Aziridine Ring-Opening Reactions with Chiral Enolates. Stereocontrolled Synthesis of 5-Substituted-3-methyl-pyrrolidin-2-ones

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A procedure for performing stereocontrolled aziridine ring-opening reactions with chiral enolates derived from (*S*,*S*)-(+)-pseudoephedrine amides has been developed leading to *γ*-aminoamides in good yields. The diastereoselectivity of the reaction becomes controlled by the presence of the chiral auxiliary on the enolate, although the stereogenic center contained in the structure of the aziridine has a striking influence on the stereochemical course of the reaction which results in the presence of the corresponding *matched* and *mismatched* combinations. Besides, the sense of the asymmetric induction of the chiral auxiliary has resulted to be the opposite to the one found with other type of electrophiles, although it is in good agreement with the trend observed in the reaction of the same kind of enolates with epoxides. Finally, the obtained *γ*-aminoamide adducts were converted into enantiopure *γ*-amino acids, *γ*-aminoesters, and pyrrolidin-2-ones using easy to perform and high yielding reactions.

Introduction

Chiral aziridines have found widespread applications in synthetic organic chemistry, and therefore, they have shown to be important intermediates for the stereocontrolled synthesis of nitrogen-containing molecules such as amino acids, heterocycles or alkaloids, among others.[1] As a consequence of the ring strain present in the molecule, the chemistry of aziridines is mainly dominated by nucleophilic ring-opening reactions[2] and in this context, many examples can be found in the literature in which nitrogen, sulfur and carbon nucleophiles have shown to react efficiently with different kind of aziridines opening a straightforward access to a wide number of functionalized nitrogen compounds.[3]

Although the use of organometallic reagents in ring-opening reactions of aziridines is well documented, the number of examples found in the literature in which metal enolates are employed as nucleophiles is still very limited,[4,5] particularly when the aforementioned enolate-promoted aziridine ring-opening reaction was carried out in an stereoselective fashion.[5] In this regard, most of these papers refer to particular substrates and only a recent work by Enders et al. reports a general procedure for performing stereocontrolled aziridine ring-opening reactions using aza-enolates derived from chiral SAMP/RAMP hydrazones.[5d]

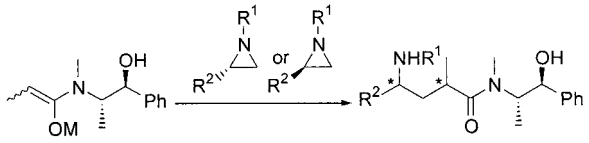

Figure 1.

Therefore, taking into account that (*S*,*S*)-(+)-pseudoephedrine, a cheap and commercially available reagent in both enantiomeric forms, has been recently used as chiral auxiliary in reactions of enolates with several electrophiles yielding the corresponding adducts with an extremely high degree of stereoselection.[6] In connection with our studies in the field of the asymmetric synthesis, we wanted to assess the ability of (*S*,*S*)-(+)-pseudoephedrine amide enolates to promote stereocontrolled ring-opening reactions with aziridines providing a straightforward access to *γ*-aminocarbonyl compounds. However, considering that both aziridine and enolate contain stereogenic centers in their structure, the double asymmetric induction in the ring-opening reaction warrants in depth investigation (Figure 1).

In this paper, the reaction between (*S*,*S*)-(+)-pseudoephedrine propionamide enolate with a variety of chiral

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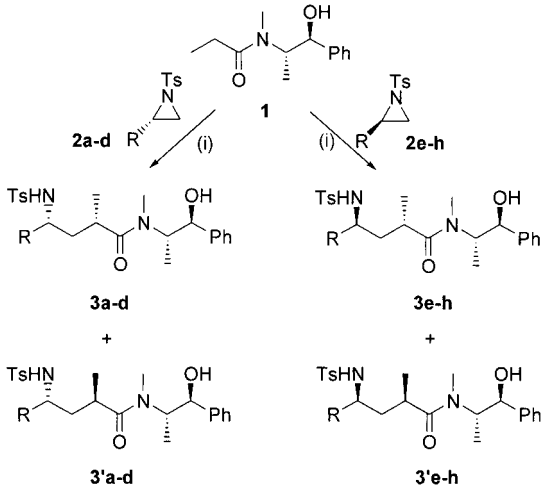
monosubstituted aziridines of specific absolute configurations is reported. The double asymmetric induction process has been studied in order to determine the optimal combination of reagents for the reaction to proceed with the highest possible degree of stereoselection and the so obtained γ-aminoamide adducts will be converted into chiral nonracemic γ-amino acids, esters, and pyrrolidin-2-ones using easy to perform and high yielding transformations. γ-Amino acids are important compounds in biochemical processes related to Parkinson disease and epilepsia[7] and also they have recently been employed for the synthesis of modified peptide analogues.[8] Pyrrolidin-2-ones have been widely used in organic synthesis as chiral auxilaries[9] and have shown to be versatile intermediates in the asymmetric synthesis of natural compounds.[10]

Results and Discussion

In a first test reaction, propionamide **1**, prepared by a previously reported procedure,[6b] was deprotonated with 2 equiv of LDA at −78 °C and reacted with activated *N*-tosylaziridine **2a** at 0 °C in the presence of 5 equiv of LiCl yielding, after 1 h reaction time, a 88:12 mixture of both possible diastereoisomers **3a** and **3′a**, which could be easily separated by flash column chromatography and fully characterized. Lowering the temperature to −20 °C increased the **3a**/**3′a** ratio to 94:6 however, at lower temperatures (−40 °C), no reaction was observed. These optimized conditions were extended to the use of other chiral monosubstituted *N*-tosylaziridines with different configurations[11] yielding the corresponding γ-aminoamide adducts in good yields and with a variable degree of diastereoselection (Scheme 1, Table 1). The absolute configuration of the newly created stereogenic center was determined on the final pyrrolidin-2-one derivatives **6a**−**h**, as outlined in the discussion.

It should be pointed out that the presence of LiCl was necessary in the reaction medium as in its absence, only starting materials were recovered. This behavior has also been observed in the reaction of pseudoephedrine amide enolates with alkyl halides,[6b] epoxides[6a] and imines,[6e] but contrasts the reaction of the same enolates with aldehydes[5d] or *tert*-butyl azodicarboxylate,[6c] in which the presence of LiCl was not necessary. We believe that the electrophilic character of aziridines is insufficient to undergo ring-opening with the nucleophile and reactivity enhancement on the enolate species, provided by the presence of lithium salts as has previously been reported,[12] is required for the reaction to proceed.

Scheme 1[a]



[a] Reagents and Conditions: (i) 1. LDA, LiCl, THF, −78 °C; 2. **2a-h**, THF, −20 °C.

Table 1. Diastereoselective Ring-opening Reaction of Aziridines 2a−h with the Lithium Enolate of 1

entry	product	R	(%) yield[a]	**3**/**3′**[b]
1	**3a**	Ph	88	96/4
2	**3b**	Me	89	89/12
3	**3c**	*i*-Pr	87	93/7
4	**3d**	Bn	93	95/5
5	**3e**	Ph	91	75/25
6	**3f**	Me	86	85/15
7	**3g**	*i*-Pr	90	77/33
8	**3h**	Bn	85	70/30

[a] Global yield as a mixture of diastereoisomers. [b] Calculated by HPLC (Chiralcel OD column, UV detector, hexane/*i*-PrOH 85:15, 0.80 mL/min).

