Candida antarctica Lipase-Catalyzed Doubly Enantioselective Aminolysis Reactions. Chemoenzymatic Synthesis of 3-Hydroxypyrrolidines and 4-(Silyloxy)-2-oxopyrrolidines with Two Stereogenic Centers

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Aminolyses of racemic and prochiral 3-hydroxyesters with racemic amines are effectively catalyzed by *Candida antarctica* lipase. In these processes, the simultaneous resolution of the ester and the amine, or the corresponding asymmetrization−resolution, takes place. In all cases, the high enantioselectivity shown by the lipase toward all the reactants allows the preparation of enantiopure 3-hydroxyamides with very high diastereomeric ratios. These 3-hydroxyamides are used as starting materials in the synthesis of 3-hydroxy- and 2-oxopyrrolidines, both containing two stereogenic centers in their structures.

Introduction

Lipase-catalyzed kinetic resolution of racemates is a well-established method for the preparation of enantiomerically enriched products.[1] In organic solvents, these enzymes have been widely used to catalyze esterification, transesterification, and aminolysis processes.[2] Usually, the reaction is carried out with a racemic or prochiral nucleophile (alcohol or amine) and an achiral acyl donor (acid or ester) or vice versa, achieving the kinetic resolution of the racemate. As the enantiorecognition of the nucleophile and the acyl donor occur at different sites of the lipase,[3] both resolutions could take place in the same reaction. These processes, named "doubly enantioselective", are much less-documented than the simple kinetic resolutions. The interest of these reactions is obvious, because if the lipase shows a high enantioselectivity toward both reagents, a product with both a high diastereomeric ratio (dr) and a high enantiomeric excess (ee), as well as the resolution of the nucleophile and the acyl donor, could be reached in only one step.

Some examples of doubly enantioselective reactions catalyzed by lipases have appeared in the literature but, in most cases, the reactions proceeded with modest diastereoselectivities,[4] except in some interesterifications, in which good diastereomeric ratios were achieved, although at low percentage of conversion.[5] The lack of a good example of this kind of processes can be due to the difficulty in matching an appropriate pair of substrates. In most cases the enantioselectivity of the enzyme toward a given substrate, for example the acyl donor, is affected by the structure of the acyl acceptor and vice versa.[6] This implies that, although high enantioselectivities are attained in the simple kinetic resolution of the substrates, no reliable prediction may be made about the outcome of the double kinetic resolutions. Nevertheless, a good criterion for selecting substrates for a doubly enantioselective process may be that their simple resolutions are efficient themselves.

Here we report some highly diastereo- as well as enantioselective aminolysis reactions mediated by *Candida antarctica* lipase (CAL B) using a racemic [(±)-**1**] and a prochiral (**4**) β-hydroxyester and racemic amines [(±)-**2a**−**c**] as substrates. Several reasons support the selection of these substrates. First of all, lipase-catalyzed aminolysis of esters is an irreversible reaction,[7] which is more convenient for a kinetic resolution process than reversible reactions,[8] namely esterification and transesterification. So far the CAL B (Novozym SP 435) has proven to be the most effective catalyst for the aminolysis reaction in organic solvents. Particularly, this enzyme has shown a great efficiency to catalyze both the simple kinetic resolution of racemic β-hydroxyesters[9] and the asymmetrization of dimethyl 3-hydroxyglutarate[10] by aminolysis reaction, as well as the enantioselective acylation of racemic amines with a broad variety of esters.[11] We chose three different primary amines as nucleophiles, bearing, respectively, a phenyl group, a furyl ring, and a linear alkyl chain at the stereocenter.

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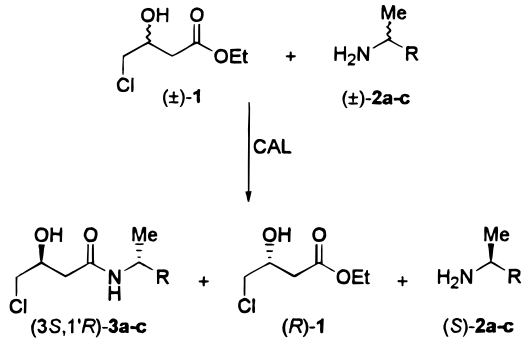
Scheme 1



Moreover, in the search for an efficient doubly enantioselective process, we also took into account the synthetic utility of the products. Thus, the presence of a leaving group (Cl) in the ester **1** allows further chemical transformations of its derivatives.[12] In addition, some optically active 3-hydroxyglutarate derivatives have been used as intermediates for the synthesis of several interesting compounds,[10,13] and optically active amines are useful intermediates in the synthesis of drugs and crop-protecting substances.[11e]

Results and Discussion

Some considerations have to be taken into account for the treatment of the results obtained in the double kinetic resolutions described herein. It is well-known that for a simple kinetic resolution, a relationship exists between the conversion *c*, the ee of the remaining substrate, ee_S, and that of the product, ee_P (eq 1).[14] For a double kinetic resolution there is a similar relationship between *c*, ee_S, and the stereoisomeric composition of the product, simply

$$c = \frac{ee_S}{ee_S + ee_P} \tag{1}$$

$$\phi_{ES} = \frac{\text{(isomers derived from A)} - \text{(isomers derived from B)}}{\text{(isomers derived from A)} + \text{(isomers derived from B)}} \tag{2}$$

considering that the term ee_P in eq 1 must be replaced by a new term, which we have named ϕ (eq 2). As there are two chiral substrates, we must define one ee_S, one ϕ, and one *c* for each one of them, that is, (ee_{ES}, ϕ_{ES}, c_{ES}) for the ester and (ee_{NU}, ϕ_{NU}, c_{NU}) for the nucleophile. Obviously, c_{ES} and c_{NU} must have the same value if both substrates are initially in equimolecular amounts. If A and B are the enantiomers of the ester, M and N the enantiomers of the nucleophile, then the stereoisomers of the product are AM, AN, BM, and BN. On the assumption that A and M are the fast-reacting enantiomers, ϕ_{ES}, c_{ES}, ϕ_{NU}, and c_{NU} are calculated as shown in eqs 3−6.

