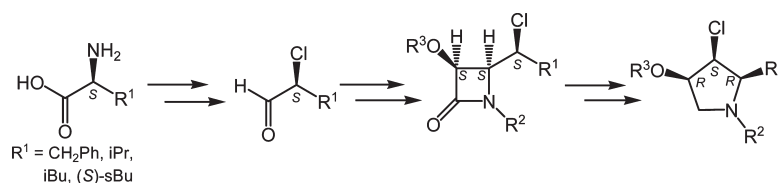


Stereoselective Synthesis of Chiral 4-(1-Chloroalkyl)- $\beta$ -Lactams Starting from Amino Acids and Their Transformation into Functionalized Chiral Azetidines and PyrrolidinesStijn Dekeukeleire,<sup>†,§</sup> Matthias D'hooghe,<sup>†</sup> Karl W. Törnroos,<sup>‡</sup> and Norbert De Kimpe<sup>\*,†</sup><sup>†</sup>Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium, and <sup>‡</sup>Department of Chemistry, University of Bergen, Allég. 41, 5007 Bergen, Norway. <sup>§</sup>Aspirant of the Fund for Scientific Research Flanders (FWO-Vlaanderen).

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Chiral short-chain  $\alpha$ -chloroaldehydes were prepared starting from enantiomerically pure amino acids in a three-step approach, thus providing a practical synthetic alternative for known organo-catalytic  $\alpha$ -chlorination procedures. The latter aldehydes proved to be useful starting materials for the stereoselective Staudinger synthesis of (3*S*,4*S*)-4-[(1*S*)-1-chloroalkyl]azetidin-2-ones in high diastereomeric ratios and good overall yields, which were used as chiral building blocks for the preparation of a number of azetidines and pyrrolidines.

## Introduction

As the concept of chirality has become an important issue and challenge in organic and medicinal chemistry, many efforts are devoted to the development of chiral approaches (often catalytic methodologies) toward  $\beta$ -lactams nowadays.<sup>1,2</sup> The Staudinger reaction, utilizing either a chiral ketene or a chiral imine, is generally acknowledged as the method of choice for the asymmetric synthesis of  $\beta$ -lactams. In that context, the use of chiral  $\alpha$ -oxy- and  $\alpha$ -amino-substituted aldehydes for the stereoselective synthesis of azetidin-2-ones has already been proven to be successful.<sup>3</sup>

The application of chiral  $\alpha$ -haloaldehydes, however, has not been evaluated until recently, when (2*S*)-2-chloropropanal, prepared via oxidation of commercially available (2*S*)-2-chloropropanol, was used as a substrate for the synthesis of chiral 4-(1-chloroethyl)- $\beta$ -lactams in our preliminary work.<sup>4</sup> To date, the enantioselective  $\alpha$ -halogenation of aldehydes has been studied to a limited extent.<sup>5,6</sup> In particular, only three major approaches toward chiral  $\alpha$ -chloroaldehydes are reported in the literature, all of them based on asymmetric catalysis. The first method involves a proline-catalyzed  $\alpha$ -chlorination of aldehydes using *N*-chlorosuccinimide as the chlorine source.<sup>7</sup> The other two approaches comprise the use of a chiral imidazolidinone as the asymmetric catalyst,<sup>8</sup> with the chlorinating agent being either

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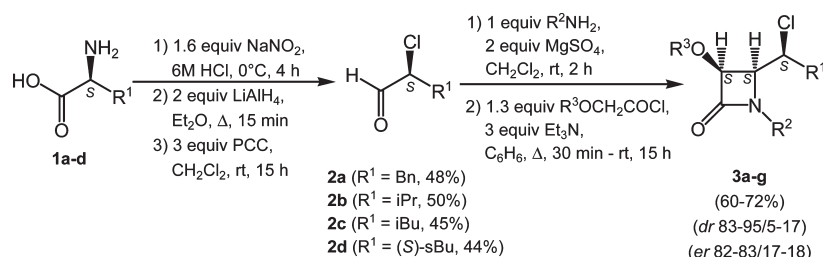
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## SCHEME 1



hexachlorocyclohexadienone<sup>8a</sup> or sodium/lithium chloride (used in combination with copper(II) triflate).<sup>8b</sup> Despite their synthetic potential, minor drawbacks are sometimes encountered applying these methods, especially in terms of substrate scope (e.g., short-chain aldehydes), workup procedures (toil-some removal of hexachlorocyclohexadienone), and cost-price (expensive catalyst (2*R*,5*R*)-diphenylpyrrolidine).

In order to provide an alternative for the oxidation of commercially available (2*S*)-chloro-1-propanol toward (2*S*)-2-chloropropanal,<sup>4</sup> a novel synthetic approach toward chiral nonracemic short-chain  $\alpha$ -chloroaldehydes is disclosed in the present report. As the synthesis evolves from enantiomerically pure  $\alpha$ -amino acids, the presented route can be considered as the first convenient noncatalytic entry into chiral  $\alpha$ -chloroaldehydes. This approach provides a valuable and interesting synthetic alternative for the known catalytic  $\alpha$ -chlorination procedures. With the intention to demonstrate their synthetic potential, the latter chiral aldehydes were used as powerful chiral inductors in the synthesis of a series of new 4-(1-chloroalkyl)- $\beta$ -lactams which in turn were shown to be eligible substrates for further elaboration toward a variety of azaheterocyclic compounds such as azetidines and pyrrolidines (“ $\beta$ -lactam synthon method”).<sup>9</sup>

## Results and Discussion

With the intention to provide a novel and practical synthetic approach toward chiral short-chain  $\alpha$ -chloroaldehydes, a three-step procedure starting from  $\alpha$ -amino acids was devised involving (i) initial conversion into  $\alpha$ -chloro acids, followed by (ii) reduction to  $\beta$ -chloroalkanol and (iii) oxidation to the corresponding  $\alpha$ -chloroaldehydes. Despite their availability and synthetic potential, chiral  $\alpha$ -amino acids have not been employed as substrates for the preparation of chiral  $\alpha$ -chloroaldehydes until now.

In order to replace the amino group of  $\alpha$ -amino acids by a chloro atom, enantiomerically pure amino acids **1** (i.e., L-phenylalanine, L-valine, L-leucine, and L-isoleucine) were treated with 1.6 equiv of sodium nitrite in a 6 M solution of hydrochloric acid for 4 h at 0 °C.<sup>10</sup> Reduction of the resulting (2*S*)-2-chloroalkanoic acids using 2 molar equiv of lithium aluminum hydride in diethyl ether under reflux for 15 min led to the formation of the corresponding alcohols,<sup>11</sup> which were subsequently subjected to an oxidation step involving treatment with 3 equiv of pyridinium chlorochromate (PCC) in

anhydrous dichloromethane for 15 h, affording the envisaged (2*S*)-2-chloroalkanal **2a–d** in 44–50% overall yield (Scheme 1). The formation of (2*S*)-2-chloroalkanal **2** starting from *S*-amino acids **1** implies anchimeric assistance of the carboxyl group during replacement of the amino group by chloride, thus resulting in a double Walden inversion at the asymmetric carbon atom. The proof that indeed the *S*-enantiomers were obtained was provided by measurement of the optical rotation of (2*S*)-2-chloro-3-phenylpropanal **2a**, as the observed  $\alpha_D^{20}$  value for this compound ( $\alpha_D^{20} = -7.1$ ,  $c = 1.0$ , CHCl<sub>3</sub>) was in accordance with literature data ( $\alpha_D^{20} = -8.8$ ,  $c = 1.0$ , CHCl<sub>3</sub>).<sup>8a</sup> This synthetic route comprises the first convenient noncatalytic entry toward chiral nonracemic  $\alpha$ -chloroaldehydes and can provide a useful alternative for known organocatalytic  $\alpha$ -chlorination procedures in terms of substrate scope, synthetic procedures, and economical considerations.

To check if any racemization had occurred during the conversion of amino acids **1** into chiral nonracemic  $\alpha$ -chloroaldehydes **2**, chiral GC analysis was performed on (2*S*)-2-chloro-3-methylbutanal **2b**, pointing to an enantiomeric ratio of 97.5/2.5. An additional proof was provided by <sup>1</sup>H NMR analysis of (2*S*,3*S*)-2-chloro-3-methylpentanal **2d**. The observation of two diastereoisomers in a 95/5 ratio in the <sup>1</sup>H NMR spectrum of the latter aldehyde **2d** can be rationalized considering the presence of two stereogenic centers, of which only one is susceptible to racemization (at the 2-position). Consequently, the appearance of a second diastereoisomer in the <sup>1</sup>H NMR spectrum can be attributed to (2*R*,3*S*)-2-chloro-3-methylpentanal. From these observations, it can be concluded that racemization only takes place to a very limited extent ( $\leq 5\%$ ), affording chiral nonracemic  $\alpha$ -chloroaldehydes **2** in high enantiomeric excess.