In all cases it was observed that the ring-opening reaction was regioselective, in the sense that only the products arising from the attack of the enolate at the less substituted carbon atom of the aziridine ring were obtained. Regarding the diastereoselectivity of the reaction, it should be noted that the stereochemistry of the stereogenic center at the α-carbon atom of the final major γ-aminoamide adducts **3a**−**h** was the same in all cases regardless the configuration of the starting aziridine. Therefore, it would appear that the stereochemical course of the reaction is controlled by the chiral auxiliary linked to the enolate species. However, the configuration of the starting aziridine has a striking influence on the diastereoselectivity of the reaction because, as illustrated in Table 1. Reaction of aziridines **2a**−**d** with the (*S*) configuration at their stereogenic center proceeded with a

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(11) Aziridines **2a**−**h** were prepared according to a previously reported procedure: Berry, M. B.; Braig, D. *Synlett* **1992**, 41.

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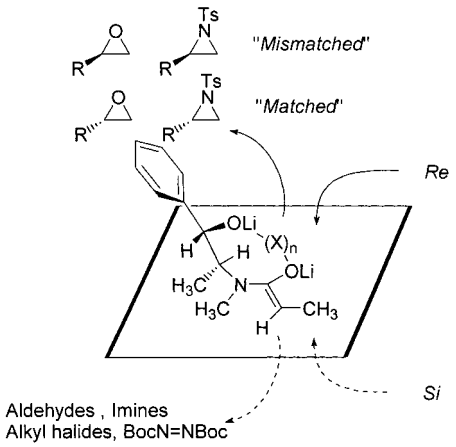


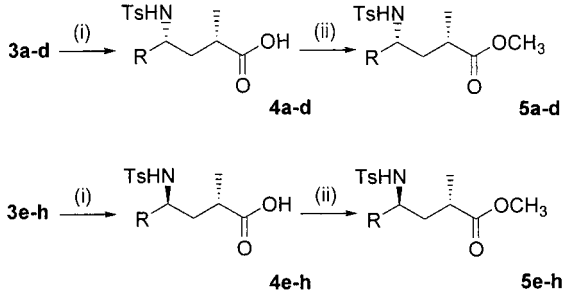
Figure 2.

high degree of diastereoselection. On the other hand, diastereoselection decreased when the corresponding enantiomeric (*R*) aziridines **2e**−**h** were used. Therefore, it can be concluded that the enolate derived from (*S*,*S*)-(+)-pseudoephedrine propionamide **1** and (*S*) aziridines **2a**−**d** form a *matched* combination leading to γ-aminoamides with a relative 1,3-*syn* configuration **3a**−**d** in good de. On the contrary, the same enolate and (*R*) aziridines **2e**−**h** form a *mismatched* combination leading to the corresponding adducts with a relative 1,3-anti configuration **3d**−**h** with poor diastereoselection.

Analysis of the sense of the asymmetric induction exerted by the chiral auxiliary (*S*,*S*)-(+)-pseudoephedrine on the newly created stereogenic center at the α-carbon of the γ-aminoamides **3a**−**h**, reveals that the attack of the aziridine electrophile on the enolate π-face occurs from the opposite face to the observed for reactions between similar enolates and electrophiles such as alkyl halides,[6b] aldehydes,[6d] imines,[6e] or dialkyl azodicarboxylates[6c] (see Figure 2). However, this trend is in accordance with the observed facial selectivity in the ring-opening reaction of epoxides with pseudoephedrine amide enolates and the same *matched-mismatched* correlation was found.[6a,13]

Next, we proceeded to convert the obtained α-methyl-γ-aminoamides **3a**−**h** to the target γ-amino acids, esters, and pyrrolidin-2-ones. The chiral auxiliary was cleanly removed by hydrolysis using 4 M H_2SO_4 in refluxing dioxane providing the corresponding α-methyl-γ-amino acids **4a**−**h** in good yield (Scheme 2, Table 2). Furthermore, the chiral auxiliary, (*S*,*S*)-(+)-pseudoephedrine, could be recovered in optically pure form from the extracts of the basic aqueous layer after workup and crystallization from hexane/EtOAc 1:1 in ca. 86% yield, allowing its recycling for further purposes. The acids **4a**−**h** were esterified by treatment with refluxing methanol under acid catalysis, affording α-methyl-γ-aminoesters **5a**−**h** in excellent yields after flash chromatography. Esters **5a**−**h** appeared to be single diastereoisomers with >99% ee as determined by ^{1}H NMR and chiral HPLC analyses of the crude reaction mixtures.[14] This indicated that both the hydrolysis and esterification steps

Scheme 2[a]



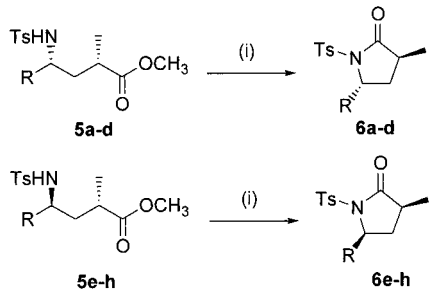
[a] Reagents and Conditions: (i) 4 M H_2SO_4/dioxane, reflux. (ii) MeOH, conc HCl, reflux.

Table 2. γ-Amino Acids 4a−h, γ-Aminoesters 5a−h, and Pyrrolidin-2-ones 6a−h Prepared

entry	R	product	(%) yield[a]	product	(%) yield[b]	product	(%) yield[c]
1	Ph	**4a**	85	**5a**	94	**6a**	77
2	Me	**4b**	87	**5b**	89	**6b**	72
3	*i*-Pr	**4c**	90	**5c**	90	**6c**	74
4	Bn	**4d**	93	**5d**	91	**6d**	76
5	Ph	**4e**	82	**5e**	92	**6e**	75
6	Me	**4f**	87	**5f**	93	**6f**	73
7	*i*-Pr	**4 g**	87	**5 g**	91	**6 g**	71
8	Bn	**4h**	85	**5h**	93	**6h**	71

[a] Yield of product **4** after standard acid−base purification. [b] Yield of product **5** after flash column chromatography purification and with ee>99% as calculated by chiral HPLC under conditions optimized for a racemic standard (Chiralcel OD column, UV detector, hexane/*i*-PrOH 90:10, 1.00 mL/min). [c] Yield of product **6** after flash column chromatography purification and with ee>99% as calculated by chiral HPLC under conditions optimized for a racemic standard (Chiralcel OD column, UV detector, hexane/*i*-PrOH 93:7, 0.75 mL/min)..

Scheme 3[a]



[a] Reagents and Conditions: (i) LHMDS, THF, −20 °C.

proceeded without racemization of either of the stereogenic centers of the starting amides **3a**−**h**.

Finally, the α-methyl-γ-aminoesters **5a**−**h** were submitted to base-promoted cyclization[15] by treatment with LHMDS in THF at −20 °C affording the 5-substituted 3-methyl-1-tosyl-pyrrolidin-2-ones **6a**−**h** in good yields and as a single diastereoisomers in >99% ee (determined by ^{1}H NMR and chiral HPLC). This indicates that the cyclization procedure proceeded without racemization of either of the stereogenic centers present in the starting compounds (Scheme 3, Table 2).

With these cyclic derivatives of known stereochemistry at the C_5 stereogenic center in hand, we proceeded to determine the absolute configuration of the newly created stereogenic center in the aziridine ring-opening reaction

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(14) For example, a racemic sample (±)-**5a** to be used as standard to optimize the HPLC separation conditions was prepared by hydrolysis/esterification of a 1:1 mixture of **3a** and **3′e**.

(15) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331.