$$\phi_{ES} = \frac{(AM + AN) - (BM + BN)}{(AM + AN) + (BM + BN)} \tag{3}$$

$$c_{ES} = \frac{ee_{ES}}{ee_{ES} + \phi_{ES}} \tag{4}$$

$$\phi_{NU} = \frac{(AM + BM) - (AN + BN)}{(AM + BM) + (AN + BN)} \tag{5}$$

$$c_{NU} = \frac{ee_{NU}}{ee_{NU} + \phi_{NU}} \tag{6}$$

Double Resolution Reactions. CAL-catalyzed reactions between ethyl (±)-4-chloro-3-hydroxybutanoate [(±)-**1**] and (±)-**2a**−**c** were carried out in 1,4-dioxane at 30 °C in the presence of 4 Å molecular sieves. In these conditions, the lipase only catalyzed the aminolysis of (±)-**1**,[15] and amides **3a**−**c** were obtained, the (3*S*,1′*R*) isomer being major in all cases (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, in the reaction of (±)-**1** with (±)-**2a**, 31% of the starting material was transformed after 6 h (entry 1). The (3*S*,1′*R*):(3*R*,1′*R*) isomeric ratio of 99:1 obtained for the amide **3a** implies that CAL is very enantioselective toward the ester. Likewise the absence of 1′*S* isomers of **3a** indicates that the enantioselectivity toward the amine **2a** is even higher. As a consequence, when the reaction was stopped at ca. 50% conversion (entry 2), the amide (3*S*,1′*R*)-**3a** was obtained with a high diastereomeric ratio (97:3) and enantiopure. Moreover, both remaining substrates **1** and **2a** were also recovered with very high ee at this conversion value. These results show that a truly effective double kinetic resolution has taken place, this being the first time that such a process is reported.

There are two columns with conversion values in Table 1; c_{NMR} is that measured in the ^{1}H NMR spectrum of the crude, and *c* is that calculated with eq 4. In all cases there is a good agreement between those values and also with the isolated yields of the amides (see Experimental Section). Even though we checked that the stereoisomeric composition of **3a** was not altered during the isolation and purification steps, the coincidence of the values of c_{RMN} and *c* corroborates this fact.

The replacement of amine **2a** by **2b** (Table 1, entry 3) did not affect the activity of the lipase but slightly altered its enantioselectivity. The ee of the remaining ester was lower than that in entry 2 (the percentages of conversion being very similar), which means that the enantioselectivity toward the ester slightly decreased when the amine was changed. Nevertheless, the amide (3*S*,1′*R*)-**3b** was also obtained with high diastereomeric ratio (96:4) and enantiopure at a high conversion. Moreover, the amide **3b** was free of the isomers derived from the amine (*S*)-**2b**, thus indicating that the CAL was still totally enantioselective toward the amine **2b**. When amine **2c** was

(11) See, for instance, (a) García, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron Lett.* **1993**, *34*, 6141. (b) Puertas, S.; Brieva, R.; Rebolledo, F.; Gotor, V. *Tetrahedron* **1993**, *49*, 4007. (c) Jaeger, K. E.; Liebeton, K.; Zonta, A.; Schimossek, K.; Reetz, M. T. *Appl. Microbiol. Biotechnol.* **1996**, *46*, 99. (d) Iglesias, L. E.; Sánchez, V. M.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymm.* **1997**, *8*, 2675. (e) Balkenhohl, F.; Ditrich, K.; Hauer, B.; Ladner, W. *J. Prakt. Chem.* **1997**, *339*, 381.

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(15) When molecular sieves were not used, a small amount of 4-chloro-3-hydroxybutanoic acid was also formed. In the absence of the enzyme, starting materials were recovered unchanged.

Table 1. CAL-Catalyzed Aminolysis of (±)-1 with (±)-2a-c

						ratio of stereoisomers of **3a**−**c**[b]				
entry	amine	*t*, h	c_{NMR}[a]	ee_{ES}	ee_{NU}	(3*S*,1′*R*)	(3*R*,1′*S*)	(3*R*,1′*R*)	(3*S*,1′*S*)	*c*[c]
1	**2a**	6	31	43	44	99	−	1	−	31
2	**2a**	24	50	92	93	97	−	3	−	49
3	**2b**	24	52	83	94	96	−	4	−	48
4	**2c**	24	32	49	51	92	−	5	3	35

[a] Calculated from the ^{1}H NMR spectrum of the crude of reaction. [b] Determined as described in the text. [c] Calculated from eqs 4 or 6.

Scheme 2

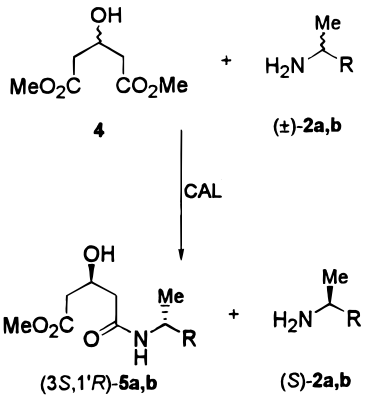


Table 2. CAL-Catalyzed Aminolysis of 4 with (±)-2a,b

					5a,b[b]		
entry	amine	*t*, h	c_{NMR}[a]	ee_{NU}	(3*S*,1′*R*)	(3*R*,1′*R*)	*c*[c]
1	**2a**	24	86	75	98	2	86
2	**2b**	30	85	72	96	4	84

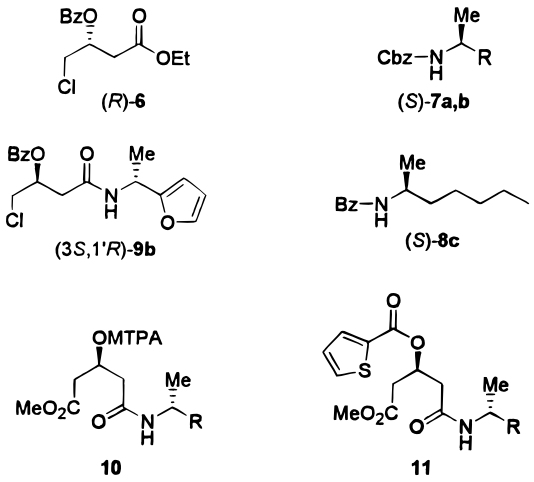
[a] Calculated from the ^{1}H NMR spectrum of the crude products of the reaction and referred to the diester **4**. [b] Ratio of stereoisomers of **5a,b** stereoisomers (3*S*,1′*S*) and (3*R*,1′*S*) were not detected. [c] Calculated from eq 6.

used (Table 1, entry 4), amide (3*S*,1′*R*)-**3c** was isolated with a high diastereomeric ratio (92:8) and enantiopure, though the reaction rate and the enantioselectivity were lower than in the previous cases. The remaining substrates were recovered with low enantiomeric excesses because the conversion (35%) was still far from 50%.

