL). The organic phases were combined and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure, affording a crude reaction product that was purified by flash chromatography (30% EtOAc/hexane) to yield 36 mg of (*S*)-(+)-**21** as a colorless oil (95%). R_f (30% EtOAc/hexane): 0.10; IR (NaCl): ν 3413, 3325, 2934, 2098, 1669, 1535, 1451, 1262, 1116, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.58−2.06 (m, 4H), 2.61−2.78 (m, 1H), 2.88−3.25 (m, 4H), 3.34 (s, 3H), 3.79 (s, 2H), 6.40 (brs, 1H), 7.09−7.17 (m, 2H), 7.18−7.25 (m, 1H), 7.26−7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.6, 36.1, 37.0, 40.8, 49.1, 58.9, 71.7, 126.7, 127.3 (2C), 128.7 (2C), 142.6, 169.2; MS (ESI^+, *m*/*z*): 299 [$(M + Na)^+$, 100%]; HRMS (ESI^+, *m*/*z*) calcd for $(C_{14}H_{20}N_4NaO_2)^+$ [$(M + Na)^+$]: 299.1478; found: 299.1476; $[\alpha]_D^{20}$ +14.0 (*c* 0.5, EtOH) for >99% ee.

Synthesis of *N*-[(*R*)-5-Amino-3-phenylpentyl]2-methoxyacetamide (11a). To a free-air suspension containing the azide (*S*)-(+)-**21** (30 mg, 0.11 mmol) and Pd−C 10% (8 mg) was connected a H_2 balloon at the same time that deoxygentated MeOH (432 μL) was carefully added to a 25 mL round-bottom flask. 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 solvent was evaporated under reduced pressure, affording 27 mg of (*R*)-(−)-**11a** as a colorless oil (99%). $[\alpha]_D^{20}$ −6.0 (*c* 1.0, EtOH) for >99% ee.

Synthesis of Allyl {(*S*)-5-[(Methoxyacetyl)amino]-3-phenylpentyl}carbamate (12a). To a solution of compound (*R*)-(−)-**11a** (13 mg, 0.05 mmol) in dry CH_2Cl_2 (0.5 mL) were successively added Et_3N (9 μL, 0.07 mmol) and allyl chloroformate (8 μL, 0.07 mmol) under nitrogen atmosphere. The mixture was stirred for 2 h at room temperature, and after this time, the solvent was evaporated under reduced pressure, obtaining a crude reaction product that was purified by flash chromatography (60% EtOAc/hexane to 100% EtOAc) to afford 17 mg of the amido carbamate (*S*)-(+)-**12a** as a colorless oil (98%). $[\alpha]_D^{20}$ +3.1 (*c* 1.0, EtOH) for >99% ee.

■ ASSOCIATED CONTENT

Supporting Information. HPLC methods and full characterization of all novel organic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors
*E-mail: vicgotfer@uniovi.es (V.G.-F.); vgs@uniovi.es (V.G.). Phone: +34 985 103448. Fax: +34 985 103448.

■ ACKNOWLEDGMENT

This work was supported by the Spanish Ministerio de Educación y Ciencia (Project CTQ2007-61126). V. G.-F. thanks the Spanish Ministerio de Ciencia e Innovación (MICINN) for a personal grant (Ramón y Cajal Program). N.R.-L. thanks Gobierno Regional de Asturias (FICYT) for a predoctoral grant (Severo Ochoa Program)

■ DEDICATION

†Dedicated to Francisco Palacios on the occasion of his 60th birthday.