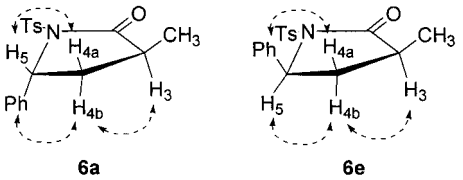

Figure 3. Observed nOe effects and proposed structure for pyrrolidin-2-ones **6a** and **6e**.

with the help of nOe difference experiments (see Figure 3). Thus, the observation of an intense nOe effect between H_5 and one of the two diastereotopic protons at C_4 as well as between H_3 and the other diastereotopic proton at C_4 for pyrrolidin-2-one **6a** suggested a relative 1,3-*trans* configuration between both CH_3 and Ph substituents. Furthermore, taking into account that C_5 had the *R* configuration (from aziridine **2a**), the configuration of the stereogenic center at C_3 had to be 3*S*. On the contrary, pyrrolidin-2-one **6e**, which had a 5*S* configuration, showed an intense nOe effect between H_5 and one of the two diastereotopic protons at C_4 as well as between H_3 and the same proton at C_4 suggesting a 1,3-*cis* relative configuration for both substituents and thus the 3*S* configuration at the newly created stereogenic center in the ring-opening reaction. This analysis was further extended to the remaining pyrrolidin-2-ones **6a**−**h**, γ-aminoamides **3a**−**h**, γ-amino acids **4a**−**h**, and γ-aminoesters **5a**−**h**.

Conclusions

In summary, a procedure for performing diastereoselective ring-opening reactions of monosubstituted *N*-tosylaziridines with (*S*,*S*)-(+)-pseudoephedrine amide enolates has been developed. The reaction proceeds with variable diastereoselectivity, depending on the configuration of the starting aziridine, although the stereochemical outcome of the reaction is controlled by the chiral auxiliary. The best combination of reagents, namely (*S*,*S*)-pseudoephedrine propionamide enolate and (*S*)-aziridines yielded the ring-opening products with an excellent degree of diastereoselection. The resulting γ-aminoamide adducts were finally converted into chiral γ-amino acids, γ-aminoesters, and pyrrolidin-2-ones which were obtained in excellent yields and in almost enantiomerically pure form.

Experimental Section

General Procedure for the Ring-Opening Reaction of Aziridines with (*S*,*S*)-(+)-Pseudoephedrine Propionamide Lithium Enolate. Synthesis of [2*S*,4*R*,1′*S*,2′*S*]-(+)-*N*,2-Dimethyl-4-phenyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)-4-(*p*-toluenesulfonylamino)butamide (3a).[16] A solution of propionamide **1** (1.00 g, 4.52 mmol) in dry THF (15 mL) was slowly added to a cooled (−78 °C) suspension of LDA (9.04 mmol) and LiCl (0.96 g, 22.60 mmol) in dry THF (20 mL). The mixture was stirred at this temperature for 1 h and allowed to reach room temperature. The mixture was cooled again to −20 °C at which temperature a THF (20 mL) solution of aziridine **2a** (1.36 g, 4.52 mmol) was dropwise added within 20 min and the resulting solution was stirred for 2 h at this temperature. The mixture was quenched with a saturated NH_4Cl solution (50 mL), extracted with CH_2Cl_2 and the combined organic fractions were collected, dried over Na_2SO_4 and filtered and the solvent was removed in vacuo to yield a yellowish oil which was flash column chromatographed (hexanes/ethyl acetate 2:8) affording diastereomerically pure amide **3a** as a colorless oil. An analytically pure sample was obtained after crystallization in Et_2O Yield: 83%. Mp: 89−91 °C (Et_2O). $[\alpha]_D^{20}$: +122.7 (*c* = 0.2, CH_2Cl_2). IR (KBr): 3355; 1607; 1342, 1165. ^{1}H NMR (δ, ppm) (2:1 rotamer ratio; *indicates minor rotamer resonances): 0.94* (d, 3H, *J* = 6.7 Hz); 1.07−1.20 (m, 6H); 2.00* (s, 3H); 2.34 (s, 3H); 2.20 (m, 1H); 2.74 (s, 3H); 2.83 (m, 1H); 2.91* (s, 3H); 2.99 (m, 1H); 3.63* (m, 1H); 3.80 (d, 1H, *J* = 10.2 Hz); 3.96 (m, 1H); 4.16* (m, 1H); 4.45−4.56 (m, 2H); 5.62* (d, 1H, *J* = 5.7 Hz); 5.70 (d, 1H, *J* = 6.0 Hz); 7.16−7.43 (m, 9H). ^{13}C NMR (δ, ppm) (2:1 rotamer ratio; *indicates minor rotamer resonances): 14.1*; 14.8; 15.0*; 15.9; 22.8; 23.0*; 25.2; 27.3*; 38.2; 38.4; 47.8; 48.0*; 49.3; 49.5*; 58.3; 74.8*; 75.6; 123.3; 123.5*; 125.8*; 125.9; 126.4; 126.6*; 126.8; 127.0*; 127.2; 127.4*; 128.1*; 128.2; 128.5*; 128.6; 128.7; 129.5*; 135.1*; 136.4; 137.3; 138.1*; 141.6*; 142.1; 143.6*; 143.7; 175.2*; 176.0. MS (EI) *m*/*z* (rel int): 338 (2), 294 (100). Anal. Calcd for $C_{28}H_{34}N_2O_4S$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.10; H, 7.01; N, 5.58.

[2*S*,4*S*,1′*S*,2′*S*]-(+)-*N*,2-Dimethyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)-4-(*p*-toluenesulfonylamino)pentanamide (3b). Yield: 78%. $[\alpha]_D^{20}$: +26.8 (*c* = 0.4, CH_2Cl_2). IR ($CHCl_3$): 3353; 1600; 1341, 1163. ^{1}H NMR (δ, ppm) (5:4 rotamer ratio; *indicates minor rotamer resonances): 0.59 (d, 3H, *J* = 6.3 Hz); 0.80* (d, 3H, *J* = 6.4 Hz); 0.91* (d, 3H, *J* = 7.5 Hz); 0.99 (d, 3H, *J* = 7.4 Hz); 1.02 (m, 3H); 1.07* (m, 1H); 1.12 (m, 1H); 1.51* (m, 1H); 1.98 (m, 1H); 2.00 (m, 1H); 2.23* (m, 1H); 2.34 (s, 3H); 2.36 (s, 3H); 2.84 (s, 3H); 2.93 (s, 3H); 3.22 (m, 1H); 3.33 (m, 1H); 4.31−4.46 (m, 2H); 5.53* (d, 1H, *J* = 10.3 Hz); 5.75 (d, 1H, *J* = 6.9 Hz); 7.18−7.50 (m, 7H); 7.64−7.72 (m, 2H). ^{13}C NMR (δ, ppm) (5:4 rotamer ratio; *indicates minor rotamer resonances): 13.3*; 14.4; 15.4; 17.4*; 17.8*; 18.0; 21.4; 22.0; 26.8; 27.0*; 31.4*; 32.3; 34.6; 40.8; 40.9*; 48.0*; 49.5; 75.6; 76.3*; 126.4*; 126.8; 126.9; 127.2*; 127.5*; 128.1; 128.3*; 128.7; 129.4*; 129.5; 138.6; 138.9*; 141.1*; 141.8; 143.2*; 142.9; 178.5*; 178.8. MS (EI) *m*/*z* (rel int): 432 (M^+, 1), 189 (100). Anal. Calcd for $C_{23}H_{32}N_2O_4S$: C, 63.86; H, 7.46; N, 6.48. Found: C, 63.93; H, 7.50; N, 4.45.