As (2*S*)-2-chloropropanal has previously been shown to be a powerful inductor for the stereoselective synthesis of 4-(1-chloroethyl)azetidin-2-ones,<sup>4</sup> a series of  $\alpha$ -chloroimines were prepared via imination of  $\alpha$ -chloroaldehydes **2** in dichloromethane in the presence of MgSO<sub>4</sub> and Et<sub>3</sub>N utilizing 1 equiv of different primary amines, which were used immediately and as such for the Staudinger synthesis of  $\beta$ -lactams upon treatment with 1.3 equiv of phenoxy-, methoxy- or benzyloxycetyl chloride in the presence of triethylamine in benzene, affording the corresponding novel (3*S*,4*S*)-4-[(1*S*)-1-chloroalkyl]azetidin-2-ones **3a–g** in good overall yields (60–72%) and high diastereomeric ratios (95–83/5–17) (Scheme 1, Table 1). These observations clearly point to a strong and general inducing effect of the  $\alpha$ -chloro atom, enabling the stereoselective synthesis of 4-(1-chloroalkyl)- $\beta$ -lactams in a convenient way. It should be noted that the reported yields are yields obtained after purification by column chromatography on silica gel.

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**TABLE 1.** Synthesis of (3*S*,4*S*)-4-[(1*S*)-1-Chloroalkyl]azetidin-2-ones **3a–g**

compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	isolated yield <sup>a</sup> (%)	diastereomeric ratio <sup>b</sup>
<b>3a</b>	Bn	cHex	Bn	63	94/6
<b>3b</b>	Bn	<i>i</i> Pr	Ph	60	95/5
<b>3c</b>	<i>i</i> Pr	<i>i</i> Pr	Bn	68	87/13
<b>3d</b>	<i>i</i> Bu	allyl	Me	72	91/9
<b>3e</b>	<i>i</i> Bu	<i>n</i> Bu	Bn	62	89/11
<b>3f</b>	( <i>S</i> )- <i>s</i> Bu	Bn	Me	64	87/13
<b>3g</b>	( <i>S</i> )- <i>s</i> Bu	<i>n</i> Pr	Ph	64	83/17

<sup>a</sup>After purification by column chromatography on silica gel. <sup>b</sup>Based on GC analysis of the crude reaction mixtures.

The relative stereochemistry of  $\beta$ -lactams **3** with regard to the protons at C3 and C4 was assigned as *cis* based on the coupling constants between these protons in <sup>1</sup>H NMR (4.9–5.1 Hz, CDCl<sub>3</sub>), in accordance with literature data.<sup>12</sup> The full configuration of  $\beta$ -lactams **3** was established by X-ray analysis of azetidin-2-one **3a**, providing the irrefutable proof for the formation of (3*S*,4*S*)-4-[(1*S*)-1-chloroalkyl]azetidin-2-ones **3** as the major stereoisomers, which is in accordance with theoretical considerations in the literature. Indeed, the origin of the asymmetric induction in the Staudinger synthesis of 4-(1-oxo- or 1-aminoalkyl)- $\beta$ -lactams has been rationalized on the basis of the magnitude of the stereoelectronic effect exerted by the  $\sigma^*(\text{C}–\text{X})$  orbital (with X = OH or NH<sub>2</sub> and C a stereogenic carbon atom) over the HOMO in the transition states.<sup>4,13</sup> Furthermore, according to a theoretical study on the hyperconjugative acceptor ability of  $\sigma$  bonds, the  $\sigma^*(\text{C}–\text{X})$  acceptor abilities increase by at least 30% when X is a halogen atom in comparison with X being an oxygen or a nitrogen atom,<sup>14</sup> which was thus acknowledged experimentally in this work.

In order to determine the enantiomeric ratio of azetidin-2-ones **3**, which can be influenced by the stability of the intermediate  $\alpha$ -chloroimines toward racemization upon imine–enamine tautomerism,  $\beta$ -lactams **3a** and **3b** were treated with either 4 or 2.5 equiv of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle alcohol) prior to <sup>1</sup>H NMR analysis (CDCl<sub>3</sub>). In the case of (3*S*,4*S*)-3-benzyloxy-4-[(1*S*)-1-chloro-2-phenylethyl]-1-cyclohexylazetidin-2-one **3a**, an enantiomeric ratio of 82/18 was observed (using 4 equiv of Pirkle alcohol), whereas for (3*S*,4*S*)-4-[(1*S*)-1-chloro-2-phenylethyl]-1-isopropyl-3-phenoxyazetidin-2-one **3b**, an enantiomeric ratio of 83/17 was found (using 2.5 equiv of Pirkle alcohol). Thus, it can be concluded that epimerization occurs only to a limited extent during imination and/or Staudinger reaction starting from  $\alpha$ -chloroaldehydes **2**, which is in accordance with previous findings.<sup>4</sup>

Because of the combination of a strained four-membered ring system, a nucleophilic nitrogen lone pair and an electrophilic center in the side chain, racemic 4-(1-haloalkyl)- $\beta$ -

lactams have already been proven to be excellent starting materials for the preparation of a large variety of novel azaheterocyclic compounds.<sup>15</sup> To demonstrate the high synthetic potential of chiral 4-(1-chloroalkyl)azetidin-2-ones **3a–g**, the preparation of a series of novel chiral 3-chloropyrrolidines was envisaged, as pyrrolidines comprise an important class of azaheterocycles because of their presence in many biologically interesting compounds.<sup>16</sup> From a synthetic point of view, 2-(1-haloalkyl)azetidines, mainly 2-(1-chloro-1-methylethyl)azetidines, are known to be suitable substrates for rearrangements toward pyrrolidines.<sup>17</sup> Furthermore, one example of a rearrangement of two racemic 4-(1-chloroethyl)-4-methyl- $\beta$ -lactams to the corresponding 4-benzyloxy-3-chloro-2,3-dimethylpyrrolidines has been reported, in which the benzyloxy group, the chloro atom, and the 2-methyl group reside at the same side (all-*cis*, previously erroneously described as the *cis*-2,3-dimethyl isomer).<sup>4</sup> In that respect, (3*S*,4*S*)-4-[(1*S*)-1-chloroalkyl]azetidin-2-ones **3a–g**, obtained as single diastereoisomers after column chromatography, were treated first with 4 equiv of monochloroalane (AlH<sub>2</sub>Cl) in diethyl ether under reflux for 4 h, affording novel (2*S*,3*S*)-2-[(1*S*)-1-chloroalkyl]azetidines **4a–g** in moderate to good yields after purification by column chromatography (Scheme 2, Table 2). Subsequently, the latter azetidines **4** underwent rearrangement via intermediate bicyclic azetidinium ions **6** toward a series of new, chiral (2*R*,3*S*,4*R*)-2-alkyl-3-chloropyrrolidines **5a–g** upon reflux in acetonitrile for 18–96 h (Scheme 2, Table 2) in analogy with the previously reported transformation of 2-(1-chloro-1-methylethyl)azetidines into the corresponding 3-chloropyrrolidines.<sup>15c</sup> Sterical hindrance due to the presence of an extra methyl group in the azetidine side chain (R<sup>1</sup> = *i*Pr and (*S*)-*s*Bu) accounts for longer reaction times in the case of 2-alkyl-3-chloropyrrolidines **5c**, **5f**, and **5g**.

Furthermore, hydrogenolysis of the benzyloxy group within pyrrolidine **5e** was performed applying 5 bar H<sub>2</sub> in the presence of 10% Pd/C and 2 equiv of HCl<sub>conc</sub> in MeOH at room temperature for 15 h, affording pyrrolidine **7** bearing a free hydroxyl group as a useful template for further derivatization (Scheme 3).

The relative configuration of 2-alkyl-3-chloropyrrolidines **5** (all-*cis*) is a direct consequence of the reaction mechanism since the formation of pyrrolidines **5** as single diastereomers can only be attributed to a S<sub>N</sub>2-based pathway via intermediate bicyclic azetidinium salts **6**.<sup>17c</sup> Furthermore, this relative configuration was confirmed by qualitative NOESY experiments performed on (2*R*,3*S*,4*R*)-4-benzyloxy-1-butyl-3-chloro-2-(2-methylpropyl)pyrrolidine **5e**.