Asymmetrization−Resolution Reactions. These processes were carried out with the prochiral substrate **4** and amines (±)-**2a,b** (Scheme 2) in the same conditions as those for (±)-**1**, but using a 2:1 molar ratio amine: diester in order to allow the 100% conversion of the diester. Although reactions were stopped when no ester could be detected in TLC, some diester **4** remained unreacted, as Table 2 shows. In both reactions the CAL catalyzed the monoaminolysis of **4**, the amidoesters **5a,b** being the only products obtained. The lipase was totally enantioselective toward the amines **2a,b**, exclusively transforming the *R* enantiomer, as had happened in the reactions with substrate (±)-**1**. Moreover, the prochiral selectivity for the ester was also high, 98:2 with amine **2a** and 96:4 with **2b**, amidoesters (3*S*,1′*R*)-**5a,b** being achieved with very high dr and enantiopure. As is indicated in Table 2, there is a good agreement between the conversions determined from the ^{1}H NMR spectrum of the crude (c_{NMR}) and those calculated from eq 6 (*c*).

Determination of the Stereoisomeric Composition and Absolute Configurations. In Scheme 3 are collected the most significant derivatives of the enzymatically prepared compounds that appear in this section.

Scheme 3



The enantiomeric excesses of all the remaining substrates (*R*)-**1** and (*S*)-**2a**−**c** were determined by chiral HPLC (see the Experimetal Section for conditions) after transforming them into suitable derivatives [(*R*)-**6**, (*S*)-**7a,b**, and (*S*)-**8c**].

The absolute configuration of the remaining ester (*R*)-**1** and amine (*S*)-**2c** were determined by comparison of their optical rotations with reported values.[12a,16] For the remaining amines **2a,b**, the *S* configuration was assigned by comparison of the retention times obtained in the HPLC analyses of their carbamates **7a,b** with those of samples of known configuration.

As the remaining ester **1** had the *R* configuration, and the remaining amines **2a**−**c** had the *S* configuration, the major stereoisomer of the enzymatically synthesized amides **3a**−**c** necessarily had the (3*S*,1′*R*) configuration.

The absolute configuration of amidoester **5a** was established as follows. As the remaining amine **2a** had the *S* configuration, the configuration at C-1′ had to be *R*. To determine the configuration at C-3, the diastereomeric mixture (3*S*,1′*R*)- and (3*R*,1′*R*)-**5a** was synthesized from **4** and (*R*)-**2a** and subsequently converted into the *O*-acetyl derivative. Its ^{1}H NMR spectrum gave two peaks at 1.89 and 1.91 ppm for the mixture of the diastereomers. The *O*-acetyl derivative of the enzymatically synthesized amidoester **5a** gave only one peak at 1.89 ppm, which corresponds to the (3*S*,1′*R*) isomer.[17] Similarly, the configuration at carbon 1′ of amidoester **5b** was *R* because the remaining amine **2b** had the *S* configuration. Taking into account that the CAL always forms the 3*S* isomer of the resulting amidoester when **4** reacts with different nucleophiles, such as ammonia, achiral amines,[10] and amine **2a**, the configuration at C-3 of **5b** was

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assumed to be *S*. Therefore, the major isomer of the enzymatically synthesized amidoester **5b** was (3*S*,1′*R*).

The stereoisomeric composition of the amides **3a**−**c** and **5a,b** were all determined by HPLC. The mixtures of the four stereoisomers—two racemic diastereomers—of the amides **3a**−**c** and **5a,b** were obtained by $AlCl_3$ catalyzed reaction of (±)-**2a**−**c** with either (±)-**1** or **4**. These mixtures, that for the sake of brevity we named *rac*-**3a**−**c** and *rac*-**5a,b**, were used to find the optimal conditions for the HPLC analysis. Whereas amides **3a**, **3c**, and **5a** were analyzed directly, the derivatization of amides **3b** and **5b** was necessary. As the absolute configurations of the minor stereoisomers were also determined by HPLC, the analysis of each product is discussed individually in the following paragraphs.

Amide 3a. For *rac*-**3a** four peaks of relative areas 1.3:1:1:1.3 (t_R: 20.4, 24.5, 27.4, 31.1 min) were obtained with the Chiralcel-OD column. These relative areas imply that peaks at 20.4 and 31.1 min, as well as peaks at 24.5 and 27.4 min, were enantiomeric couples. The enzymatically obtained amide **3a** gave only two peaks at 20.4 and 24.5 min, with 99:1 relative areas, thus corresponding to the peak at 20.4 min to the (3*S*,1′*R*) isomer. The comparison of these retention times with those of the mixture of diastereomers (3*S*,1′*R*)-**3a** and (3*R*,1′*R*)-**3a**, prepared by $AlCl_3$-catalyzed reaction of (±)-**1** and optically active (*R*)-**2a,** showed that the minor stereoisomer of the enzymatic sample was the (3*R*,1′*R*).

Amide 3b. Amide **3b** had to be transformed into its *O*-benzoyl derivative **9b** for its analysis. *rac*-**9b** gave three peaks of relative areas 1:1:2 (t_R: 15.2, 16.3, 18.9 min) with the Chiralcel-OD column, which means that the third peak contained two stereoisomers. Besides, the two first peaks were partially overlapped. The enzymatic sample **9b**, which mainly contained the (3*S*,1′*R*) isomer, gave only one peak at 15.2 min. Due to the partial overlapping, the presence of a small amount of the stereoisomer at 16.3 min could not be discarded. As nothing was detected at 18.9 min, it must be concluded that the enzyme only formed either one or two out of the four possible stereoisomers of the amide. To decide whether there were one or two isomers, the two samples of **9b**—*rac* and enzymatic—were analyzed with an achiral HPLC column (Lichrosorb). *rac*-**9b** gave two peaks of equal areas at 8.8 and 10.7 min, whereas the enzymatic sample gave the same two peaks but with relative areas 4:96. This means that only two stereoisomers were formed by the enzyme, and that they were diastereomers. Moreover, as the enantiomeric excess of the remaining amine (*S*)-**2b** was higher than that of the remaining ester (*R*)-**1** (see Table 1, entry 3), the configuration of the minor isomer must be (3*R*,1′*R*).

