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Asymmetric Synthesis of 1-(2- and 3-Haloalkyl)azetidin-2-ones as Precursors for Novel Piperazine, Morpholine, and 1,4-Diazepane Annulated Beta-Lactams

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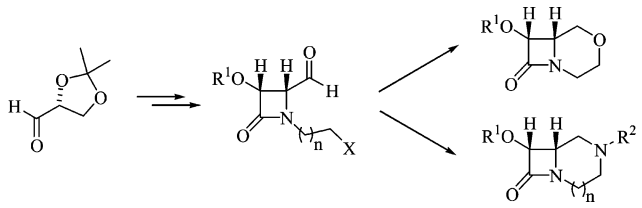

A high-yielding, asymmetric synthesis of novel 4-formyl-1-(2- and 3-haloalkyl)azetidin-2-ones was developed as valuable starting materials for the synthesis of different enantiomerically enriched bicyclic azetidin-2-ones, such as piperazine, morpholine, and 1,4-diazepane annulated β-lactam derivatives. Especially the hydride reduction of 4-imidoyl-1-(2- and 3-haloalkyl)azetidin-2-ones turned out to be an efficient and straightforward method for the preparation 2-substituted piperazines and 1,4-diazepanes.

Introduction

The Staudinger reaction, in which an imine and an acid chloride react in the presence of a base, comprises a very reliable and robust method for the preparation of β-lactam derivatives.[1−4] Because β-lactams are widely recognized for their antibiotic activity, in addition to macrolides and fluoroquinolones, research in this area remains indispensable to provide new entries toward azetidin-2-ones with potential biological activity.[5] Up to now, no examples of Staudinger reactions leading to 1-(2- and 3-haloalkyl)azetidin-2-ones have been reported, probably because of the instability of the requisite *N*-alkylidene-(2- and 3-haloalkyl)-amines. However, the synthesis of 1-(2- and 3-haloalkyl)-azetidin-2-ones by means of the Staudinger reaction could pave the way for the preparation of a large variety of different biological interesting compounds such as bicyclic β-lactams and other azaheterocycles. In addition, the fact that asymmetric induction during the Staudinger reaction has been thoroughly investigated in the past[1,6,7] urged us to evaluate this methodology for the synthesis of novel optically active 1-(2- and 3-haloalkyl)-azetidin-2-ones and their conversion into different fused azaheterocycles such as piperazine, morpholine, and 1,4-diazepane annulated β-lactam derivatives.

Results and Discussion

Whereas 4-formyl-β-lactams have already proven their potential in the stereocontrolled synthesis of heterocycles, amino acids, amino sugars, etc.,[8] their 1-(2- and 3-haloalkyl) derivatives have not been synthesized and evaluated up to now. Therefore, (*R*)-glyceraldehyde acetonide **1** was treated with different ω-haloalkylammonium halides to prepare the corresponding functionalized imines **2** and **4** (Scheme 1). When 2-chloroethylammonium chloride and 3-bromopropylammonium bromide were used, the condensation reaction with (*R*)-glyceraldehyde acetonide **1** toward the corresponding chiral imines **2** and **4** could be performed in almost quantitative yields. In contrast, when 2-bromoethylammonium bromide was used, a complex reaction mixture was obtained, probably due to the lability of the corresponding *N*-(2-bromoethyl)imine. Imines **2** and **4** had to be handled with care, i.e., no heating above room temperature and immediate further elaboration, as decomposition of the latter compounds occurred relatively easy (after 1 day at room temperature, the purity of the imines was reduced to less than 50%). Imines **2** and **4** turned out to be valuable starting materials for the preparation of 1-(ω-haloalkyl)-β-lactams **3** and **5** through a Staudinger reaction. Treatment of the latter imines **2** and **4** with 1.3 equiv of benzyloxy-, phenoxy-, or methoxyacetyl chloride in dichloromethane in the presence of triethylamine afforded the optically active corresponding β-lactams **3** and **5** in high yield and with high diastereomeric excess (Scheme 1, Table 1).