In order to establish its enantiomeric ratio, esterification of 4-hydroxypyrrolidine **7** was performed utilizing 1 equiv of (1*S*)-(-)-camphanic chloride in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 15 h in the presence of 0.1 equiv of DMAP and 2 equiv of Et<sub>3</sub>N, pointing to a diastereomeric ratio of 86/14 (based on GC/MS analysis). Consequently, an enantiomeric ratio of 86/14 can be assigned to the starting pyrrolidine **5e**.

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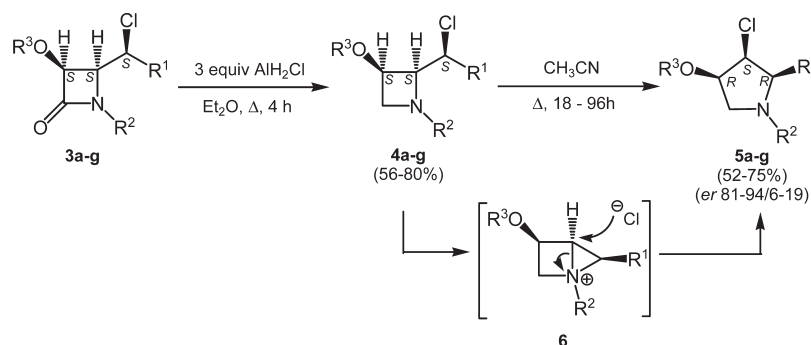
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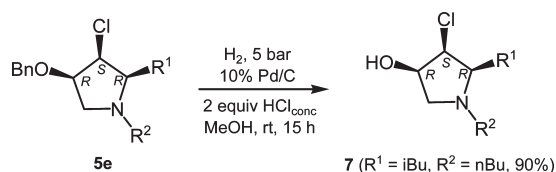
## SCHEME 2

TABLE 2. Synthesis of (2*R*,3*S*,4*R*)-2-Alkyl-3-chloropyrrolidines **5a–g**

compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	isolated yield <sup>a</sup> (%)	enantiomeric ratio
<b>5a</b>	Bn	cHex	Bn	71	82/18
<b>5b</b>	Bn	<i>i</i> Pr	Ph	75	87/13
<b>5c</b>	<i>i</i> Pr	<i>i</i> Pr	Bn	74	94/6
<b>5d</b>	<i>i</i> Bu	allyl	Me	52	81/19
<b>5e</b>	<i>i</i> Bu	<i>n</i> Bu	Bn	75	86/14
<b>5f</b>	( <i>S</i> )- <i>s</i> Bu	Bn	Me	68	100/0 <sup>b</sup>
<b>5g</b>	( <i>S</i> )- <i>s</i> Bu	<i>n</i> Pr	Ph	67	100/0 <sup>b</sup>

<sup>a</sup>After purification by column chromatography on silica gel. <sup>b</sup>These compounds were isolated as single diastereomers due to the presence of an additional chiral center [R<sup>1</sup> = (*S*)-*s*Bu].

## SCHEME 3



When (2*R*,3*S*,4*R*)-1-allyl-3-chloro-4-methoxy-2-(2-methylpropyl)pyrrolidine **5d** was treated with 1 equiv of L-tartaric acid in THF at room temperature for 15 h, a diastereomeric ratio of 81/19 was found for the resulting salt (based on <sup>1</sup>H NMR analysis, CD<sub>3</sub>OD), which points to an enantiomeric ratio of 81/19 for pyrrolidine **5d**.

In addition, when pyrrolidines **5a–c** were treated with 3 (for pyrrolidines **5a** and **5b**) or 1 (in the case of pyrrolidine **5c**) equiv of Pirkle alcohol prior to <sup>1</sup>H NMR analysis (CDCl<sub>3</sub>), enantiomeric ratios of 82/18, 87/13, and 94/6, respectively, were observed.

These observations confirm the high enantiomeric purity of pyrrolidines **5** and corroborate the significance of amino acids as synthons for the convenient preparation of chiral pyrrolidines in a straightforward way.

In conclusion, a convenient and straightforward noncatalytic protocol for the synthesis of chiral short-chain α-chloroaldehydes is disclosed, providing a useful synthetic alternative for known organocatalytic α-chlorination procedures. Furthermore, the latter (2*S*)-2-chloroalkanals were shown to be suitable starting materials for the synthesis of novel chiral (3*S*,4*S*)-4-[(1*S*)-1-chloroalkyl]azetidin-2-ones in high diastereomeric and enantiomeric ratios. The latter β-lactams were subsequently elaborated toward a series of chiral nonracemic 2-alkyl-3-chloropyrrolidines via ring

transformation of 2-(1-chloroalkyl)azetidines with retention of enantiomeric purity.

## Experimental Section

**Synthesis of (2*S*)-2-Chloroalkanals **2**.** As a representative example, the synthesis of (2*S*)-2-chloro-3-phenylpropanal **2a** starting from L-phenylalanine **1a** is described.

To a stirred solution of 8.26 g of L-phenylalanine **1a** (50 mmol) in 6 M HCl (250 mL) at 0 °C was added 5.52 g of NaNO<sub>2</sub> (80 mmol, 1.6 equiv) in small portions. After stirring for 4 h at 0 °C, the reaction mixture was extracted with Et<sub>2</sub>O (3 × 125 mL). The combined organic fractions were dried overnight over calcium chloride dihydrate, and after removal of the drying agent through filtration and evaporation of the solvent in vacuo, crude (2*S*)-2-chloro-3-phenylpropionic acid was obtained. Subsequently, 2.88 g of LiAlH<sub>4</sub> (76 mmol, 2 molar equiv based on the estimated quantitative yield of the crude (2*S*)-2-chloro-3-phenylpropionic acid) was added in small portions to a solution of (2*S*)-2-chloro-3-phenylpropionic acid in anhydrous Et<sub>2</sub>O (150 mL) at 0 °C. After heating under reflux for 15 min, water (20 mL) was added to neutralize the residual hydride. After decantation of the solvent, the residue was washed with Et<sub>2</sub>O (3 × 75 mL). After drying (MgSO<sub>4</sub>) of the combined organic fractions and filtration, the solvent was evaporated under reduced pressure, affording crude (2*S*)-2-chloro-3-phenylpropan-1-ol. Then, 19.18 g of pyridinium chlorochromate (89 mmol, 3 equiv based on the estimated quantitative yield of the crude (2*S*)-2-chloro-3-phenylpropan-1-ol) was added to a solution of (2*S*)-2-chloro-3-phenylpropan-1-ol (30 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (150 mL). After stirring for 15 h at room temperature, the reaction mixture was filtered over silica gel and the filter cake was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL). After evaporation of the solvent under reduced pressure, the crude (2*S*)-2-chloro-3-phenylpropanal **2a** was obtained in 48% overall yield with regard to amino acid **1a** (purity > 90% based on <sup>1</sup>H NMR, CDCl<sub>3</sub>). The spectral data of compound **2a** were in accordance with those reported in the literature.<sup>8a</sup>

Due to their instability, (2*S*)-2-chloroalkanals **2** were not subjected to further purification and were used immediately and as such in the next reaction step.

**Synthesis of (3*S*,4*S*)-4-[(1*S*)-1-Chloroalkyl]azetidin-2-ones **3a–g**.** As a representative example, the synthesis of (3*S*,4*S*)-3-benzyloxy-4-[(1*S*)-1-chloro-2-phenylethyl]-1-cyclohexylazetidin-2-one **3a** is described.

To a solution of 1.69 g of (2*S*)-2-chloro-3-phenylpropanal **2a** (10 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) were added 2.41 g of MgSO<sub>4</sub> (20 mmol, 2 equiv) and 0.99 g of cyclohexylamine (10 mmol, 1 equiv). After stirring for 1.5 h at room temperature, the drying agent was removed through filtration and the solvent was evaporated under reduced pressure. Then, benzene (50 mL) was added, and after evaporation of the residual dichloromethane

under vacuo, 3.04 g of Et<sub>3</sub>N (30 mmol, 3 equiv) was added, after which the reaction mixture was heated to reflux temperature. Subsequently, a solution of 2.40 g of benzyloxyacetyl chloride (13 mmol, 1.3 equiv) in benzene (10 mL) was added dropwise to the boiling solution in benzene. After complete addition, the reaction mixture was stirred overnight (15 h) at room temperature. Subsequently, the reaction mixture was washed with water (50 mL), and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). After drying (MgSO<sub>4</sub>) and evaporation of the solvent, the crude reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc 4/1), affording pure (3*S*,4*S*)-3-benzyloxy-4-[(1*S*)-1-chloro-2-phenylethyl]-1-cyclohexylazetidin-2-one **3a** in 63% yield.