Amide 3c. For *rac*-**3a** four peaks of equal areas (t_R: 29.7, 34.7, 37.7, and 40.4 min) were obtained with the Chiralcel-OD column. The enzymatically obtained amide **3c**, containing mainly the (3*S*,1′*R*) isomer, gave three peaks at 29.7, 34.7, and 40.4 min, with relative areas of 5:92:3. As the enzymatic formation of the (3*R*,1′*S*) isomer was highly improbable because the enzyme should have accepted simultaneously the disfavored enantiomers of the two substrates, the two minor isomers detected had to be the (3*S*,1′*S*) and the (3*R*,1′*R*). The unequivocal assignment of the peaks to these two enantiomers was not possible; however, based on their relative areas and on the ee's of the remaining substrates, we tentatively assigned them as shown in Table 1.

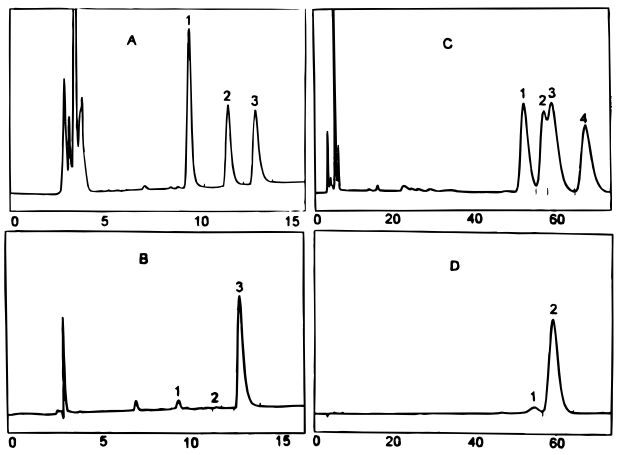


Figure 1. HPLC chromatograms of compounds **10** (with Lichrosorb column) and **11** (with Chiralcel OD column). A: *rac*-**10**. B: Chemoenzymatically synthesized **10**; relative area 96:4. C: *rac*-**11**. D: Chemoenzymatically synthesized **11**; relative area 96:4.

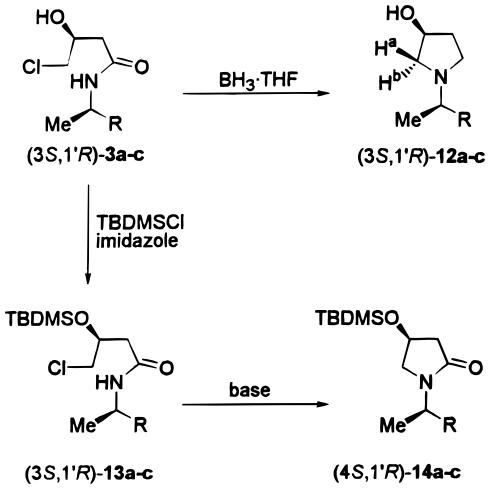
Amide 5a. For *rac*-**5a** four peaks of equal areas (t_R: 21.0, 25.7, 29.0, 30.6 min) were obtained with the Chiralcel-OD column. The enzymatically obtained amide **5a** gave only two peaks at 21.0 and 25.7 min of relative area 98:2. Comparison of these retention times with those of the mixture of (3*S*,1′*R*)- and (3*R*,1′*R*)-**5a**, obtained by $AlCl_3$-catalyzed reaction of **4** and optically active (*R*)-**2a**, showed that the major stereoisomer of the enzymatic sample was the (3*S*,1′*R*) and that the minor stereoisomer was the (3*R*,1′*R*).

Amide 5b. The stereoisomers of this compound were not resolved in the HPLC chiral column. Several derivatives of **5b** were prepared, but none of them gave a good separation of the four stereoisomers in the available columns. However, the combination of the results for two different derivatives of **5b**, the MTPA ester **10** and the *O*-(2-thienylcarbonyl) ester **11**, allowed us to determine the stereoisomeric composition of the enzymatically obtained **5b** (Figure 1).

From chromatogram B we deduced that there was a 96% of the major stereoisomer and that the other 4% may correspond either to one or to two stereoisomers. To decide whether the minor peak corresponded to one or to two isomers, derivative **11** was analyzed. As chromatogram D shows, there was a 4% amount of one single stereoisomer. Therefore, the chemoenzymatically prepared samples **10** and **11** were composed of only two out of the four possible stereoisomers, in a 96:4 ratio. Finally, the enzymatically synthesized **11** gave two peaks of relative areas 96:4 when analyzed in an achiral column (chromatogram not shown), indicating that those two stereoisomers were diastereomers and not enantiomers.

In conclusion, the CAL transformed the *R* enantiomer of the amines **2a**−**c**, the *S* enantiomer of the ester **1**, and the pro-*R* group of ester **4**, affording the amides **3a**−**c** and **5a,b** with (3*S*,1′*R*) configuration. The minor stereoisomers of the amides **3a** and **5a** were (3*R*,1′*R*), which means that the lipase was totally enantioselective to the amine **2a**. On the basis of these results and on the fact that the ee's of the remaining amines (*S*)-**2a**−**c** were always higher than those of the remaining ester (*R*)-**1**, the same configuration (3*R*,1′*R*) for the minor stereoisomer of the amides **3b,c** and **5b** was assumed. The stereochemical preference of the CAL toward the *R*

Scheme 4



enantiomer of the amines follows the rule proposed by Kazlauskas for secondary alcohols and the isosteric primary amines.[18]

Synthesis of 3-Hydroxypyrrolidines and 4-(Silyloxy)-2-oxopyrrolidines. Optically active 4-chloro-3-hydroxybutanamides obtained in this work could be transformed by reduction into 1,3-amino alcohols. Due to the presence of the leaving group at C-4 position, the resulting amine function could experiment a cyclization reaction to yield 3-pyrrolidinols. Optically active 3-pyrrolidinols are constituents of several bioactive compounds[19] and can be used as intermediates for the synthesis of other interesting molecules.[20]

Treatment of amides (3*S*,1′*R*)-**3a**−**c** with BH_3·THF[21] gave the corresponding pyrrolidinols (3*S*,1′*R*)-**12a**−**c** (Scheme 4) with very high yields (96% for **12a** and **12c**) and high purity in most cases. To ensure that no significant epimerization occurred during the cyclization step, the 1.3:1 mixture of diastereomers of amide *rac*-**3a** was transformed into pyrrolidinol *rac*-**12a**. Its ^{1}H NMR spectrum in $CDCl_3$ showed separate signals for the H^b proton (see Scheme 4) of the two diastereomers at 2.76 (dd) and 2.97 (dd) ppm, respectively. In contrast, the spectrum of the chemoenzymatically synthesized pyrrolidinol (3*S*,1′*R*)-**12a** showed only the signal at 2.76 ppm, which excluded the presence of the minor diastereomer. Therefore, no significant racemization of any of the two stereogenic centers occurred during the cyclization step.