Azetidin-2-ones **3** and **5** could be easily converted into the premised 4-formyl-1-(2- and 3-haloalkyl)azetidin-2-ones **7** and **9** by consecutive hydrolysis in THF in the presence of *p*-toluenesulfonic acid (PTSA) toward diols **6** and **8** and oxidation of the resulting diols by sodium periodate in a two phase system of water and dichloromethane (Scheme 2, Table 2). The e.e. values of the 4-formyl-1-(2- and 3-haloalkyl)azetidin-2-ones **7** and **9** were equal to the d.e. values of their starting products **3** and **5** (e.e. values obtained by chiral GC).

Subsequently, the synthetic potential of 4-formyl-1-haloalkyl-β-lactams **7** and **9**, prepared by an asymmetric approach, toward novel bicyclic β-lactam derivatives was investigated for the first time. Thus, 1-(2-haloethyl)azetidin-2-ones **7a**,**b** were treated with 2 equiv of $NaBH_4$ in methanol under reflux for 1 h, furnishing the corresponding chiral 4-hydroxymethyl-β-lactams **10** in 86−89% yield (Scheme 3). Treatment of the latter alcohols **10** with NaH in DMSO resulted in a complex reaction mixture,

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SCHEME 1

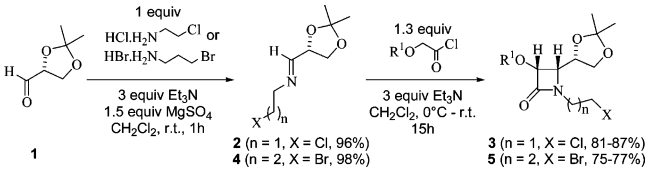


TABLE 1. Synthesis of 1-(*ω*-Haloalkyl)-*β*-lactams 3a−c and 5a,b

compound	R^1	*n*	X	yield (%)	d.e. (%)[a]
3a	Bn	1	Cl	86	87
3b	Ph	1	Cl	87	88
3c	Me	1	Cl	81	83
5a	Bn	2	Br	77	88
5b	Me	2	Br	75	91

[a] Determined by means of ^{1}H NMR and GC.

SCHEME 2

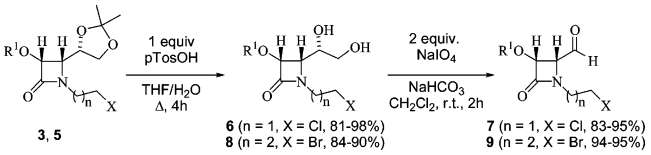
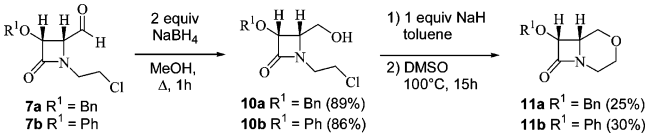


TABLE 2. Synthesis of 4-(1,2-Dihydroxyethyl)azetidin-2-ones 6 and 8 and of 4-Formyl-*β*-lactams 7 and 9

compound	R^1	*n*	X	yield (%)	d.e. (%)[a]
6a	Bn	1	Cl	98	87
6b	Ph	1	Cl	92	88
6c	Me	1	Cl	81	83
8a	Bn	2	Br	84	88
8b	Me	2	Br	90	88
7a	Bn	1	Cl	94	87
7b	Ph	1	Cl	95	88
7c	Me	1	Cl	83	83
9a	Bn	2	Br	95	88
9b	Me	2	Br	94	91

[a] Determined by means of ^{1}H NMR and GC.