[2*S*,4*R*,1′*S*,2′*S*]-(+)-*N*,2-Dimethyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)-4-(*p*-toluenesulfonyl)hexanamide (3c). Yield: 80%. $[\alpha]_D^{20}$: +36.1 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3353; 1600; 1341, 1163. ^{1}H NMR (δ, ppm) (3:2 rotamer ratio; *indicates minor rotamer resonances): 0.47−0.62 (m, 6H); 0.82−0.99 (m, 6H); 1.07−1.57 (m, 3H); 2.11 (m, 1H); 2.22 (s, 3H); 2.24* (s, 3H); 2.54* (m, 1H); 2.65 (s, 3H); 2.79* (s, 3H); 3.01 (m, 1H); 3.37 (m, 1H); 4.24−4.51 (m, 2H); 4.72−4.78* (m, 2H); 5.56 (d, 1H, *J* = 8.9 Hz); 5.64* (d, 1H, *J* = 8.2 Hz); 7.03−7.40 (m, 7H); 7.57−7.62 (m, 2H). ^{13}C NMR (δ, ppm) (3:2 rotamer ratio; *indicates minor rotamer resonances): 8.8*; 9.2; 13.1; 13.9*; 14.9*; 15.5; 16.6*; 16.8; 17.1*; 18.3; 19.4*; 20.9; 26.3; 26.5*; 30.9*; 31.5; 31.7; 31.8; 33.3*; 33.6; 56.1*; 56.8; 75.2; 75.4*; 126.2*; 126.3; 126.9; 127.0*; 127.7; 127.8; 128.1*; 128.9; 129.0*; 129.2; 138.8; 138.9*; 141.0*; 141.7; 142.2*; 142.3; 177.6*; 178.0. MS (EI) *m*/*z* (rel int): 252 (66), 155 (100). Anal. Calcd for $C_{25}H_{36}N_2O_4S$: C, 65.19; H, 7.88; N, 6.08. Found: C, 65.10; H, 7.97; N, 6.03.

[2*S*,4*R*,1′*S*,2′*S*]-(+)-*N*,2-Dimethyl-5-phenyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyl-ethyl)-4-(*p*-toluenesulfonylamino)pentamide (3d). Yield: 88%. $[\alpha]_D^{20}$: +52.6 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3358; 1603; 1340, 1160. ^{1}H NMR (δ, ppm) (4:3 rotamer ratio; *indicates minor rotamer resonances): 0.93−0.98 (m, 6H); 1.07−1.15 (m, 2H); 1.64* (m, 1H); 1.76 (m, 1H); 2.09* (m, 2H): 2.34* (s, 3H); 2.37 (s, 3H); 2.45 (m, 2H); 2.78 (m, 1H); 2.83 (s, 3H); 2.95* (s, 3H); 3.35 (m, 1H); 3.57* (m, 1H); 4.08* (m, 1H); 4.56−4.75 (m, 2H); 5.73* (m, 1H); 5.95 (d, 1H, *J* = 8.5 Hz); 6.81−6.91 (m, 2H); 7.14−7.60 (m, 10H); 7.65* (d, 2H, *J* = 8.0 Hz); 7.75 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (δ, ppm) (4:3 rotamer ratio; *indicates minor rotamer resonances): 12.8; 13.7*; 16.6*; 17.3; 20.5*; 20.9; 30.5*; 31.2; 33.8; 36.9*; 37.4; 39.7; 41.4; 41.6*; 53.1*; 54.5; 74.4; 74.8*; 125.7*; 126.1; 127.3*; 126.9; 127.1*; 127.3; 127.6*; 127.9; 128.0*; 128.2; 128.4*; 128.6; 128.7; 129.1*; 129.2*; 129.8; 137.3*; 137.6; 138.2; 138.3*; 140.9*; 141.4; 142.3*; 142.5; 177.9*; 178.0. MS (EI) *m*/*z*

(16) For general experimental procedures see: Vicario, J. L.; Badía; D.; Domínguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610.

(rel int): 155 (72), 91 (100). Anal. Calcd for $C_{29}H_{36}N_2O_4S$: C, 68.47; H, 7.13; N, 5.51. Found: C, 68.51; H, 7.19; N, 5.45.

[2*S*,4*S*,1′*S*,2′*S*]-(+)-*N*,2-Dimethyl-4-phenyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyl-ethyl)-4-(*p*-toluenesulfonylamino)-butamide (3e). Yield: 67%. $[\alpha]_D^{20}$: +88.4 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3355; 1617; 1348, 1163. ^1H NMR (*δ*, ppm): 0.91−1.12 (m, 6H); 1.17−1.25 (m, 2H); 2.13 (m, 1H); 2.33 (s, 3H); 2.90 (s, 3H); 3.06 (m, 1H); 3.44 (m, 1H); 4.41−4.55 (m, 2H); 5.77 (d, 1H, *J* = 9.5 Hz); 6.81−7.39 (m, 12H); 7.66 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (*δ*, ppm): 14.1; 17.6; 20.5; 31.8; 33.3; 37.1; 40.4; 54.9; 74.8; 125.2; 125.6; 126.5; 126.9; 127.3; 127.9; 128.0; 128.9; 136.3; 137.1; 141.4; 142.2; 176.3. MS (EI) *m*/*z* (rel int): 338 (9), 294 (100). Anal. Calcd for $C_{29}H_{36}N_2O_4S$: C, 68.47; H, 7.13; N, 5.51. Found: C, 68.55; H, 7.06; N, 5.59.

[2*S*,4*R*,1′*S*,2′*S*]-(−)-*N*,2-Dimethyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)-4-(*p*-toluenesulfonylamino)pentanamide (3f). Yield: 73%. Mp: 86−89 °C (Et_2O). $[\alpha]_D^{20}$: −23.5 (*c* = 0.1, CH_2Cl_2). IR (KBr): 3350; 1601; 1342, 1160. ^1H NMR (*δ*, ppm): 0.71 (d, 3H, *J* = 6.5 Hz); 1.02 (d, 3H, *J* = 7.2 Hz); 1.07 (d, 3H, *J* = 7.3 Hz); 1.11−1.18 (m, 2H); 2.09 (m, 1H); 2.34 (s, 3H); 3.03 (s, 3H); 3.15 (m, 1H); 3.49 (m, 1H); 4.58 (d, 1H, *J* = 7.6 Hz); 4.99 (m, 2H); 7.28−7.66 (m, 7H); 7.98 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (*δ*, ppm): 14.6; 15.7; 18.5; 21.0; 21.6; 31.8; 33.9; 42.1; 49.2; 75.6; 126.6; 127.0; 127.9; 128.5; 129.2; 137.2; 141.7; 143.3; 177.1. MS (EI) *m*/*z* (rel int): 432 (M^+, 5), 189 (100). Anal. Calcd for $C_{23}H_{32}N_2O_4S$: C, 63.86; H, 7.46; N, 6.48. Found: C, 63.81; H, 7.51; N, 4.53.

[2*S*,4*S*,1′*S*,2′*S*]-(+)-*N*,2,5-Trimethyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyletyl)-4-(*p*-toluenesulfonylamino)-hexanamide (3g). Yield: 68%. Mp: 103−105 °C (Et_2O). $[\alpha]_D^{20}$: +12.3 (*c* = 0.3, CH_2Cl_2). IR (KBr): 3350; 1618; 1344, 1158. ^1H NMR (*δ*, ppm): 0.50 (d, 3H, *J* = 6.7 Hz); 0.62 (d, 3H, *J* = 6.7 Hz); 0.87 (d, 3H, *J* = 6.7 Hz); 1.09 (d, 3H, *J* = 6.7 Hz); 1.12−1.36 (m, 2H); 2.08 (m, 1H); 2.36 (s, 3H); 2.88 (s, 3H); 3.09 (m, 1H); 3.15 (m, 1H); 4.77 (m, 2H); 5.49 (m, 1H); 7.09 (d, 2H, *J* = 8.0 Hz); 7.19−7.44 (m, 5H); 7.67 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (*δ*, ppm): 14.3; 17.5; 17.8; 17.9; 19.9; 21.3; 29.5; 31.6; 32.7; 36.3; 57.9; 74.0; 126.2; 126.9; 127.4; 127.8; 129.9; 138.1; 141.3; 142.5; 177.3. MS (EI) *m*/*z* (rel int): 252 (41), 91 (100). Anal. Calcd for $C_{25}H_{36}N_2O_4S$: C, 65.19; H, 7.88; N, 6.08. Found: C, 65.23; H, 7.81; N, 6.00.