The enzymatically obtained amides **3a**−**c** are also immediate precursors of γ-lactams. Optically active γ-lactams are used as synthetic intermediates[22] and as chiral auxiliaries.[23] As a base was required for the cyclization of **3a**−**c**, the hydroxyl group had to be protected in order to prevent side reactions.[24] Silylation of amides (3*S*,1′*R*)-**3a**−**c**, and subsequent treatment of the *O*-silylated amides (3*S*,1′*R*)-**13a**−**c** with NaH or *t*-BuOK, afforded (3*S*,1′*R*)-**14a**−**c** in good yields.

The NMR spectra of compunds (4*S*,1′*R*)-**14a,b** showed the presence of only one diastereomer, thus ruling out the possibility of epimerization. However, the ^{1}H NMR spectrum of (4*S*,1′*R*)-**14c** had a small amount of the minor stereoisomer, due to the fact that its precursor amide **3c** had a 92:8 dr (see Table 1).

Conclusions

The work presented in this paper demonstrates that doubly enantioselective enzymatic reactions can be efficiently performed with a rational selection of the enzyme, substrates, and experimental conditions. Besides the interest of these reactions from the enzymatic point of view, these enzymatic processes have a great synthetic value because the diastereo- and enantioselective formation of one product, starting from racemic substrates, is achieved in one single step. Moreover, the enzymatically formed products are useful for the chemoenzymatic synthesis of some interesting optically active heterocycles.

Experimental Section

General. *Candida antarctica* lipase B, SP 435, was donated by Novo Nordisk Co. It was kept under vacuum (rt, 10^{-4} Torr) for 2 days before use. All reagents were purchased from Aldrich Chemie. Solvents were distilled over a suitable desiccant and stored under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). Chiral HPLC analyses were performed using a Chiralcel OD column (Daicel). For nonchiral HPLC analyses, a Lichrosorb column was used.

General Procedure for the Enzymatic Aminolysis of (±)-1. Ester (±)-**1** (5 mmol, 833 mg) and the corresponding amine (±)-**2a**−**c** (5 mmol) were added to a suspension of CA lipase (1 g) and 700 mg of 4 Å molecular sieves (activated powder) in 1,4-dioxane (20 mL) under nitrogen atmosphere. The suspension was shaken at 30 °C and 250 rpm until the desired conversion was reached. At completion, the enzyme and the molecular sieves were filtered over a Celite pad and washed with CH_2Cl_2 (4 × 10 mL). $HCl_{(g)}$ was bubbled through the organic solution to form the corresponding amine hydrochloride, which was extracted with H_2O (5 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 5 mL) to minimize the loss of amide **3a**−**c**. The combined organic extracts were dried, evaporated, and analyzed by ^{1}H NMR to determine the conversion. Finally, the remaining substrate (*S*)-**1** and the product (3*S*,1′*R*)-**3a**−**c** were separated by flash chromatography (hexane:AcOEt 1:1). Yields of amides **3a**−**c** are referred to the initial amount of ester **1**.

(3*S*,1′*R*)- 4-Chloro-3-hydroxy-*N*-(1-phenylethyl)butanamide (3a). Yield, 45%. White solid; mp 88−90 °C; $[\alpha]^{25}_D$ +53.0 (*c* 1.0, $CHCl_3$), >99% ee, 99:1 dr; IR (KBr): 3443, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, d, *J* = 7.0 Hz), 2.38−2.57 (2H, m), 3.40−3.65 (2H, m), 4.17 (1H, m), 5.09 (1H, m), 6.32 (1H, br d, *J* = 6.7 Hz), 7.20−7.42 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.83, 39.40, 48.07, 48.79, 68.37, 125.82, 127.19, 128.50, 142.85, 170.40; MS *m*/*z* 241 (M^+, 80), 120 (71), 106 (100), 105 (97). Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.76; H, 6.58; N, 5.52.

(3*S*,1′*R*)- 4-Chloro-*N*-[1-(2-furyl)ethyl]-3-hydroxybutanamide (3b). Yield, 44%. White solid; mp 86−87 °C; $[\alpha]^{25}_D$ +83.5 (*c* 1.0, $CHCl_3$), >99% ee, 96:4 dr; IR (KBr): 3350, 3283,

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(24) For example, the epoxidation of the chlorohydrin and the subsequent β-elimination and epoxide opening.

1640, 1549 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (3H, d, $J = 7.0$ Hz), 2.41−2.62 (2H, m), 3.50−3.65 (2H, m), 4.20 (2H, m), 5.21 (1H, m), 6.19 (1H, dt, $J = 0.9$, 3.2 Hz), 6.25 (1H, br s), 6.31 (1H, dd, $J = 1.8$, 3.2 Hz), 7.34 (1H, dd, $J = 0.9$, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 19.21, 39.38, 42.72, 48.02, 68.33, 105.50, 110.06, 141.70, 154.80, 170.32; MS *m/z* 231 (M^+, 100), 110 (80), 95 (78). Anal. Calcd for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.09; N, 6.05. Found: C, 52.06; H, 6.20; N, 5.94.

(3*S*,1′*R*)-4-Chloro-*N*-(2-heptyl)-3-hydroxybutanamide (3c). Yield, 32%. White solid, mp 70−72 °C; $[\alpha]^{25}_D$ −24 (*c* 0.95, $CHCl_3$), >99% ee, 92:8 dr; IR (KBr): 3350, 1636, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, $J = 6.7$ Hz), 1.14 (3H, d, $J = 6.5$ Hz), 1.20−1.39 (6H, m), 1.39−1.51 (2H, m), 2.43−2.55 (2H, m), 3.51−3.63 (2H, m), 3.99 (1H, m), 4.19 (1H, m), 4.34 (1H, d, $J = 4.7$ Hz), 5.62 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 13.52, 20.22, 22.07, 25.26, 31.18, 36.09, 39.41, 44.90, 47.84, 68.19, 170.29; MS *m/z* 235 (M^+, 5), 186 (38), 166 (42), 164 (83), 44 (100). Anal. Calcd for $C_{11}H_{22}ClNO_2$: C, 56.04; H, 9.41; N, 5.94. Found: C, 56.15; H, 9.28; N, 5.71.