**(3*S*,4*S*)-3-Benzyloxy-4-[(1*S*)-1-chloro-2-phenylethyl]-1-cyclohexylazetidin-2-one 3a:** White crystals; mp 113.7 °C; *R*<sub>f</sub> = 0.38 (hexane/EtOAc 4/1), yield 63%; [α]<sub>D</sub> = −10 (*c* = 0.06, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.17–1.25 and 1.57–2.02 (3H and 7H, *m*), 2.84 (1H, dd, *J* = 14.0, 9.4 Hz), 3.36 (1H, dd, *J* = 14.0, 2.1 Hz), 3.36–3.47 (1H, *m*), 3.85 (1H, dd, *J* = 9.4, 5.0 Hz), 4.28 (1H, ddd, *J* = 9.4, 9.4, 2.1 Hz), 4.67 (1H, d, *J* = 5.0 Hz), 4.77 and 5.03 (2 × 1H, *2d*, *J* = 11.3 Hz), 7.13–7.15, 7.24–7.26 and 7.28–7.42 (10H, *3m*); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 25.3, 25.4, 25.7, 30.8, and 31.1 (5 × CH<sub>2</sub>), 40.7 (CH<sub>2</sub>), 54.9 (CH), 61.3 (CH), 64.3 (CH), 73.2 (CH<sub>2</sub>), 80.4 (CH), 126.9, 128.3, 128.4, 128.6, and 129.7 (10 × CH), 136.9 and 137.2 (2 × C), 167.4 (C); IR (KBr, cm<sup>−1</sup>) ν<sub>C=O</sub> = 1724; ν<sub>max</sub> = 2928, 1151, 1058, 988, 751, 698; MS (70 eV) *m/z* (%) 398/400 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>24</sub>H<sub>28</sub>ClNO<sub>2</sub>: C, 72.44; H, 7.09; N, 3.52. Found: C, 72.46; H, 7.23; N, 3.51.

**(3*S*,4*S*)-4-[(1*S*)-1-Chloro-2-phenylethyl]-1-isopropyl-3-phenoxyazetidin-2-one 3b:** White crystals; mp 98.7 °C; *R*<sub>f</sub> = 0.13 (hexane/EtOAc 9/1); yield 60%; [α]<sub>D</sub> = −49 (*c* = 0.12, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.37 and 1.46 (2 × 3H, *2d*, *J* = 6.8 Hz), 2.91 (1H, dd, *J* = 14.3, 9.4 Hz), 3.47 (1H, dd, *J* = 14.3, 2.2 Hz), 3.93 (1H, sept, *J* = 6.8 Hz), 4.03 (1H, dd, *J* = 9.5, 4.9 Hz), 4.49 (1H, ddd, *J* = 9.5, 9.4, 2.2 Hz), 5.27 (1H, d, *J* = 4.9 Hz), 7.03–7.08, 7.17–7.21 and 7.25–7.39 (10H, *3m*); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.83 and 20.88 (2 × CH<sub>3</sub>), 41.0 (CH<sub>2</sub>), 47.4 (CH), 61.5 (CH), 63.9 (CH), 80.3 (CH), 116.1 (2 × CH), 122.8 (CH), 127.2, 128.6, 129.6, and 129.8 (7 × CH), 136.9 (C), 157.6 (C), 165.9 (C); IR (KBr, cm<sup>−1</sup>) ν<sub>C=O</sub> = 1741; ν<sub>max</sub> = 2971, 1494, 1230, 748, 696, 688; MS (70 eV) *m/z* (%) 344/6 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>20</sub>H<sub>22</sub>ClNO<sub>2</sub>: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.93; H, 6.22; N, 3.82.

**(3*S*,4*S*)-3-Benzyloxy-4-[(1*S*)-1-chloro-2-methylpropyl]-1-isopropylazetidin-2-one 3c:** Light-yellow oil; *R*<sub>f</sub> = 0.24 (hexane/EtOAc 6/1); yield 68%; [α]<sub>D</sub> = −47 (*c* = 0.23, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.91 and 1.00 (2 × 3H, *2d*, *J* = 6.8 Hz), 1.29 and 1.42 (2 × 3H, *2d*, *J* = 7.2 Hz), 2.17 (1H, sept × d, *J* = 6.8, 2.2 Hz), 3.81–3.88 (2H, *m*), 4.18 (1H, dd, *J* = 9.9, 2.2 Hz), 4.53 (1H, d, *J* = 5.0 Hz), 4.68 and 4.93 (2 × 1H, *2d*, *J* = 11.8 Hz), 7.28–7.36 (5H, *m*); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 15.5, 20.7, 20.87, and 20.94 (4 × CH<sub>3</sub>), 29.7 (CH), 47.3 (CH), 60.5 (CH), 70.1 (CH), 72.8 (CH<sub>2</sub>), 80.4 (CH), 127.7, 128.0, and 128.6 (5 × CH), 137.2 (C), 167.5 (C); IR (NaCl, cm<sup>−1</sup>) ν<sub>C=O</sub> = 1747; ν<sub>max</sub> = 2969, 1335, 1052, 731, 697; MS (70 eV) *m/z* (%) 310/2 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>17</sub>H<sub>24</sub>ClNO<sub>2</sub>: C, 65.90; H, 7.81; N, 4.52. Found: C, 66.07; H, 8.10; N, 4.29.

**(3*S*,4*S*)-1-Allyl-4-[(1*S*)-1-chloro-3-methylbutyl]-3-methoxyazetidin-2-one 3d:** Light-yellow oil; *R*<sub>f</sub> = 0.12 (hexane/EtOAc 6/1); yield 72%; [α]<sub>D</sub> = −58 (*c* = 0.48, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.90 and 0.95 (2 × 3H, *2d*, *J* = 6.9 Hz), 1.52–1.57 (2H, *m*), 1.89–2.03 (1H, *m*), 3.58 (3H, *s*), 3.81 (1H, dd, *J* = 9.4, 5.0 Hz), 3.91 (1H, dd, *J* = 15.4, 7.2 Hz), 4.14–4.24 (2H, *m*), 4.45 (1H, d, *J* = 5.0 Hz), 5.21–5.27 (2H, *m*), 5.72–5.85 (1H, *m*); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.5 and 23.7 (2 × CH<sub>3</sub>), 24.5 (CH), 43.3 (CH<sub>2</sub>), 44.1 (CH<sub>2</sub>), 59.3 (CH<sub>3</sub>), 62.01 and 62.07 (2 × CH), 83.4 (CH), 119.1 (CH<sub>2</sub>), 131.5 (CH), 167.8 (C); IR (NaCl, cm<sup>−1</sup>)

ν<sub>C=O</sub> = 1755; ν<sub>max</sub> = 2957, 1353, 1215, 1031, 929; MS (70 eV) *m/z* (%) 246/8 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>12</sub>H<sub>20</sub>ClNO<sub>2</sub>: C, 58.65; H, 8.20; N, 5.70. Found: C, 58.73; H, 8.46; N, 5.52.

**(3*S*,4*S*)-3-Benzyloxy-1-butyl-4-[(1*S*)-1-chloro-3-methylbutyl]-azetidin-2-one 3e:** Light-yellow oil; *R*<sub>f</sub> = 0.31 (hexane/EtOAc 6/1); yield 62%; [α]<sub>D</sub> = −56 (*c* = 0.22, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 and 0.92 (2 × 3H, *2d*, *J* = 6.6 Hz), 0.92 (3H, *t*, *J* = 7.3 Hz), 1.30 (2H, sext, *J* = 7.3 Hz), 1.45–1.70 (4H, *m*), 1.88–1.99 (1H, *m*), 3.32 (1H, ddd, *J* = 13.8, 8.3, 5.5 Hz), 3.54 (1H, ddd, *J* = 13.8, 8.0, 8.0 Hz), 3.78 (1H, dd, *J* = 9.9, 5.0 Hz), 4.18–4.26 (1H, *m*), 4.61 (1H, d, *J* = 5.0 Hz), 4.67 and 4.95 (2 × 1H, *2d*, *J* = 11.6 Hz), 7.27–7.38 (5H, *m*); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.8, 20.5, and 23.8 (3 × CH<sub>3</sub>), 20.2 (CH<sub>2</sub>), 24.5 (CH), 29.5 (CH<sub>2</sub>), 41.4 (CH<sub>2</sub>), 43.3 (CH<sub>2</sub>), 62.3 (2 × CH), 73.0 (CH<sub>2</sub>), 80.8 (CH), 128.03, 128.09, and 128.5 (5 × CH), 137.0 (C), 168.0 (C); IR (NaCl, cm<sup>−1</sup>) ν<sub>C=O</sub> = 1754; ν<sub>max</sub> = 2957, 1455, 1115, 736, 697; MS (70 eV) *m/z* (%) 338/40 (M<sup>+</sup> + 1, 40), 304 (M<sup>+</sup> + 1-Cl, 100). Anal. Calcd for C<sub>19</sub>H<sub>28</sub>ClNO<sub>2</sub>: C, 67.54; H, 8.35; N, 4.15. Found: C, 67.32; H, 8.48; N, 4.23.