[2*S*,4*S*,1′*S*,2′*S*]-(+)-*N*,2-Dimethyl-5-phenyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyl-ethyl)-4-(*p*-toluenesulfonylamino)-pentamide (3h). Yield: 56%. Mp: 98−101 °C (Et_2O). $[\alpha]_D^{20}$: +97.5 (*c* = 0.1, CH_2Cl_2). IR (KBr): 3350; 1611; 1348, 1161. ^1H NMR (*δ*, ppm): 0.80−0.90 (m, 6H); 1.02−1.23 (m, 2H); 2.11 (m, 1H); 2.31 (s, 3H); 2.43−2.51 (m, 2H): 2.88 (s, 3H); 3.01 (m, 1H); 3.28 (m, 1H); 4.33−4.54 (m, 2H); 5.48 (d, 1H, *J* = 9.5 Hz); 6.81−7.52 (m, 12H); 7.78 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (*δ*, ppm): 14.2; 17.5; 20.9; 31.3; 32.4; 38.9; 39.2; 41.3; 52.1; 74.3; 125.7 125.9; 126.2; 126.5; 127.4; 127.8; 128.3; 128.8; 136.2; 137.5; 141.2; 142.3; 176.5. MS (EI) *m*/*z* (rel int): 329 (3), 91 (100). Anal. Calcd for $C_{29}H_{36}N_2O_4S$: C, 68.47; H, 7.13; N, 5.51. Found: C, 68.55; H, 7.06; N, 5.59.

General Procedure for the Hydrolysis of Amides 3a−h. Synthesis of [2*S*,4*R*]-(+)-2-Methyl-4-phenyl-4-(*p*-toluenesulfonylamino)butanoic Acid (4a). A solution of *γ*-aminoamide **3a** (0.33 g, 1.16 mmol) in dioxane (10 mL) was slowly added over a cooled (0 °C) 4 M H_2SO_4 solution (10 mL). When the addition was complete the mixture was refluxed for 5 h. The reaction was quenched with water, carefully basified to pH = 12 and washed with EtOAc. The aqueous layer was carefully driven to pH = 3 and extracted with CH_2Cl_2 (3 × 20 mL). After drying (Na_2SO_4), filtering and removing the solvent from the basic organic extracts it was possible to recover, after crystallization (hexanes/EtOAc) pure (+)-(*S*,*S*)-pseudoephedrine in 83% yield. The collected organic acidic extracts were dried over Na_2SO_4 and filtered and the solvent was removed in vacuo yielding the wanted acid as a colorless oil. Yield: 85%. $[\alpha]_D^{20}$: +21.6 (*c* = 0.3, CH_2Cl_2). IR ($CHCl_3$): 3455; 1710; 1341, 1163. ^1H NMR (*δ*, ppm): 1.11 (d, 3H, *J* = 7.0 Hz); 2.45 (s, 3H); 2.77 (m, 1H); 3.02 (m, 1H); 3.17 (m, 1H); 3.35 (m, 1H); 4.65 (m, 1H); 6.95−7.19 (m, 5H); 7.28 (d, 2H, *J* = 8.2 Hz); 7.65 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (*δ*, ppm): 14.2; 21.3; 42.3; 44.7; 47.9; 126.6; 126.8; 127.9; 128.1; 129.3; 136.6; 138.8; 143.2; 184.3. MS (EI) *m*/*z* (rel int): 331 (M^+, 55), 155 (100).

[2*S*,4*S*]-(−)-2-Methyl-4-(*p*-toluenesulfonylamino)pentanoic Acid (4b). Yield: 87%. $[\alpha]_D^{20}$: −25.9 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3453; 1711; 1343, 1160. ^1H NMR (*δ*, ppm): 0.90 (d, 3H, *J* = 6.7 Hz); 1.06 (d, 3H, *J* = 7.0 Hz); 1.35 (m, 1H); 1.76 (m, 1H); 2.35 (s, 3H); 2.54 (m, 1H); 3.33 (m, 1H); 5.10 (m, 1H); 7.21 (d, 2H, *J* = 8.2 Hz); 7.67 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (*δ*, ppm): 17.2; 21.0; 21.8; 35.8; 40.4; 48.3; 126.6; 129.5; 138.3; 143.1; 182.0. MS (EI) *m*/*z* (rel int): 285 (M^+, 28), 155 (100).

[2*S*,4*R*]-(−)-2,5-Dimethyl-4-(*p*-toluenesulfonylamino)-hexanoic Acid (4c). Yield: 90%. $[\alpha]_D^{20}$: −8.6 (*c* = 0.1, CH_2Cl_2). IR ($CHCl_3$): 3450; 1711; 1340, 1166. ^1H NMR (*δ*, ppm): 0.71 (d, 6H, *J* = 6.8 Hz); 0.97 (d, 3H, *J* = 6.9 Hz); 1.26 (m, 1H); 1.57 (m, 2H); 2.31 (s, 3H); 2.38 (m, 1H); 3.10 (m, 1H); 5.48 (m, 1H); 7.15 (d, 2H, *J* = 7.9 Hz); 7.65 (d, 2H, *J* = 7.9 Hz). ^{13}C NMR (*δ*, ppm): 16.2; 17.3; 17.9; 21.1; 31.4; 34.4; 35.4; 51.3; 126.3; 129.5; 138.3; 142.4; 181.3. MS (EI) *m*/*z* (rel int): 313 (M^+, 10), 189 (100).

[2*S*,4*R*]-(−)-2-Methyl-5-phenyl-4-(*p*-toluenesulfonylamino)pentanoic Acid (4d). Yield: 87%. $[\alpha]_D^{20}$: −26.4 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3451; 1710; 1341, 1164. ^1H NMR (*δ*, ppm): 1.03 (d, 3H, *J* = 7.1 Hz); 1.39 (m, 1H); 1.76 (m, 1H); 2.37 (s, 3H); 2.58 (m, 1H); 2.86 (m, 2H); 3.52 (m, 1H); 5.30 (m, 1H); 7.02−7.24 (m, 5H); 7.36 (d, 2H, *J* = 8.1 Hz); 7.72 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (*δ*, ppm): 16.2; 21.4; 36.3; 37.8; 41.8; 51.5; 126.2; 126.6; 128.4; 129.1; 129.4; 136.6; 137.9; 142.5; 180.4. MS (EI) *m*/*z* (rel int): 361 (M^+, 28), 91 (100).

[2*S*,4*S*]-(+)-2-Methyl-4-phenyl-4-(*p*-toluenesulfonylamino)butanoic Acid (4e). Yield: 82%. $[\alpha]_D^{20}$: +44.3 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3455; 1710; 1341, 1163. ^1H NMR (*δ*, ppm): 1.08 (d, 3H, *J* = 7.1 Hz); 2.39 (s, 3H); 2.71 (m, 1H); 3.12 (m, 1H); 3.21 (m, 1H); 3.33 (m, 1H); 4.58 (m, 1H); 7.02−7.21 (m, 5H); 7.33 (d, 2H, *J* = 8.1 Hz); 7.62 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (*δ*, ppm): 14.4; 21.6; 42.1; 45.3; 48.8; 126.3; 126.7; 127.9; 128.2; 129.5; 136.4; 138.9; 143.2; 184.1. MS (EI) *m*/*z* (rel int): 331 (M^+, 48), 155 (100).