Chiral HPLC Analysis of the Remaining Substrates of the Enzymatic Reactions. Ethyl (*R*)-4-Chloro-3-hydroxybutanoate (1). $[\alpha]^{25}_D$ +21.0 (*c* 1.0, $CHCl_3$, 99% ee). Lit.[12a] for (*S*)-**1**: $[\alpha]^{25}_D$ −11.7 (*c* 5.75, $CHCl_3$, 55% ee). The enantiomeric excess was determined by chiral HPLC analysis of its *O*-benzoyl derivative (*R*)-**6**: t_R 14.3 min; for (±)-**6** t_R 13.0 and 14.3 min; Rs 2.2 (*n*-hexane:propan-2-ol 96:4, 0.5 mL/min).

(*S*)-1-Phenylethylamine (2a). The hydrochloride of (*S*)-**2a** was conventionally transformed into its benzyl carbamate (*S*)-**7a**,[25] which was analyzed by chiral HPLC: t_R 13.1 min; for (±)-**7b** t_R 13.1 and 15.2 min; Rs 2.8 (*n*-hexane:propan-2-ol 90:10, 0.8 mL/min). For the assignment of the HPLC peaks, enantiopure (*R*)-**7a** was synthesized from commercial (*R*)-**2a**. For (*S*)-**7a**: $[\alpha]^{25}_D$ −35.2 (*c* 1.0, $CHCl_3$, 93% ee).

(*S*)-2-Furylethylamine (2b). The hydrochloride of (*S*)-**2b** was transformed into its benzyl carbamate (*S*)-**7b**,[25] which was analyzed by chiral HPLC:[11d] t_R 14.8 min; for (±)-**7b** t_R 14.8 and 17.0 min; Rs 2.6 (*n*-hexane:propan-2-ol 90:10, 0.6 mL/min). For (*S*)-**7b**: $[\alpha]^{25}_D$ −59.6 (*c* 1.0, $CHCl_3$, 94% ee).

(*S*)-2-Heptylamine (2c). $[\alpha]^{25}_D$ +0.4 (*c* 10, MeOH, 51% ee). Lit.[16] for (*R*)-**2c**: $[\alpha]^{25}_D$ −0.8 (*c* 10, MeOH). The enantiomeric excess was determined by chiral HPLC analysis of its benzamide derivative (*S*)-**8c**, obtained by treatment of (*S*)-**2c** with benzoyl chloride and pyridine: t_R 13.6 min; for (±)-**8c** t_R 12.1 and 13.6 min; Rs 1.9 (*n*-hexane:propan-2-ol 95:5, 1 mL/min). For (*S*)-**8c**: $[\alpha]^{25}_D$ +9.0, (*c* 1.0, $CHCl_3$, 51% ee).

General Procedure for the Enzymatic Aminolysis of 4. The same procedure as for (±)-**1** was followed, except that 10 mmol of the racemic amines (±)-**2a,b** were used.

Methyl (3*S*,1′*R*)-3-Hydroxy-4-[*N*-(1-phenylethyl)carbamoyl]butanoate (5a). Yield, 69%. White solid; mp 60−61 °C; $[\alpha]^{25}_D$ +62.2 (*c* 1.0, $CHCl_3$), >99% ee, 98:2 dr; IR (KBr): 3400, 3331, 1726, 1643, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (3H, d, $J = 6.9$ Hz), 2.32−2.43 (2H, m, $J = 3.8$, 8.1, 15.2 Hz), 2.44−2.57 (2H, m, $J = 4.9$, 7.9, 16.1 Hz), 3.68 (3H, s), 4.16 (1H, d, $J = 3.5$ Hz, OH), 4.38 (1H, m), 5.11 (1H, m), 6.49 (1H, da, $J = 7.0$ Hz, NH), 7.22−7.40 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.74, 40.60, 41.65, 48.46, 51.53, 65.06, 125.76, 128.32, 126.96, 142.98, 170.40, 172.06; MS *m/z* 265 (M^+, 7), 120 (100), 106 (69), 105 (80). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.27; H, 6.99; N, 5.21.

Methyl (3*S*,1′*R*)-4-{*N*-[1-(2-Furyl)ethyl]carbamoyl}-3-hydroxybutanoate (5b). Yield, 65%. White solid; mp 40−41 °C; $[\alpha]^{25}_D$ +82.1 (*c* 1.0, $CHCl_3$), >99% ee, 96:4 dr; IR (KBr): 3295, 1730, 1647, 1547 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3H, d, $J = 7.0$ Hz), 2.37 (2H, m), 2.48 (2H, m), 3.63 (3H, s), 4.17 (1H, br s, OH), 4.34 (1H, m), 5.14 (1H, m), 6.13 (1H, d, $J = 3.2$ Hz), 6.24 (1H, dd, $J = 1.9$, 3.2 Hz), 6.51 (1H, da, $J = 8.6$ Hz, NH), 7.28 (1H, dd, $J = 0.9$, 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.17, 40.52, 41.67, 42.51, 51.59, 65.05, 105.29, 109.95, 141.62, 155.03, 170.38, 172.12; MS *m/z* 255 (M^+, 4), 110 (100), 95 (61). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.56; H, 6.99; N, 5.49.

General Procedure for the $AlCl_3$-Catalyzed Synthesis of Amides *rac*-3a-c and *rac*-5a,b as Standards for the Chiral HPLC Analysis. The corresponding amine (±)-**2a−c** (9 mmol) was added over a stirred suspension of $AlCl_3$ (4.5 mmol, 600 mg) in 1,2-dichloroethane (2 mL) at 0 °C. After allowing to warm to room temperature, the corresponding ester, (±)-**1** or **4** (3 mmol), was added. The mixture was stirred overnight and quenched with water (2 mL). After stirring for 30 min, the mixture was filtered through Celite and the organic phase separated. The aqueous phase was extracted with dichloromethane, and the combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was chromatographed using hexane:AcOEt 2:1 as eluent, affording the correponding amides in 9−34% yield.