**(3*S*,4*S*)-1-Benzyl-4-[(1*S*,2*S*)-1-chloro-2-methylbutyl]-3-methoxyazetidin-2-one 3f:** Colorless oil; *R*<sub>f</sub> = 0.19 (hexane/EtOAc 6/1); yield 64%; [α]<sub>D</sub> = −11 (*c* = 0.32, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.86 (3H, *t*, *J* = 7.4 Hz), 0.99 (3H, d, *J* = 6.6 Hz), 1.14–1.29 and 1.31–1.46 (2 × 1H, *2m*), 1.83–1.94 (1H, *m*), 3.58 (3H, *s*), 3.83 (1H, dd, *J* = 10.0, 5.1 Hz), 4.21 (1H, dd, *J* = 10.0, 2.5 Hz), 4.37 (1H, d, *J* = 14.6 Hz), 4.40 (1H, d, *J* = 5.1 Hz), 4.86 (1H, d, *J* = 14.6 Hz), 7.29–7.37 (5H, *m*); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 11.9 (CH<sub>3</sub>), 17.2 (CH<sub>3</sub>), 22.9 (CH<sub>2</sub>), 36.9 (CH), 45.5 (CH<sub>2</sub>), 59.3 (CH, and CH<sub>3</sub>), 70.2 (CH), 83.6 (CH), 127.8, 128.7, and 128.8 (5 × CH), 135.9 (C), 168.1 (C); IR (NaCl, cm<sup>−1</sup>) ν<sub>C=O</sub> = 1755; ν<sub>max</sub> = 2964, 1454, 1350, 1216, 1075, 1033, 721, 700; MS (70 eV) *m/z* (%) 296/8 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>16</sub>H<sub>22</sub>ClNO<sub>2</sub>: C, 64.97; H, 7.50; N, 4.74. Found: C, 65.12; H, 7.88; N, 4.57.

**(3*S*,4*S*)-4-[(1*S*,2*S*)-1-Chloro-2-methylbutyl]-3-phenoxy-1-propylazetidin-2-one 3g:** Light-yellow oil; *R*<sub>f</sub> = 0.25 (hexane/EtOAc 7/1); yield 64%; [α]<sub>D</sub> = −140 (*c* = 0.46, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.89 and 0.93 (2 × 3H, *2t*, *J* = 7.4 Hz), 1.09 (3H, d, *J* = 6.6 Hz), 1.22–1.84 (4H, *m*), 2.01–2.09 (1H, *m*), 3.36 (1H, ddd, *J* = 13.8, 8.3, 5.5 Hz), 3.54 (1H, ddd, *J* = 13.8, 7.8, 7.8 Hz), 4.18 (1H, dd, *J* = 9.8, 5.1 Hz), 4.36 (1H, dd, *J* = 9.8, 2.2 Hz), 5.22 (1H, d, *J* = 5.1 Hz), 7.01–7.11 and 7.29–7.35 (5H, *2m*); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 11.5 and 12.0 (2 × CH<sub>3</sub>), 17.2 (CH<sub>3</sub>), 20.8 and 23.1 (2 × CH<sub>2</sub>), 37.0 (CH), 43.9 (CH<sub>2</sub>), 60.1 (CH), 69.9 (CH), 80.5 (CH), 116.0 (2 × CH), 122.6 (CH), 129.8 (2 × CH), 157.6 (C), 166.5 (C); IR (NaCl, cm<sup>−1</sup>) ν<sub>C=O</sub> = 1758; ν<sub>max</sub> = 2964, 1598, 1495, 1232, 752, 690; MS (70 eV) *m/z* (%) 310/2 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>17</sub>H<sub>24</sub>ClNO<sub>2</sub>: C, 65.90; H, 7.81; N, 4.52. Found: C, 66.12; H, 8.14; N, 4.33.

**Synthesis of (2*S*,3*S*)-2-[(1*S*)-1-chloroalkyl]azetidines 4a–g.** As a representative example, the synthesis of (2*S*,3*S*)-3-benzyloxy-2-[(1*S*)-1-chloro-2-phenylethyl]-1-cyclohexylazetidine **4a** is described.

To an ice-cooled solution of 2.40 g of aluminum(III) chloride (18 mmol, 3 equiv) in dry Et<sub>2</sub>O (40 mL) was added 0.68 g of LiAlH<sub>4</sub> (18 mmol, 3 equiv) in small portions. The reaction mixture was stirred for 30 min at room temperature, after which a solution of 2.40 g of (3*S*,4*S*)-3-benzyloxy-4-[(1*S*)-1-chloro-2-phenylethyl]-1-cyclohexylazetidin-2-one **3a** (6 mmol, 1 equiv) in dry Et<sub>2</sub>O (10 mL) was added dropwise. After 4 h at reflux temperature, water (20 mL) was added carefully to neutralize the residual hydride. After decantation of the solvent, the residue was extracted with Et<sub>2</sub>O (3 × 20 mL) and the combined organic fractions were dried (MgSO<sub>4</sub>). After filtration of the drying agent and evaporation of the solvent, the crude reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc 6/1), providing pure (2*S*,3*S*)-3-benzyloxy-2-[(1*S*)-1-chloro-2-phenylethyl]-1-cyclohexylazetidine **4a** in 76% yield.

**(2S,3S)-3-Benzyl-2-[(1S)-1-chloro-2-phenylethyl]-1-cyclohexylazetidine 4a:** Colorless oil;  $R_f = 0.36$  (hexane/EtOAc 6/1); yield 76%;  $[\alpha]_D = -11$  ( $c = 0.08$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.03–1.30 and 1.43–1.89 ( $2 \times 5\text{H}$ ,  $2m$ ), 2.53–2.70 (1H, m), 2.95 (1H, dd,  $J = 14.6$ , 10.2 Hz), 3.24 (1H, dd,  $J = 8.8$ , 6.6 Hz), 3.46 (1H, dd,  $J = 14.6$ , 1.9 Hz), 3.47–3.56 (1H, m), 3.75 (1H, dd,  $J = 7.4$ , 7.4 Hz), 4.28 (1H, ddd,  $J = 7.4$ , 6.6, 2.4 Hz), 4.43 (1H, d,  $J = 11.6$  Hz), 4.51–4.57 (1H, m), 4.64 (1H, d,  $J = 11.6$  Hz), 7.18–7.39 (10H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  24.9, 25.3, 26.0, 26.9, and 31.2 ( $5 \times \text{CH}_2$ ), 40.5 ( $\text{CH}_2$ ), 52.8 ( $\text{CH}_2$ ), 62.0 (CH), 68.7 ( $2 \times \text{CH}$ ), 70.7 (CH), 71.3 ( $\text{CH}_2$ ), 126.6, 127.94, 127.99, 128.4, 128.5, and 129.5 ( $10 \times \text{CH}$ ), 137.8 and 138.6 ( $2 \times \text{C}$ ); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2927$ , 1453, 1112, 909, 730, 697; MS (70 eV)  $m/z$  (%) 384/6 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{24}\text{H}_{30}\text{ClNO}$ : C, 75.08; H, 7.88; N, 3.65. Found: C, 74.93; H, 8.02; N, 3.49.