[2*S*,4*R*]-(−)-2-Methyl-4-(*p*-toluensulfonylamino)pentanoic Acid (4f). Yield: 87%. $[\alpha]_D^{20}$: −13.5 (*c* = 0.1, CH_2Cl_2). IR ($CHCl_3$): 3453; 1710; 1341, 1160. ^1H NMR (*δ*, ppm): 0.97 (d, 3H, *J* = 6.5 Hz); 1.02 (d, 3H, *J* = 7.2 Hz); 1.34 (m, 1H); 1.79 (m, 1H); 2.41 (s, 3H); 2.52 (m, 1H); 3.31 (m, 1H); 5.08 (sa, 1H); 7.23 (d, 2H, *J* = 8.0 Hz); 7.75 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (*δ*, ppm): 17.6; 21.5; 21.9; 35.6; 40.8; 48.6; 126.8; 129.4; 137.7; 142.6; 180.9. MS (EI) *m*/*z* (rel int): 285 (M^+, 31), 155 (100).

[2*S*,4*S*]-(+)-2,5-Dimethyl-4-(*p*-toluensulfonylamino)-hexanoic Acid (4g). Yield: 87%. $[\alpha]_D^{20}$: +36.3 (*c* = 0.3, CH_2Cl_2). IR ($CHCl_3$): 3453; 1706; 1339, 1163. ^1H NMR (*δ*, ppm): 0.63 (d, 3H, *J* = 6.8 Hz); 0.94 (d, 3H, *J* = 7.0 Hz); 1.07 (d, 3H, *J* = 7.0 Hz); 1.45 (m, 1H); 2.00 (m, 1H); 2.33 (s, 3H); 2.42 (m, 2H); 3.35 (m, 1H); 4.29 (m, 1H); 7.22 (d, 2H, *J* = 8.1 Hz); 7.85 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (*δ*, ppm): 14.3; 15.6; 20.0; 21.6; 27.5; 30.3; 37.8; 51.4; 127.6; 129.3; 135.5; 144.7; 180.5. MS (EI) *m*/*z* (rel int): 313 (M^+, 12), 189 (100).

[2*S*,4*S*]-(+)-2-Methyl-5-phenyl-4-(*p*-toluenesulfonylamino)pentanoic Acid (4h). Yield: 85%. $[\alpha]_D^{20}$: +38.9 (*c* = 0.1, CH_2Cl_2). IR ($CHCl_3$): 3450; 1710; 1341, 1162. ^1H NMR (*δ*, ppm): 1.03 (d, 3H, *J* = 6.9 Hz); 1.41 (m, 1H); 1.87 (m, 1H); 2.45 (s, 3H); 2.62 (m, 1H); 2.71 (m, 2H); 3.41 (m, 1H); 4.78 (m, 1H); 7.01−7.28 (m, 5H); 7.23 (d, 2H, *J* = 8.1 Hz); 7.70 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (*δ*, ppm): 16.3; 21.2; 35.4; 37.5; 41.2; 51.7; 126.1; 126.5; 128.3; 128.7; 129.6; 136.5; 137.6; 142.5; 181.3. MS (EI) *m*/*z* (rel int): 361 (M^+, 31), 91 (100).

General Procedure for the Esterification of Acids 4a−h. Synthesis of [2*S*,4*R*]-(+)-Methyl 2-methyl-4-phenyl-4-(*p*-toluenesulfonylamino)butanoate (5a). A solution of acid **4a** (0.98 g, 2.82 mmol) in MeOH (15 mL) was added concd HCl (5 mL) and the mixture was refluxed for 12 h. The reaction was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). After drying (Na_2SO_4), filtering and removing the solvent from the collected organic fractions ester **5a** was isolated after flash column chromatography purification (hexanes/EtOAc 1:1). Yield: 94%. $[\alpha]_D^{20}$: +10.3 (*c* = 0.2, CH_2Cl_2).

IR ($CHCl_3$): 3450; 1712; 1341, 1160. ^1H NMR (δ, ppm): 1.13 (d, 3H, J = 7.0 Hz); 2.41 (s, 3H); 2.76 (m, 1H); 2.98 (m, 1H); 3.15 (m, 1H); 3.36 (m, 1H); 3.42 (s, 3H); 4.57 (m, 1H); 6.98 (m, 2H); 7.21 (m, 3H); 7.26 (d, 2H, J = 8.2 Hz); 7.63 (d, 2H, J = 8.2 Hz). ^{13}C NMR (δ, ppm): 14.3; 21.1; 42.4; 44.5; 47.7; 51.1; 126.6; 126.9; 127.7; 128.2; 129.3; 136.4; 138.8; 143.0; 174.6. MS (EI) *m*/*z* (rel int): 361 (M^+, 1), 91 (100). Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.21; H, 6.38; N, 3.93.

[2*S*,4*S*]-(−)-Methyl 2-methyl-4-(*p*-toluenesulfonylamino)pentanoate (5b). Yield: 89%. Mp: 78−80 °C (Hexanes/AcOEt 1:1). $[\alpha]_D^{20}$: −19.7 (*c* = 0.1, CH_2Cl_2). IR (KBr): 3450; 1715; 1347, 1165. ^1H NMR (δ, ppm): 0.89 (d, 3H, J = 6.5 Hz); 1.01 (d, 3H, J = 7.0 Hz); 1.37 (m, 1H); 1.78 (m, 1H); 2.35 (s, 3H); 2.51 (m, 1H); 3.30 (m, 1H); 3.60 (s, 3H); 5.19 (d, 1H, J = 8.9 Hz); 7.23 (d, 2H, J = 8.2 Hz); 7.71 (d, 2H, J = 8.2 Hz). ^{13}C NMR (δ, ppm): 16.8; 21.3; 21.6; 36.1; 40.8; 48.1; 51.6; 126.8; 129.4; 138.1; 143.0; 177.2. MS (EI) *m*/*z* (rel int): 299 (M^+, 3), 91 (100). Anal. Calcd for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68. Found: C, 56.20; H, 7.15; N, 4.63.

[2*S*,4*R*]-(−)-Methyl 2,5-dimethyl-4-(*p*-toluenesulfonylamino)hexanoate (5c). Yield: 90%. $[\alpha]_D^{20}$: −6.3 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3454; 1710; 1341, 1164. ^1H NMR (δ, ppm): 0.65 (d, 6H, J = 6.8 Hz); 0.91 (d, 3H, J = 6.9 Hz); 1.30 (m, 1H); 1.58 (m, 2H); 2.30 (s, 3H); 2.36 (m, 1H); 3.11 (m, 1H); 3.53 (s, 3H); 5.40 (d, 1H, J = 9.0 Hz); 7.16 (d, 2H, J = 7.9 Hz); 7.67 (d, 2H, J = 7.9 Hz). ^{13}C NMR (δ, ppm): 16.3; 17.0; 17.7; 21.1; 31.2; 34.0; 35.6; 51.4; 56.7; 126.5; 129.1; 138.5; 142.6; 176.9. MS (EI) *m*/*z* (rel int): 327 (M^+, 1), 91 (100). Anal. Calcd for $C_{16}H_{25}NO_4S$: C, 58.69; H, 7.70; N, 4.28. Found: C, 58.61; H, 7.63; N, 4.36.