SCHEME 3



with no traces of the desired bicyclic *β*-lactams **11**. On the other hand, deprotonation of the alcohols **10** by means of NaH in toluene (resulting in precipitation of the formed sodium salts), followed by removal of solvent under reduced pressure and addition of DMSO afforded optically active bicyclic *β*-lactams **11** after stirring overnight at 100 °C (Scheme 3). The bicyclic *β*-lactams **11** were purified by column chromatography. An analogous ring closure has been reported starting from 1-(1,2-dibromopropyl)-4-hydroxymethyl-*β*-lactams.[9] Our methodology comprises a new asymmetric approach not only toward the 2-iso-oxacepham skeleton, but also for the preparation of novel substituted morpholine derivatives, which can be applied as appetite suppressants, antidepressants, antitumor agents, antioxidants, and antibiotics.[10]

SCHEME 4

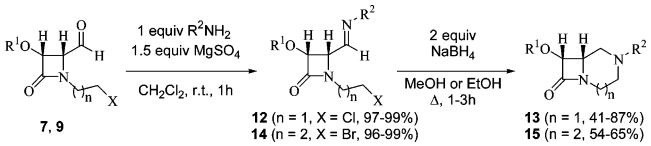


TABLE 3. Synthesis of 4-Imidoyl-*β*-lactams 12 and 14 and of Diazabicycloalkanones 13 and 15

R^1	R^2	*n*	compound (% yield)	compound (% yield)
Bn	Allyl	1	**12a** (98)	**13a** (81)
Bn	^{i}Pr	1	**12b** (97)	**13b** (59)
Me	Allyl	1	**12c** (98)	**13c** (87)
Me	^{t}Bu	1	**12d** (99)	**13d** (41)
Me	Bn	1	**12e** (97)	**13e** (63)
Bn	Allyl	2	**14a** (98)	**15a** (65)
Bn	^{t}Bu	2	**14b** (96)	**15b** (54)
Me	Allyl	2	**14c** (99)	**15c** (62)
Me	^{i}Pr	2	**14d** (98)	**15d** (57)
Me	Bn	2	**14e** (99)	**15e** (59)

In addition to the preparation of 4-oxa-1-azabicyclo[4.2.0]-octan-8-ones **11**, a synthesis of their nitrogen counterparts was developed to broaden the scope of this methodology. Conversion of 4-formyl-1-(*ω*-haloalkyl)-*β*-lactams **7** and **9** into the corresponding novel 4-imidoyl-*β*-lactams **12** and **14** upon condensation with different primary amines, followed by reduction of the latter azetidin-2-ones **12** and **14** with $NaBH_4$ in refluxing methanol or ethanol yielded the corresponding optically active bicyclic *β*-lactams **13** and **15** in good to high yields in a one step procedure (Scheme 4, Table 3).[11] In a few cases, the corresponding 4-aminomethyl-2-azetidinones were formed as minor constituents (<20%). The reductive ring closure of monocyclic α-(*N*-haloalkylamino)imines toward the corresponding diazaheterocycles comprises a new and very elegant methodology in organic synthesis. In the literature, analogous piperazine annulated *β*-lactams have been prepared either by cyclization of Boc-protected 4-aminomethyl-1-(2-hydroxyethyl)-*β*-lactams in a four-step approach, involving mesylation, *N*-deprotection, base-induced ring closure and *N*-protection,[12] or by intramolecular dipolar cycloaddition of 4-vinyl-2-azetidinones.[13] The presented methodology comprises an elegant and efficient alternative for these approaches. The yields appeared to be lower when sterically hindering substituents were present at the imidoyl nitrogen (R^2 = ^{t}Bu, ^{i}Pr). Because of the steric hindrance, ring closure proceeded slower and reflux in ethanol instead of methanol was needed for the cyclization. The fact that 1,4-diazabicyclo[4.2.0]octan-8-ones **13** and 1,5-diazabicyclo[5.2.0]-nonan-9-ones **15** cannot only be considered as novel bicyclic *β*-lactam skeletons, but also as bicyclic piperazine and 1,4-diazepane derivatives adds significant value to the biological relevance of these target compounds. *β*-Lactams **13** are of particular interest due to their structural resemblance to the unsaturated isodethiaazacephems, which are known as potent

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(11) See supporting information (Table 4) for detailed reaction conditions for any specific case in the synthesis of azetidin-2-ones **13** and **15**.