**(2S,3S)-2-[(1S)-1-Chloro-2-phenylethyl]-1-isopropyl-3-phenoxyazetidine 4b:** Colorless oil;  $R_f = 0.22$  (hexane/EtOAc 9/1); yield 56%;  $[\alpha]_D = -52$  ( $c = 0.15$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.01 and 1.02 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.3$  Hz), 2.90 (1H, dd,  $J = 14.3$ , 9.8 Hz), 3.20 (1H, sept,  $J = 6.3$  Hz), 3.32–3.44 (3H, m), 3.79 (1H, dd,  $J = 8.8$ , 6.6 Hz), 4.68 (1H, ddd,  $J = 9.8$ , 9.8, 2.0 Hz), 4.86 (1H, ddd,  $J = 6.6$ , 6.6, 2.2 Hz), 6.79–6.89, 6.95–7.00 and 7.15–7.31 (10H,  $3m$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  15.3 and 21.0 ( $2 \times \text{CH}_3$ ), 40.7 ( $\text{CH}_2$ ), 50.8 ( $\text{CH}_2$ ), 52.0 (CH), 64.4 (CH), 67.7 (CH), 69.1 (CH), 115.0 ( $2 \times \text{CH}$ ), 121.5 (CH), 126.8, 128.4, 129.5, 129.7, and 129.8 ( $7 \times \text{CH}$ ), 138.2 (C), 157.0 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2964$ , 1599, 1494, 1237, 750, 698, 691; MS (70 eV)  $m/z$  (%) 330/2 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{ClNO}$ : C, 72.82; H, 7.33; N, 4.25. Found: C, 73.01; H, 7.51; N, 3.96.

**(2S,3S)-3-Benzyl-2-[(1S)-1-chloro-2-methylpropyl]-1-isopropylazetidine 4c:** Light-yellow oil;  $R_f = 0.22$  (hexane/EtOAc 4/1); yield 73%;  $[\alpha]_D = -85$  ( $c = 0.51$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.90 and 0.95 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.6$  Hz), 1.01 and 1.02 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.9$  Hz), 2.17 (1H, sept  $\times$  d,  $J = 6.6$ , 2.3 Hz), 3.13 (1H, dd,  $J = 8.5$ , 6.1 Hz), 3.22 (1H, d,  $J = 8.5$  Hz), 3.27 (1H, sept,  $J = 6.9$  Hz), 3.62 (1H, dd,  $J = 10.3$ , 6.6 Hz), 4.08 (1H, ddd,  $J = 6.6$ , 6.1, 1.8 Hz), 4.32 (1H, d,  $J = 12.1$  Hz), 4.45 (1H, dd,  $J = 10.3$ , 2.3 Hz), 4.61 (d,  $J = 12.1$  Hz), 7.25–7.36 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8, 16.0, 20.8, and 20.9 ( $4 \times \text{CH}_3$ ), 30.1 ( $\text{CH}_2$ ), 48.6 (CH), 50.4 (CH), 65.8 (CH), 70.6 and 70.7 ( $2 \times \text{CH}$  and  $\text{CH}_2$ ), 127.5, 127.7, and 128.4 ( $5 \times \text{CH}$ ), 138.00 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2964$ , 1454, 1200, 1107, 734, 697; MS (70 eV)  $m/z$  (%) 296/8 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{17}\text{H}_{26}\text{ClNO}$ : C, 69.02; H, 8.86; N, 4.73. Found: C, 69.29; H, 9.11; N, 4.40.

**(2S,3S)-1-Allyl-2-[(1S)-1-chloro-3-methylbutyl]-3-methoxyazetidine 4d:** Colorless oil;  $R_f = 0.28$  (hexane/EtOAc 6/1); yield 66%;  $[\alpha]_D = -112$  ( $c = 0.24$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.83 and 0.86 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.9$  Hz), 1.33–1.41 (2H, m), 1.81–1.94 (1H, m), 2.71 (1H, dd,  $J = 9.2$ , 5.5 Hz), 2.80 (1H, dd,  $J = 13.1$ , 8.0 Hz), 3.12 (1H, dd,  $J = 9.6$ , 6.3 Hz), 3.18 (3H, s), 3.34 (1H, d,  $J = 9.2$  Hz), 3.80 (1H, dd  $\times$  t,  $J = 13.1$ , 5.0, 1.7 Hz), 3.88 (1H, ddd,  $J = 6.3$ , 5.5, 1.1 Hz), 4.30–4.38 (1H, m), 5.01–5.13 (2H, m), 5.70–5.83 (1H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  20.7 and 23.8 ( $2 \times \text{CH}_3$ ), 24.6 (CH), 43.1 ( $\text{CH}_2$ ), 55.6 ( $\text{CH}_2$ ), 56.2 ( $\text{CH}_3$ ), 61.7 ( $\text{CH}_2$ ), 62.3 (CH), 73.0 and 73.2 ( $2 \times \text{CH}$ ), 117.6 ( $\text{CH}_2$ ), 134.4 (CH); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2956$ , 1465, 1366, 1190, 1111, 920, 689; MS (70 eV)  $m/z$  (%) 232/4 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{12}\text{H}_{22}\text{ClNO}$ : C, 62.19; H, 9.57; N, 6.04. Found: C, 61.95; H, 9.76; N, 5.84.

**(2S,3S)-3-Benzyl-1-butyl-2-[(1S)-1-chloro-3-methylbutyl]-azetidine 4e:** Colorless oil;  $R_f = 0.40$  (hexane/EtOAc 6/1); yield 74%;  $[\alpha]_D = -96$  ( $c = 0.27$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94–0.99 (9H, m), 1.33–1.55 (6H, m), 1.99–2.12 (1H, m), 2.24–2.32 (1H, m), 2.84 (1H, dd,  $J = 9.0$ , 5.2 Hz), 3.18–3.32 (2H, m), 3.60 (1H, d,  $J = 9.0$  Hz), 4.19–4.24 (1H, m),

4.37 (1H, d,  $J = 12.1$  Hz), 4.52–4.60 (1H, m), 4.68 (1H, d,  $J = 12.1$  Hz), 7.33–7.40 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_2$  and  $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 24.6 (CH), 29.6 ( $\text{CH}_2$ ), 43.2 ( $\text{CH}_2$ ), 56.9 ( $\text{CH}_2$ ), 59.3 ( $\text{CH}_2$ ), 62.5 (CH), 70.6 ( $\text{CH}_2$ ), 71.0 (CH), 73.7 (CH), 127.7, 127.8, and 128.3 ( $5 \times \text{CH}$ ), 137.9 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2925$ , 1447, 1110, 732, 697; MS (70 eV)  $m/z$  (%) 324/6 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{19}\text{H}_{30}\text{ClNO}$ : C, 70.45; H, 9.34; N, 4.32. Found: C, 70.32; H, 9.59; N, 4.13.

**(2S,3S)-1-Benzyl-2-[(1S,2S)-1-chloro-2-methylbutyl]-3-methoxyazetidine 4f:** White crystals; mp 54.6 °C;  $R_f = 0.27$  (hexane/EtOAc 7/1); yield 80%;  $[\alpha]_D = -123$  ( $c = 1.15$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.92 (3H, t,  $J = 7.4$  Hz), 1.02 (3H, d,  $J = 6.6$  Hz), 1.21–1.34 and 1.45–1.60 ( $2 \times 1\text{H}$ ,  $2m$ ), 1.75–1.88 (1H, m), 2.77 (1H, dd,  $J = 8.9$ , 5.5 Hz), 3.22 (3H, s), 3.27 (1H, d,  $J = 8.9$  Hz), 3.39 (1H, d,  $J = 12.7$  Hz), 3.49 (1H, dd,  $J = 10.2$ , 6.1 Hz), 3.90 (1H, ddd,  $J = 6.1$ , 5.5, 1.1 Hz), 4.40 (1H, d,  $J = 12.7$  Hz), 4.47 (1H, dd,  $J = 10.2$ , 2.8 Hz), 7.22–7.35 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  12.0 ( $\text{CH}_3$ ), 17.0 ( $\text{CH}_3$ ), 23.6 ( $\text{CH}_2$ ), 37.6 (CH), 55.5 ( $\text{CH}_2$ ), 56.1 ( $\text{CH}_3$ ), 62.7 ( $\text{CH}_2$ ), 69.9 and 70.2 ( $2 \times \text{CH}$ ), 73.6 (CH), 127.1, 128.3, and 129.3 ( $5 \times \text{CH}$ ), 137.7 (C); IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2935$ , 1452, 1357, 1185, 1105, 1045, 732, 695; MS (70 eV)  $m/z$  (%) 282/4 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{16}\text{H}_{24}\text{ClNO}$ : C, 68.19; H, 8.58; N, 4.97. Found: C, 68.33; H, 8.81; N, 4.71.