[2*S*,4*R*]-(−)-Methyl 2-methyl-5-phenyl-4-(*p*-toluenesulfonylamino)pentanoate (5d). Yield: 91%. Mp: 138−141 °C (*n*-Pentane). $[\alpha]_D^{20}$: −19.9 (*c* = 0.5, CH_2Cl_2). IR (KBr): 3453; 1715; 1342, 1164. ^1H NMR (δ, ppm): 0.98 (d, 3H, J = 7.0 Hz); 1.45 (m, 1H); 1.80 (m, 1H); 2.39 (s, 3H); 2.60 (m, 3H); 3.51 (m, 1H); 3.63 (s, 3H); 5.24 (m, 1H); 6.98 (m, 2H); 7.18 (m, 3H); 7.24 (d, 2H, J = 8.0 Hz); 7.73 (d, 2H, J = 8.0 Hz). ^{13}C NMR (δ, ppm): 16.3; 21.1; 35.8; 37.5; 41.4; 51.4; 53.3; 126.1; 126.6; 128.1; 128.9; 129.3; 136.9; 137.9; 142.8; 177.1. MS (EI) *m*/*z* (rel int): 375 (M^+, 1), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 64.01; H, 6.61; N, 3.79.

[2*S*,4*S*]-(+)-Methyl 2-methyl-4-phenyl-4-(*p*-toluenesulfonylamino)butanoate (5e). Yield: 92%. $[\alpha]_D^{20}$: +72.3 (*c* = 0.1, CH_2Cl_2). IR ($CHCl_3$): 3450; 1712; 1341, 1160. ^1H NMR (δ, ppm): 1.10 (d, 3H, J = 7.0 Hz); 2.39 (s, 3H); 2.78 (m, 1H); 3.02 (m, 1H); 3.11 (m, 1H); 3.36 (m, 1H); 3.45 (s, 3H); 4.52 (m, 1H); 7.00 (m, 2H); 7.25 (m, 3H); 7.33 (d, 2H, J = 8.2 Hz); 7.63 (d, 2H, J = 8.2 Hz). ^{13}C NMR (δ, ppm): 14.3; 21.4; 42.5; 44.5; 47.6; 51.2; 126.6; 126.8; 127.5; 128.4; 129.1; 136.4; 138.7; 143.0; 174.5. MS (EI) *m*/*z* (rel int): 361 (M^+, 1), 91 (100). Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.09; H, 6.51; N, 3.79.

[2*S*,4*R*]-(−)-Methyl 2-methyl-4-(*p*-toluenesulfonylamino)pentanoate (5f). Yield: 93%. $[\alpha]_D^{20}$: −9.2 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 3457; 1713; 1343, 1160. ^1H NMR (δ, ppm): 0.95 (d, 3H, J = 6.5 Hz); 1.07 (d, 3H, J = 7.2 Hz); 1.31 (m, 1H); 1.76 (m, 1H); 2.39 (s, 3H); 2.54 (m, 1H); 3.31 (m, 1H); 3.60 (s, 3H); 4.98 (d, 1H, J = 8.7 Hz); 7.25 (d, 2H, J = 8.0 Hz); 7.71 (d, 2H, J = 8.0 Hz). ^{13}C NMR (δ, ppm): 17.7; 21.3; 21.7; 35.7; 40.9; 48.2; 51.5; 126.8; 129.5; 137.9; 143.0; 176.7. MS (EI) *m*/*z* (rel int): 299 (M^+, 3), 91 (100). Anal. Calcd for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68. Found: C, 56.21; H, 7.00; N, 4.59.

[2*S*,4*S*]-(+)-Methyl 2,5-dimethyl-4-(*p*-toluenesulfonylamino)hexanoate (5g). Yield: 91%. Mp: 112−114 °C (*n*-heptane). $[\alpha]_D^{20}$: +52.4 (*c* = 0.2, CH_2Cl_2). IR (KBr): 3455; 1710; 1340, 1165. ^1H NMR (δ, ppm): 0.61 (d, 3H, J = 6.8 Hz); 0.91 (d, 3H, J = 7.0 Hz); 1.02 (d, 3H, J = 7.0 Hz); 1.59 (m, 1H); 2.08 (m, 1H); 2.34 (s, 3H); 2.44 (m, 2H); 3.30 (m, 1H); 3.53 (s, 3H); 4.20 (dd, 1H, J = 3.6, 9.3 Hz); 7.23 (d, 2H, J = 8.1 Hz); 7.86 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ, ppm): 15.1; 15.9; 18.8; 21.3; 27.7; 30.8; 36.9; 51.2; 62.6; 127.9; 129.1; 135.5; 144.6; 176.3. MS (EI) *m*/*z* (rel int): 327 (M^+, 1), 155 (100). Anal. Calcd for $C_{16}H_{25}NO_4S$: C, 58.69; H, 7.70; N, 4.28. Found: C, 58.76; H, 7.77; N, 4.21.

[2*S*,4*S*]-(+)-Methyl 2-Methyl-5-phenyl-4-(*p*-toluenesulfonylamino)pentanoate (5h). Yield: 93%. $[\alpha]_D^{20}$: +68.4 (*c* = 0.5, CH_2Cl_2). IR ($CHCl_3$): 3457; 1714; 1342, 1163. ^1H NMR (δ, ppm): 1.05 (d, 3H, J = 6.8 Hz); 1.43 (m, 1H); 1.85 (m, 1H); 2.43 (s, 3H); 2.65 (m, 3H); 3.47 (m, 1H); 3.60 (s, 3H); 5.02 (m, 1H); 7.03 (m, 2H); 7.15 (m, 3H); 7.26 (d, 2H, J = 8.0 Hz); 7.64 (d, 2H, J = 8.0 Hz). ^{13}C NMR (δ, ppm): 16.2; 21.0; 35.5; 37.7; 41.3; 51.8; 53.3; 126.2; 126.6; 128.3; 128.8; 129.4; 136.9; 137.7; 142.6; 177.5. MS (EI) *m*/*z* (Int. Rel.): 375 (M^+, 4), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 64.07; H, 6.79; N, 3.68.

General Procedure for the Lactamization of Esters 5a−h. Synthesis of [3*S*,5*R*]-(−)-3-Methyl-5-phenyl-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (6a). A solution of LHMDS (1.02 mmol) in THF was slowly added over a cooled (−20 °C) solution of **5a** (0.37 g, 1.02 mmol) in dry THF (15 mL). The mixture was stirred for 45 min at this temperature and quenched with a 4 M HCl solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the collected organic fractions were dried over Na_2SO_4 and filtered and the solvent was removed in vacuo yielding pyrrolidin-2-one **6a** after flash column chromatography purification (hexanes/EtOAc 8:2). Yield: 74%. Mp: 88−91 °C (*n*-Pentane). $[\alpha]_D^{20}$: −4.7 (*c* = 0.1, CH_2Cl_2). IR (KBr): 1720; 1343, 1162. ^1H NMR (δ, ppm): 0.73 (d, 3H, J = 7.3 Hz); 2.46 (s, 3H); 2.89 (m, 1H); 3.53 (dt, 1H, J = 3.1, 8.3 Hz); 4.02 (dd, 1H, J = 3.2, 6.8 Hz); 4.15 (dd, 1H, J = 6.8, 8.3 Hz); 6.91 (m, 2H); 7.19 (m, 3H); 7.33 (d, 2H, J = 8.1 Hz); 7.96 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ, ppm): 10.7; 21.6; 41.2; 42.6; 51.2; 127.1; 127.3; 127.9; 128.6; 129.6; 134.8; 138.4; 145.2; 175.0. MS (EI) *m*/*z* (rel int): 329 (M^+, 2), 118 (100). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.72; H, 5.85; N, 4.28.