(3*S*,1′*R*)-3-Hydroxy-*N*-(1-phenylethyl)pyrrolidine (12a). Over a solution of amide (3*S*,1′*R*)-**3a** (0.7 mmol, 169 mg) in anhydrous THF (20 mL) was added 1 M BH_3·THF (2 mL). The reaction mixture was refluxed under nitrogen for 4 h. Then, the excess of borane was destroyed at room temperature with H_2O (2 mL). After distilling the solvents at reduced pressure, the resulting solid was dissolved in 6 N HCl (5 mL) and refluxed for 3 h. The solvent was evaporated at reduced pressure, and, finally, the remaining solid was dissolved in 5% LiOH (5 mL) and extracted with dichloromethane. The organic phase was dried and concentrated to yield 129 mg (96%) of the pure product. White solid; mp 75−77 °C; $[\alpha]^{25}_D$ +34.8 (*c* 1.0, $CHCl_3$); IR (KBr): 3200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (3H, d, $J = 6.4$ Hz), 1.65 (1H, m), 2.08 (1H, m), 2.37 (1H, m), 2.51 (1H, dd, $J = 5.6$, 10.5 Hz), 2.64 (1H, m), 2.76 (1H, dd, $J = 2.5$, 10.5 Hz), 3.26 (1H, q, $J = 6.7$ Hz), 3.90 (1H, br s, OH), 4.23 (1H, m), 7.12−7.31 (5H, m); ^{13}C NMR ($CDCl_3$) δ 22.52, 34.43, 51.32, 61.52, 65.40, 70.57, 126.86, 126.98, 128.14, 144.41; MS *m/z* 191 (M^+, 9), 176 (100), 105 (73). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.43; H, 8.71; N, 7.12.

(3*S*,1′*R*)-*N*-[1-(2-Furyl)ethyl]-3-hydroxypyrrolidine (12b). Prepared as described for **12a**, except that the acid treatment was carried out using 3 N HCl, stirring the mixture for 1 h at room temperature. The reaction crude was purified by flash chromatography using CH_2Cl_2:MeOH:(30% NH_4OH) 400:30:1 as eluent, obtaining a 69% yield of the pure product. White solid; mp 49−50 °C; $[\alpha]^{25}_D$ +36.9 (*c* 1.0, $CHCl_3$); IR (KBr): 3424 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (3H, d, $J = 6.9$ Hz), 1.72 (1H, m), 2.13 (1H, m), 2.48 (1H, m), 2.64 (1H, dd, $J = 5.4$, 10.3 Hz), 2.72−2.84 (2H, m), 2.90 (1H, br s, OH), 3.68 (1H, q, $J = 6.9$ Hz), 4.32 (1H, m), 6.17 (1H, d, $J = 3.0$ Hz), 6.31 (1H, dd, $J = 1.8$, 3.0 Hz), 7.35 (1H, dd, $J = 0.9$, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.20, 34.26, 49.21, 55.77, 60.04, 70.39, 106.55, 109.70, 141.37, 155.52; MS *m/z* 181 (M^+, 13), 166 (100), 95 (84). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.19; H, 8.51; N, 7.92.

(3*S*,1′*R*)-*N*-(2-Heptyl)-3-hydroxypyrrolidine (12c). Prepared from (3*S*,1′*R*)-**3c** (0.7 mmol, 165 mg) as described for **12a**. Yield, 96%. Oil; $[\alpha]^{25}_D$ +15.9 (*c* 1.0, $CHCl_3$); IR (neat): 3340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3H, t, $J = 6.9$ Hz), 0.99 (3H, d, $J = 6.5$ Hz), 1.10−1.48 (7H, m), 1.51 (1H, m), 1.66 (1H, m), 2.09 (1H, m), 2.19−2.39 (2H, m), 2.52−2.70 (2H, m), 2.84 (1H, m), 3.54 (1H, br s, OH), 4.25 (1H, m); ^{13}C NMR ($CDCl_3$) δ 13.95, 17.36, 22.53, 25.54, 32.04, 34.48, 34.78, 49.60, 58.72, 60.00, 70.60; MS *m/z* 184 [$(M - 1)^+$, 35], 114 (100), 57 (42); HRMS *m/z* calcd for $C_{11}H_{23}NO$ 184.1701 (M − 1), found 184.1704.

(3*S*,1′*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-chloro-*N*-(1-phenylethyl)butanamide (13a). TBDMS chloride (1.4 mmol, 211 mg), imidazole (2.1 mmol, 143 mg), and a catalytic amount of DMAP (5 mg) were added under nitrogen over a solution of amide (3*S*,1′*R*)-**3a** (0.7 mmol, 169 mg) in dried dichloromethane (3 mL). The reaction was stirred overnight and stopped by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was washed twice with dichloromethane, and the combined organic extracts were dried and concentrated. Flash chromatography of the crude product (hexane:Et_2O 2:1) afforded 227 mg (91%) of the pure product.

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White solid; mp 104−106 °C; $[\alpha]^{25}_D$ +45.6 (*c* 1.0, $CHCl_3$); IR (KBr): 3267, 1640, 1561 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (3H, s), 0.1 (3H, s), 0.82 (9H, s), 1.50 (3H, d, J = 6.9 Hz), 2.42 (1H, dd, J = 6.2, 14.6 Hz), 2.57 (1H, dd, J = 4.7, 14.6 Hz), 3.55 (2H, d, J = 5.16 Hz), 4.32 (1H, m), 5.11 (1H, m), 6.20 (1H, br s, NH), 7.32 (5H, m); ^{13}C NMR ($CDCl_3$) δ −5.08, −4.93, 17.76, 21.67, 25.50, 41.89, 47.98, 48.78, 69.36, 126.18, 128.52, 127.27, 142.76, 168.74; MS *m*/*z* 355 (M^+, <1), 298 (M^+-57, 49), 194 (84), 105 (100). Anal. Calcd for $C_{18}H_{30}ClNO_2Si$: C, 60.73; H, 8.49; N, 3.93. Found: C, 60.72; H, 8.36; N, 3.83.

(3*S*,1′*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-chloro-*N*-[1-(2-furyl)ethyl]butanamide (13b). Prepared from (3*S*,1′*R*)-**3b** (0.7 mmol, 162 mg) as described for **13a**. Yield, 228 mg (94%). White solid; mp 62−64 °C; $[\alpha]^{25}_D$ +57.8 (*c* 0.8, $CHCl_3$); IR (KBr): 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3H, s), 0.10 (3H, s), 0.83 (9H, s), 1.46 (3H, d, J = 6.7 Hz), 2.33−2.62 (2H, m), 3.52 (2H, d, J = 5.5 Hz), 4.29 (1H, m), 5.19 (1H, m), 6.16 (1H, dt, J = 3.4 Hz), 6.28 (1H, dd, J = 1.8, 3.4 Hz), 6.44 (1H, br d, NH), 7.31 (1H, dd, J = 0.9, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ −5.21, −4.98, 17.69, 19.46, 25.44, 41.78, 42.59, 47.89, 69.34, 105.53, 109.95, 141.59, 154.88, 168.74; MS *m*/*z* 345 (M^+, 4), 288 (24), 194 (78), 95 (100), 75 (80). Anal. Calcd for $C_{16}H_{28}ClNO_3Si$: C, 55.55; H, 8.16; N, 4.05. Found: C, 55.34; H, 8.28; N, 4.43.