**(2S,3S)-2-[(1S,2S)-1-Chloro-2-methylbutyl]-3-phenoxy-1-propylazetidine 4g:** Light-yellow oil;  $R_f = 0.41$  (hexane/EtOAc 7/1); yield 79%;  $[\alpha]_D = -85$  ( $c = 0.56$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 and 0.89 ( $2 \times 3\text{H}$ ,  $2t$ ,  $J = 7.4$ , 7.2 Hz), 1.04 (3H, d,  $J = 6.6$  Hz), 1.21–1.59 (4H, m), 1.78–1.88 (1H, m), 2.23 (1H, ddd,  $J = 11.0$ , 9.6, 5.2 Hz), 3.02 (1H, dd,  $J = 9.4$ , 5.5 Hz), 3.21 (1H, ddd,  $J = 11.0$ , 10.2, 6.3 Hz), 3.51–3.56 (2H, m), 4.65 (1H, dd,  $J = 10.5$ , 2.8 Hz), 4.78 (1H, ddd,  $J = 5.5$ , 5.5, 1.5 Hz), 6.71–6.76, 6.83–6.99 and 7.21–7.30 (5H,  $3m$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  11.9 ( $2 \times \text{CH}_3$ ), 17.0 ( $\text{CH}_3$ ), 20.5 and 23.6 ( $2 \times \text{CH}_2$ ), 37.4 (CH), 57.4 ( $\text{CH}_2$ ), 61.5 ( $\text{CH}_2$ ), 69.1 (CH), 69.8 and 70.6 ( $2 \times \text{CH}$ ), 115.0 ( $2 \times \text{CH}$ ), 121.4 (CH), 129.7 ( $2 \times \text{CH}$ ), 156.7 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2961$ , 1599, 1494, 1238, 751, 690; MS (70 eV)  $m/z$  (%) 296/8 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{17}\text{H}_{26}\text{ClNO}$ : C, 69.02; H, 8.86; N, 4.73. Found: C, 69.22; H, 9.08; N, 4.42.

**Synthesis of (2R,3S,4R)-2-Alkyl-3-chloropyrrolidines 5a–g.** As a representative example, the synthesis of (2R,3S,4R)-2-benzyl-4-benzyl-3-chloro-1-cyclohexylpyrrolidine **5a** is described.

A solution of 1.54 g of (2S,3S)-3-benzyl-2-[(1S)-1-chloro-2-phenylethyl]-1-cyclohexylazetidine **4a** (4 mmol) in acetonitrile (25 mL) was stirred for 18 h at reflux temperature. After evaporation of the solvent, the crude reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc 7/1), affording pure (2R,3S,4R)-2-benzyl-4-benzyl-3-chloro-1-cyclohexylpyrrolidine **5a** in 71% yield.

**(2R,3S,4R)-2-Benzyl-4-benzyl-3-chloro-1-cyclohexylpyrrolidine 5a:** Light-yellow oil;  $R_f = 0.35$  (hexane/EtOAc 7/1); yield 71%;  $[\alpha]_D = -18$  ( $c = 1.30$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.06–1.25 and 1.63–1.84 ( $2 \times 5\text{H}$ ,  $2m$ ), 2.57–2.70 (1H, m), 2.92 (1H, dd,  $J = 13.2$ , 4.4 Hz), 2.96–3.12 (3H, m), 3.39–3.42 (1H, m), 3.94 (1H, ddd,  $J = 8.4$ , 8.4, 4.2 Hz), 4.21–4.26 (1H, m), 4.35 and 4.61 ( $2 \times 1\text{H}$ ,  $2d$ ,  $J = 11.6$  Hz), 7.19–7.34 (10H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  23.7, 25.6, 26.4, 26.5, and 33.1 ( $5 \times \text{CH}_2$ ), 36.1 ( $\text{CH}_2$ ), 48.5 ( $\text{CH}_2$ ), 56.8 (CH), 63.7 (CH), 64.2 (CH), 71.4 ( $\text{CH}_2$ ), 77.4 (CH), 126.4, 127.9, 128.6, and 129.5 ( $10 \times \text{CH}$ ), 137.6 and 139.0 ( $2 \times \text{C}$ ); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2925$ , 1452, 1139, 738, 698; MS (70 eV)  $m/z$  (%) 384/6 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{24}\text{H}_{30}\text{ClNO}$ : C, 75.08; H, 7.88; N, 3.65. Found: C, 74.84; H, 8.05; N, 3.36.

**(2R,3S,4R)-2-Benzyl-3-chloro-1-isopropyl-4-phenoxy-pyrrolidine 5b:** Light-yellow oil;  $R_f = 0.37$  (hexane/EtOAc 7/1); yield 75%;  $[\alpha]_D = -22$  ( $c = 0.56$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,



$\text{CDCl}_3$ )  $\delta$  1.00 and 1.17 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.3$  Hz), 2.96 (1H, dd,  $J = 13.2$ , 4.4 Hz), 3.03–3.25 (3H, m), 3.21 (1H, d,  $J = 8.0$  Hz), 3.32–3.42 (1H, m), 4.33 (1H, dd,  $J = 4.4$ , 4.4 Hz), 4.65 (1H, ddd,  $J = 8.0$ , 8.0, 4.4 Hz), 6.85–6.98 and 7.18–7.30 (10H, 2m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  13.5 and 22.4 ( $2 \times \text{CH}_3$ ), 35.9 ( $\text{CH}_2$ ), 47.4 ( $\text{CH}_2$ ), 48.1 (CH), 63.2 (CH), 65.3 (CH), 76.2 (CH), 116.1 ( $2 \times \text{CH}$ ), 122.0 (CH), 126.6, 128.7, 129.5, 129.7 ( $7 \times \text{CH}$ ), 138.7 (C), 157.5 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2964$ , 1597, 1493, 1238, 750, 691; MS (70 eV)  $m/z$  (%) 330/2 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{ClNO}$ : C, 72.82; H, 7.33; N, 4.25. Found: C, 73.06; H, 7.56; N, 3.87.

**(2R,3S,4R)-4-Benzoyloxy-3-chloro-1,2-diisopropylpyrrolidine 5c:** White crystals; mp 45.1 °C;  $R_f = 0.11$  (hexane/EtOAc 4/1); yield 74%;  $[\alpha]_D = -37$  ( $c = 1.56$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 and 1.06 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.8$  Hz), 1.32 and 1.39 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.3$  Hz), 2.27 (1H, sept  $\times$  d,  $J = 6.8$ , 2.2 Hz), 3.61–3.72 (1H, m), 3.79–3.91 (1H, m), 4.04–4.14 (1H, m), 4.28–4.39 (2H, m), 4.44 and 4.70 ( $2 \times 1\text{H}$ ,  $2d$ ,  $J = 12.1$  Hz), 5.22 (1H, dd,  $J = 10.2$ , 2.2 Hz), 7.29–7.37 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  15.3, 15.7, 18.2, and 20.5 ( $4 \times \text{CH}_3$ ), 29.4 (CH), 51.0 ( $\text{CH}_2$ ), 54.1 (CH), 63.2 (CH), 68.5 and 70.3 ( $2 \times \text{CH}$ ), 71.6 ( $\text{CH}_2$ ), 127.9, 128.3, and 128.7 ( $5 \times \text{CH}$ ), 136.4 (C); IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2966$ , 1454, 1140, 734, 695; MS (70 eV)  $m/z$  (%) 296/8 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{17}\text{H}_{26}\text{ClNO}$ : C, 69.02; H, 8.86; N, 4.73. Found: C, 69.36; H, 9.09; N, 4.44.

**(2R,3S,4R)-1-Allyl-3-chloro-4-methoxy-2-(2-methylpropyl)pyrrolidine 5d:** Colorless oil;  $R_f = 0.27$  (hexane/EtOAc 4/1); yield 52%;  $[\alpha]_D = -7$  ( $c = 0.22$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85 and 0.92 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.9$  Hz), 1.21–1.43 (1H, m), 1.56–1.76 (2H, m), 2.82 (1H, dd,  $J = 10.6$ , 8.8 Hz), 2.89–2.96 (2H, m), 3.04 (1H, dd,  $J = 10.6$ , 8.0 Hz), 3.36 (3H, s), 3.34–3.44 (1H, m), 3.93 (1H, ddd,  $J = 8.8$ , 8.0, 4.0 Hz), 4.44 (1H, dd,  $J = 4.0$ , 3.6 Hz), 5.10–5.19 (2H, m), 5.77–5.90 (1H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  22.1 and 24.1 ( $2 \times \text{CH}_3$ ), 25.4 (CH), 38.6 ( $\text{CH}_2$ ), 54.0 ( $\text{CH}_2$ ), 56.3 ( $\text{CH}_2$ ), 57.4 ( $\text{CH}_3$ ), 63.36 and 63.40 ( $2 \times \text{CH}$ ), 79.5 (CH), 118.0 ( $\text{CH}_2$ ), 134.6 (CH); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2955$ , 1466, 1367, 1216, 1144, 992, 919; MS (70 eV)  $m/z$  (%) 232/4 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{12}\text{H}_{22}\text{ClNO}$ : C, 62.19; H, 9.57; N, 6.04. Found: C, 61.89; H, 9.73; N, 5.76.