[3*S*,5*S*]-(+)-3,5-Dimethyl-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (6b). Yield: 77%. Mp: 98−100 °C (Et_2O). $[\alpha]_D^{20}$: +86.4 (*c* = 0.01, CH_2Cl_2). IR (KBr): 1725; 1340, 1163. ^1H NMR (δ, ppm): 1.43 (d, 3H, J = 6.5 Hz); 1.55 (d, 3H, J = 6.1 Hz); 1.82 (m, 2H); 2.41 (s, 3H); 2.69 (m, 1H); 4.30 (m, 1H); 4.98 (d, 1H, J = 8.7 Hz); 7.31 (d, 2H, J = 8.0 Hz); 7.96 (d, 2H, J = 8.0 Hz). ^{13}C NMR (δ, ppm): 14.5; 15.6; 21.5; 25.7; 36.7; 59.6; 128.5, 129.7; 135.5; 144.5; 177.2. MS (EI) *m*/*z* (rel int): 267 (M^+, 2), 188 (100). Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.49; H, 6.50; N, 5.29.

[3*S*,5*R*]-(+)-3-Methyl-5-(1-methylethyl)-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (6c). Yield: 72%. Mp: 112−115 °C (Et_2O). $[\alpha]_D^{20}$: +78.6 (*c* = 0.1, CH_2Cl_2). IR (KBr): 1722; 1343, 1161. ^1H NMR (δ, ppm): 0.64 (d, 3H, J = 6.8 Hz); 0.90 (d, 3H, J = 7.0 Hz); 1.12 (d, 3H, J = 7.0 Hz); 1.39 (m, 1H); 2.21 (m, 1H); 2.42 (s, 3H); 2.48 (m, 1H); 2.75 (m, 1H); 4.26 (dt, 1H, J = 3.9, 7.8 Hz); 7.31 (d, 2H, J = 8.1 Hz); 7.94 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ, ppm): 13.9; 15.3; 18.0; 21.4; 25.5; 29.0; 36.3; 62.7; 128.3; 129.8; 135.6; 144.5; 177.4. MS (EI) *m*/*z* (rel int): 295 (M^+, 1), 155 (100). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 61.11; H, 7.25; N, 4.88.

[3*S*,5*R*]-(+)-5-Benzyl-3-methyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (6d). Yield: 76%. Mp: 143−145 °C (Et_2O). $[\alpha]_D^{20}$: +73.7 (*c* = 0.1, CH_2Cl_2). IR (KBr): 1722; 1342, 1160. ^1H NMR (δ, ppm): 1.05 (d, 3H, J = 7.1 Hz); 1.41 (m, 2H); 2.13 (m, 2H); 2.36 (m, 1H); 2.43 (s, 3H); 2.63 (dd, 1H, J = 10.0, 12.8 Hz); 3.84 (dd, 1H, J = 3.6, 12.8 Hz); 4.45 (m, 1H); 7.21−7.35 (m, 7H); 8.02 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ, ppm): 16.0; 21.6; 31.5; 36.7; 42.4; 59.5; 126.8; 128.1; 128.2; 128.6; 129.5; 136.2; 136.7; 144.9; 176.7. MS (EI) *m*/*z* (rel int): 343 (M^+, 3), 155 (100) Anal.Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.54; H, 6.11; N, 4.17.

[3*S*,5*S*]-(+)-3-Methyl-5-phenyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (6e). Yield: 71%. $[\alpha]_D^{20}$: +88.6 (*c* = 0.2, CH_2Cl_2). IR ($CHCl_3$): 1720; 1343, 1162. ^1H NMR (δ, ppm): 0.82 (d, 3H, J = 7.3 Hz); 2.49 (s, 3H); 3.11 (m, 1H); 3.48 (dt, 1H, J = 2.9, 11.0 Hz); 4.04 (dd, 1H, J = 2.9, 8.8 Hz); 4.31 (dd, 1H, J = 8.8, 11.0 Hz); 7.03 (m, 2H); 7.18 (m, 3H); 7.30 (d, 2H, J = 8.1 Hz); 8.00 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ, ppm): 10.7; 21.6; 41.2; 42.6; 51.2; 127.1; 127.3; 127.9; 128.6; 129.6; 134.8; 138.4; 145.2; 175.0. MS (EI) *m*/*z* (rel int): 329 (M^+, 1), 118

(100). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.72; H, 5.85; N, 4.28.

[3*S*,5*R*]-(−)-3,5-Dimethyl-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (6f). Yield: 75%. Mp: 119−121 °C (Et_2O). $[\alpha]_D^{20}$: −13.7 (c = 0.1, CH_2Cl_2). IR (KBr): 1728; 1340, 1164. ^{1}H NMR (δ, ppm): 1.11 (d, 3H, J = 7.0 Hz); 1.16 (d, 3H, J = 6.6 Hz); 2.11 (m, 2H); 2.43 (s, 3H); 2.83 (m, 1H); 4.28 (m, 1H); 7.27 (d, 2H, J = 8.0 Hz); 7.91 (d, 2H, J = 8.0 Hz). ^{13}C NMR (δ, ppm): 14.5; 15.7; 21.5; 25.8; 36.5; 59.6; 128.3; 129.5; 135.6; 144.7; 177.3. MS (EI) m/z (rel int): 267 (M^+, 1), 188 (100). Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.31; H, 6.53; N, 5.18.

[3*S*,5*S*]-(+)-3-Methyl-5-(1-methylethyl)-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (6g). Yield: 73%. Mp: 86−89 °C (Et_2O). $[\alpha]_D^{20}$: +75.7 (c = 0.1, CH_2Cl_2). IR (KBr): 1725; 1342, 1161. ^{1}H NMR (δ, ppm): 0.62 (d, 3H, J = 6.8 Hz); 0.89 (d, 3H, J = 6.9 Hz); 1.10 (d, 3H, J = 7.1 Hz); 1.37 (m, 1H); 2.19 (m, 2H); 2.39 (s, 3H); 2.74 (m, 1H); 4.24 (dt, 1H, J = 4.0, 7.9 Hz); 7.27 (d, 2H, J = 8.1 Hz); 7.90 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ, ppm): 13.9; 15.2; 18.0; 21.5; 25.3; 29.0; 36.3; 62.9; 128.1, 129.3; 135.7; 144.7; 177.0. MS (EI) m/z (rel int): 295 (M^+, 3), 155 (100). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 58.31; H, 6.53; N, 5.18.

[3*S*,5*S*]-(+)-5-Benzyl-3-methyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (6h). Yield: 71%. $[\alpha]_D^{20}$: −95.3 (c = 0.1, CH_2Cl_2). IR ($CHCl_3$): 1723; 1342, 1161. ^{1}H NMR (δ, ppm): 1.00 (d, 3H, J = 6.9 Hz); 1.64 (m, 2H); 2.11 (m, 2H); 2.37 (m, 1H); 2.43 (s, 3H); 2.81 (dd, 1H, J = 9.4, 13.3 Hz); 3.34 (dd, 1H, J = 3.3, 13.3 Hz); 4.49 (m, 1H); 7.21−7.35 (m, 7H); 7.98 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ, ppm): 14.7; 21.6; 31.6; 35.5; 40.0; 58.7; 126.9, 128.1, 128.2, 128.6, 129.3; 135.8; 136.2; 144.9; 175.7. MS (EI) m/z (rel int): 343 (M^+, 1), 155 (100). Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.39; H, 6.23; N, 4.01.

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