■ REFERENCES

(1) Melchiorre, C.; Bolognesi, M. L.; Minarini, A.; Rosini, M.; Tumiatti, V. *J. Med. Chem.* **2010**, *53*, 5906–5914.
(2) Minarini, A.; Milelli, A.; Tumiatti, V.; Rosini, M.; Bolognesi, M. L.; Melchiorre, C. *Amino Acids* **2010**, *38*, 383–392.
(3) Palmer, A. J.; Wallace, H. M. *Amino Acids* **2010**, *38*, 415–422.
(4) Huang, X.; Roushan, M.; Emge, T. J.; Bi, W.; Thiagarajan, S.; Cheng, J.-H.; Yang, R.; Li, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7871–7874.
(5) Bazzicalupi, C.; Bencini, A.; Lippolis, V. *Chem. Soc. Rev.* **2010**, *39*, 3709–3728.
(6) Alfonso, I. *Mini-Rev. Org. Chem.* **2008**, *5*, 33–46.
(7) Qian, Z. G.; Xia, X. X.; Lee, S. Y. *Biotechnol. Bioeng.* **2011**, *108*, 93–103.
(8) Shearman, J. W.; Myers, R. M.; Brenton, J. D.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 62–65.
(9) Gaedda, T. M.; Yu, X.-Y.; Miyazawa, A. *Tetrahedron* **2010**, *66*, 1249–1253.
(10) Casero, R. A., Jr.; Woster, P. M. *J. Med. Chem.* **2009**, *52*, 4551–4573.
(11) Csuk, R.; Schwartz, S.; Kluge, R.; Stroehl, D. *Eur. J. Med. Chem.* **2010**, *45*, 5718–5723.
(12) Vergara, F. M. F.; Henriques, M. G. M. O.; Candea, A. L. P.; Wardell, J. L.; De Souza, M. V. N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4937–4938.
(13) Carta, F.; Temperini, C.; Innocenti, A.; Scozzafava, A.; Kaila, K.; Supuran, C. T. *J. Med. Chem.* **2010**, *53*, 5511–5522.
(14) Cinelli, M. A.; Cordero, B.; Dexheimer, T. S.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem.* **2009**, *17*, 7145–7155.
(15) Altava, B.; Burguete, M. I.; Carbó, N.; Escorihuela, J.; Luis, S. V. *Tetrahedron: Asymmetry* **2010**, *21*, 982–989.
(16) Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* **1994**, *50*, 4455–4466.
(17) Maeda, T.; Furusho, Y.; Shiro, M.; Takata, T. *Chirality* **2006**, *18*, 691–697.
(18) Burguete, M. I.; Escorihuela, J.; Luis, S. V.; Lledos, A.; Ujaque, G. *Tetrahedron* **2008**, *64*, 9717–9724.
(19) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4759–4762.
(20) Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190–10193.
(21) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484–491.
(22) Zhou, Y.; Dong, J.; Zhang, F.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 588–600.
(23) Ishi-i, T.; Iguchi, R.; Snip, E.; Ikeda, M.; Shinkai, S. *Langmuir* **2001**, *17*, 5825–5833.
(24) Colombo, F.; Annunziata, R.; Raimondi, L.; Benaglia, M. *Chirality* **2006**, *18*, 446–456.
(25) Castagnolo, D.; Raffi, F.; Giorgi, G.; Botta, M. *Eur. J. Org. Chem.* **2009**, 334–337.
(26) Mutulis, F.; Kreicberga, J.; Yahorava, S.; Mutule, I.; Borisova-Jan, L.; Yahorau, A.; Muceniece, R.; Azena, S.; Veiksina, S.; Petrovska, R.; Wikberg, J. E. S. *Bioorg. Med. Chem.* **2007**, *17*, 5787–5810.
(27) Wutts, P. G. M.; Greene, T. W. *Greene's protective groups in organic synthesis*, 4th ed.; John Wiley & Sons Inc.: Hoboken, NJ, 2007.
(28) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231–261.
(29) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354. Recently an update of this perennial review has been published: García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111*, PR110–PR180.
(30) Berkessel, A.; Ong, M.-C.; Nachi, M.; Neudörfl, J.-M. *ChemCatChem* **2010**, *2*, 1215–1218.
(31) Busto, E.; Gotor-Fernández, V.; Montejo-Bernardo, J.; García-Granda, S.; Gotor, V. *Org. Lett.* **2007**, *9*, 4203–4206.
(32) Ríos-Lombardía, N.; Busto, E.; García-Urdiales, E.; Gotor-Fernández, V.; Gotor, V. *J. Org. Chem.* **2009**, *74*, 2571–2574.
(33) García-Urdiales, E.; Busto, E.; Ríos-Lombardía, N.; Gotor-Fernández, V.; Gotor, V. *ChemBioChem* **2009**, *10*, 2875–2883.
(34) Busto, E.; Gotor-Fernández, V.; Montejo-Bernardo, J.; García-Granda, S.; Gotor, V. *Tetrahedron* **2009**, *65*, 8393–8401.
(35) Ríos-Lombardía, N.; Busto, E.; Gotor-Fernández, V.; Gotor, V. *Eur. J. Org. Chem.* **2010**, 484–493.
(36) Ríos-Lombardía, N.; Gotor-Fernández, V.; Gotor, V. *J. Org. Chem.* **2011**, *76*, 811–819.
(37) Sheldon, R. A. *Adv. Synth. Catal.* **2007**, *349*, 1289–1307.
(38) Brady, D.; Jordaan, J. *Biotechnol. Lett.* **2009**, *31*, 1639–1650.
(39) Hanefeld, U.; Gardossi, L.; Magner, E. *Chem. Soc. Rev.* **2009**, *38*, 453–468.
(40) Verma, S. K.; Acharya, B. N.; Kaushik, M. P. *Org. Lett.* **2010**, *12*, 4232–4235.
(41) Fuentes de Arriba, A. L.; Seisdedos, D. G.; Simón, L.; Alcázar, V.; Raposo, C.; Morán, J. R. *J. Org. Chem.* **2010**, *75*, 8303–8306.
(42) Carrea, G.; Riva, S. *Organic Synthesis with Enzymes in Non-Aqueous Medium*; Wiley-VCH: Weinheim, 2008.
(43) Cammenberg, M.; Hult, K.; Park, S. *ChemBioChem* **2006**, *7*, 1745–1749.
(44) Ditrich, K. *Synthesis* **2008**, 2283–2287.
(45) Rodríguez-Mata, M.; Gotor-Fernández, V.; González-Sabín, J.; Rebolledo, F.; Gotor, V. *Org. Biomol. Chem.* **2011**, *9*, 2274–2278.