**(2R,3S,4R)-4-Benzoyloxy-1-butyl-3-chloro-2-(2-methylpropyl)pyrrolidine 5e:** Colorless oil;  $R_f = 0.31$  (hexane/EtOAc 6/1); yield 75%;  $[\alpha]_D = -13$  ( $c = 0.58$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 and 0.96 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.3$  Hz), 0.90 (3H, t,  $J = 6.6$  Hz), 1.22–1.51 and 1.60–1.82 (4H and 3H, 2m), 2.10–2.27 (1H, m), 2.64–2.88 (3H, m), 3.19 (1H, dd,  $J = 10.2$ , 8.0 Hz), 4.10–4.22 (1H, m), 4.44–4.47 (1H, m), 4.45 and 4.70 ( $2 \times 1\text{H}$ ,  $2d$ ,  $J = 11.6$  Hz), 7.28–7.42 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.1, and 24.1 ( $3 \times \text{CH}_3$ ), 20.6, 25.4, 30.1, and 38.3 ( $3 \times \text{CH}_2$  and CH), 53.9 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 63.4 (CH), 64.7 (CH), 71.6 ( $\text{CH}_2$ ), 76.8 (CH), 128.0 and 128.6 ( $5 \times \text{CH}$ ), 137.6 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2954$ , 1455, 1366, 1142, 734, 696; MS (70 eV)  $m/z$  (%) 324/6 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{19}\text{H}_{30}\text{ClNO}$ : C, 70.45; H, 9.34; N, 4.32. Found: C, 70.22; H, 9.66; N, 4.15.

**(2R,3S,4R)-1-Benzyl-3-chloro-2-[(1S)-1-methylpropyl]-4-methoxypyrrolidine 5f:** Colorless oil;  $R_f = 0.32$  (hexane/EtOAc 6/1); yield 68%;  $[\alpha]_D = +10$  ( $c = 1.13$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (3H, t,  $J = 7.4$  Hz), 1.10 (3H, d,  $J = 7.2$  Hz), 1.15–1.25 and 1.64–1.75 ( $2 \times 1\text{H}$ , 2m), 1.96–2.03 (1H, m), 2.74 (1H, dd,  $J = 10.6$ , 7.4 Hz), 2.85–2.95 (1H, m), 3.05 (1H, dd,  $J = 10.6$ , 10.6 Hz), 3.37 (3H, s), 3.53 and 3.93 ( $2 \times 1\text{H}$ ,  $2d$ ,  $J = 14.0$  Hz), 3.87–4.00 (1H, m), 4.65 (1H, dd,  $J = 4.2$ , 4.2 Hz),

7.22–7.39 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7 ( $\text{CH}_3$ ), 16.3 ( $\text{CH}_3$ ), 26.3 ( $\text{CH}_2$ ), 37.6 (CH), 54.4 ( $\text{CH}_2$ ), 57.4 ( $\text{CH}_3$ ), 61.6 ( $\text{CH}_2$ ), 64.1 (CH), 71.2 (CH), 79.0 (CH), 127.1, 128.3, and 128.5 ( $5 \times \text{CH}$ ), 139.9 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2961$ , 1452, 1374, 1221, 1125, 729, 694; MS (70 eV)  $m/z$  (%) 282/4 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{16}\text{H}_{24}\text{ClNO}$ : C, 68.19; H, 8.58; N, 4.97. Found: C, 68.52; H, 8.91; N, 4.67.

**(2R,3S,4R)-3-Chloro-2-[(1S)-1-methylpropyl]-4-phenoxy-1-propylpyrrolidine 5g:** Light-yellow oil;  $R_f = 0.31$  (hexane/EtOAc 7/1); yield 67%;  $[\alpha]_D = +4$  ( $c = 0.63$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94 ( $2 \times 3\text{H}$ , 2t,  $J = 7.4$  Hz), 1.07 (3H, d,  $J = 7.2$  Hz), 1.11–1.21 and 1.53–1.69 (1H and 3H, 2m), 1.90–1.98 (1H, m), 2.39–2.48 and 2.57–2.67 ( $2 \times 1\text{H}$ , 2m), 2.83 (1H, dd,  $J = 8.3$ , 3.9 Hz), 3.02 (1H, dd,  $J = 10.9$ , 7.4 Hz), 3.41 (1H, dd,  $J = 10.9$ , 9.4 Hz), 4.70–4.74 (1H, m), 4.77–4.84 (1H, m), 6.98–7.05 and 7.30–7.35 (5H, 2m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7 and 11.8 ( $2 \times \text{CH}_3$ ), 16.2 ( $\text{CH}_3$ ), 22.7 and 26.2 ( $2 \times \text{CH}_2$ ), 37.3 (CH), 54.9 ( $\text{CH}_2$ ), 60.2 ( $\text{CH}_2$ ), 63.7 (CH), 71.8 (CH), 75.6 (CH), 116.2 ( $2 \times \text{CH}$ ), 121.9 (CH), 129.7 ( $2 \times \text{CH}$ ), 157.6 (C); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{max}} = 2961$ , 1599, 1493, 1237, 752, 735, 690; MS (70 eV)  $m/z$  (%) 296/8 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{17}\text{H}_{26}\text{ClNO}$ : C, 69.02; H, 8.86; N, 4.73. Found: C, 69.33; H, 9.11; N, 4.41.

**Synthesis of (2R,3S,4R)-1-Butyl-3-chloro-4-hydroxy-2-(2-methylpropyl)pyrrolidine 7.** Palladium on activated carbon (0.019 g, 10% Pd) was added to a solution of 0.19 g of (2R,3S,4R)-4-benzoyloxy-1-butyl-3-chloro-2-(2-methylpropyl)pyrrolidine **5e** (0.6 mmol, 1 equiv) and  $\text{HCl}_{\text{conc}}$  (1.2 mmol, 2 equiv) in methanol (5 mL), and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred at room temperature for 16 h while applying 5 bar of hydrogen gas. After filtration of the heterogeneous mixture through Celite and evaporation of the solvent in vacuo, the crude reaction product was purified by column chromatography on silica gel (hexane/EtOAc 4/1), affording pure (2R,3S,4R)-1-butyl-3-chloro-4-hydroxy-2-(2-methylpropyl)pyrrolidine **7** in 90% yield.

**(2R,3S,4R)-1-Butyl-3-chloro-4-hydroxy-2-(2-methylpropyl)pyrrolidine 7:** Light-brown crystals; mp 82.3 °C;  $R_f = 0.11$  (hexane/EtOAc 4/1); yield 75%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.90 and 0.96 ( $2 \times 3\text{H}$ ,  $2d$ ,  $J = 6.1$  Hz), 0.91 (3H, t,  $J = 6.6$  Hz), 1.26–1.49 and 1.64–1.73 (5H and 2H, 2m), 2.15–2.24 (2H, m), 2.64–2.77 (1H, m), 2.74 (1H, dd,  $J = 10.5$ , 8.3 Hz), 2.83 (1H, ddd,  $J = 9.4$ , 4.3, 4.3 Hz), 3.00 (1H, dd,  $J = 10.5$ , 6.6 Hz), 4.35–4.41 (1H, m), 4.47 (1H, dd,  $J = 4.3$ , 4.3 Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.1, and 24.1 ( $3 \times \text{CH}_3$ ), 20.7, 25.4, 30.5, and 39.2 ( $3 \times \text{CH}_2$  and CH), 53.9 ( $\text{CH}_2$ ), 58.1 ( $\text{CH}_2$ ), 64.5 (CH), 68.1 (CH), 70.8 (CH); IR (NaCl,  $\text{cm}^{-1}$ )  $\nu_{\text{OH}} = 3040$ ;  $\nu_{\text{max}} = 2955$ , 1462, 1139, 918, 726; MS (70 eV)  $m/z$  (%) 234/6 ( $\text{M}^+ + 1$ , 100). Anal. Calcd for  $\text{C}_{12}\text{H}_{24}\text{ClNO}$ : C, 61.65; H, 10.35; N, 5.99. Found: C, 61.88; H, 10.56; N, 5.73.

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**Supporting Information Available:** Crystallographic data of compound **3a** and spectroscopic data of compounds **3b–g**, **4b–g**, and **5b–g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.