(3*S*,1′*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-chloro-*N*-(2-heptyl)butanamide (13c). Prepared from (3*S*,1′*R*)-**3c** (0.7 mmol, 165 mg) as described for **13a**. Yield, 206 mg (84%). White solid; mp 51−53 °C; $[\alpha]^{25}_D$ −6.1 (*c* 1.0, $CHCl_3$); IR (KBr): 3269, 1640, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (3H, s), 0.10 (3H, s), 0.78−0.92 (12H, m), 1.09 (3H, d, J = 6.5 Hz), 1.21−1.48 (8H, m), 2.36 (1H, dd, J = 6.0, 15.0 Hz), 2.50 (1H, dd, J = 4.7, 15.0 Hz), 3.50 (2H, d, J = 5.2 Hz), 3.91 (1H, m), 4.29 (1H, m), 5.88 (1H, br d, J = 8.2 Hz, NH); ^{13}C NMR ($CDCl_3$) δ −5.06, −4.96, 13.85, 17.75, 20.67, 22.37, 25.52, 31.51, 36.54, 25.52, 41.94, 45.06, 47.98, 69.38, 168.84; MS *m*/*z* 334 (M^+ − 15, 4), 292 (M^+ − 57, 100). Anal. Calcd for $C_{17}H_{36}ClNO_2Si$: C, 58.34; H, 10.37; N, 4.00. Found: C, 58.23; H,10.28; N, 4.20.

(4*S*,1′*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-oxo-*N*-(1-phenylethyl)pyrrolidine (14a). NaH (1 mmol, 24 mg) was added over a solution of (3*S*,1′*R*)-**13a** (0.6 mmol, 214 mg) in anhydrous THF (30 mL) under nitrogen. The reaction mixture was refluxed until the substrate was consumed (3 h). After cooling to room temperature, saturated aqueous solution of NH_4Cl (30 mL) was added and the product was extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried and concentrated. Flash chromatography of the crude product (hexane:AcOEt 2:1) afforded 174 mg (91%) of the pure product. White solid; mp 67−69 °C; $[\alpha]^{25}_D$ +70.3 (*c* 1.0, $CHCl_3$); IR (KBr): 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.05 (3H, s), 0.02 (3H, s), 0.81 (9H, s), 1.49 (3H, d, J = 7.2 Hz), 2.37 (1H, dd, J = 2.2, 16.7 Hz), 2.65 (1H, dd, J = 6.0, 16.7 Hz), 2.92 (1H, dd, J = 1.82, 10.3 Hz), 3.47 (1H, dd, J = 5.2, 10.3 Hz), 4.39 (1H, m), 5.51 (1H, q, J = 7.2 Hz), 7.20−7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ −5.10, −5.01, 16.55, 17.67, 25.47, 41.81, 48.17, 51.70, 65.33, 127.07, 126.65, 128.32, 139.94, 172.25; MS *m*/*z* 262 (M^+ − 57, 74), 158 (94), 105 (100). Anal. Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66; H, 9.15; N, 4.38. Found: C, 67.55; H, 9.04; N, 4.58.

(4*S*,1′*R*)-4-(*tert*-Butyldimethylsilyloxy)-*N*-[1-(2-furyl)-ethyl]-2-oxopyrrolidine (14b). Potassium *tert*-butoxide (0.6 mmol, 67 mg) was added portionwise over a solution of (3*S*,1′*R*)-**13b** (0.6 mmol, 208 mg) in anhydrous THF (30 mL) in an ice bath. The reaction mixture was allowed to warm and stirred for 1 h. After adding 30 mL of a saturated aqueous solution of NH_4Cl, the product was extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried and concentrated. Flash chromatography of the crude product (hexane:AcOEt 2:1) afforded 117 mg (63%) of the pure product. Oil; $[\alpha]^{25}_D$ +77.8 (*c* 1.2, $CHCl_3$); IR (KBr): 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 (3H, s), 0.02 (3H, m), 0.81 (9H, s), 1.43 (3H, d, J = 7.3 Hz), 2.35 (1H, dd, J = 16.8, 3.7 Hz), 2.62 (1H, dd, J = 16.8, 6.4 Hz), 2.92 (1H, dd, J = 3.1, 10.1 Hz), 3.49 (1H, dd, J = 10.1, 5.7 Hz), 4.4 (1H, m), 5.45 (1H, m), 6.21 (1H, dd, J = 1.1, 3.2 Hz), 6.28 (H, dd, J = 1.9, 3.2 Hz), 7.32 (H, dd, J = 1.1, 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ −5.08, −5.01, 15.61, 17.68, 25.44, 41.52, 43.68, 51.79, 65.17, 106.61, 109.82, 141.98, 153.36, 172.02; MS *m*/*z* 252 (M^+ − 57, 77), 158 (88), 95 (100); HRMS *m*/*z* calcd for $C_{16}H_{27}NO_3Si$ 309.1760, found 309.1787.

(4*S*,1′*R*)-4-(*tert*-Butyldimethylsilyloxy)-*N*-(2-heptyl)-2-oxopyrrolidine (14c). Prepared from (3*S*,1′*R*)-**13c** (0.6 mmol, 210 mg) as described for **14a**. Yield, 118 mg (62%). White solid; mp 46−48 °C; $[\alpha]^{25}_D$ −9.2 (*c* 1.2, $CHCl_3$); IR (KBr): 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.86 (12H, s), 1.06 (3H, d, J = 6.8 Hz), 1.11−1.50 (8H, m), 2.32 (1H, dd, J = 3.0, 16.8 Hz), 2.59 (1H, dd, J = 6.2, 16.8 Hz), 3.07 (1H, dd, J = 2.5, 10.4 Hz), 3.45 (1H, dd, J = 5.4, 10.4 Hz), 4.22 (1H, m), 4.40 (1H, m); ^{13}C NMR ($CDCl_3$) δ −5.03, −4.90, 13.96, 17.77, 18.29, 25.52, 22.44, 25.62, 31.55, 33.78, 41.94, 45.94, 51.05, 65.26, 172.26; MS *m*/*z* 298 (M^+ − 15, 7), 256 (M^+ − 57, 100), 242 (48), 214 (54). Anal. Calcd for $C_{17}H_{35}NO_2Si$: C, 65.12; H, 11.25; N, 4.47. Found: C, 64.98; H, 10.99; N, 4.35.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **12c** and **14b**, and HPLC chromatograms for compounds **3a,c**, **5a**, and **9b** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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