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antibacterial agents.[14] Piperazine derivatives are frequently used as antifungals, antidepressants, antivirals, and serotoninreceptor (5-HT) antagonists/agonists,[15] and carbon-monosubstituted piperazines have been reported as farnesyl transferase inhibitors and neurokinin-1 antagonists.[16] Also, diazepanes in general and 1,4-benzodiazepines in particular have received a lot of attention because of their value in psychotherapy (e.g., diazepam, the active compound in Valium).[17]

In conclusion, a new asymmetric synthesis of novel 4-formyl-1-(2- and 3-haloalkyl)azetidin-2-ones has been developed as valuable starting materials for the synthesis of different optically active bicyclic azetidin-2-ones, such as piperazine, morpholine, and 1,4-diazepane annulated β-lactam derivatives. Especially the reduction of 4-imidoyl-1-(2- and 3-haloalkyl)azetidin-2-ones with $NaBH_4$ turned out to be a promising method for the synthesis of 2-substituted piperazines and 1,4-diazepanes as interesting new targets with potential biological activity.

Experimental Section

(*R*)-Glyceraldehyde acetonide **1** was synthesized according to literature procedures.[18,19]

Synthesis of 1-(2-chloroethyl)-β-lactams 3 and 1-(3-Bromopropyl)-β-lactams 5. As a representative example, the synthesis of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)azetidin-2-one **3a** is described. In a 100 mL flask, 2.82 g (14.8 mmol, 1 equiv) of 2-chloro-*N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)ethylamine **2** was dissolved in 50 mL dry CH_2Cl_2, and 4.48 g (44.4 mmol, 3 equiv) of triethylamine was added to the mixture, which was cooled to 0 °C. Subsequently, a mixture of 3.54 g (19.2 mmol, 1.3 equiv) of benzyloxyacetyl chloride in 20 mL of dry CH_2Cl_2 was added dropwise. The reaction mixture was allowed to warm slowly to room temperature (over a period of about 2 h) and was stirred overnight at room temperature. Then, water (50 mL) was added to the reaction mixture and the organic layer was isolated. The aqueous fraction was additionally extracted twice with 25 mL of CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), and the solvent was evaporated under vacuum. Further purification was performed by flash chromatography on silica gel (petroleum ether/EtOAc 6/1).

(3*R*,4*S*)-3-Benzyloxy-1-(2-chloroethyl)-4-((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)azetidin-2-one 3a. Colorless oil, 86% yield, TLC Rf 0.05 (petroleum ether/ EtOAc 6/1), $[\alpha]_D = +59°$ (*c* 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.34 and 1.44 (6H, 2 × s), 3.57−3.78 (6H, m), 4.15 (1H, d × d, $J = 8.8$ Hz, $J = 6.6$ Hz), 4.34 (1H, d × t, $J = 9.1$ Hz, $J = 6.3$ Hz), 4.64 (1H, d, $J = 11.7$ Hz), 4.67 (1H, d, $J = 5.2$ Hz), 4.91 (1H, d, $J = 11.7$ Hz), 7.26−7.40 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 25.1, 26.8, 40.8, 42.8, 60.8, 66.7, 72.9, 76.9, 80.4, 109.6, 127.8, 128.1, 128.5, 136.8, 167.9. **IR** (NaCl, cm^{-1}): $\nu_{C=O} = 1763$. **MS** (70 eV) *m*/*z* (%): 342/0 (M^++1, 100). Anal. Calcd for $C_{17}H_{22}ClNO_4$: C 60.09; H 6.53; N 4.12. Found: C 60.35; H 6.40; N 4.26.

Synthesis of 4-Formyl-β-lactams 7 and 9. The conversion of 4-((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)azetidin-2-ones **3** and **5** into 4-formyl-β-lactams **7** and **9** was performed according to a literature procedure.[20]As a representative example, the synthesis of (2*R*,3*R*)-3-benzyloxy-1-(2-chloroethyl)-4-oxoazetidine-2-carbaldehyde **7a** is described. To a solution of 3.39 g of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)azetidin-2-one **3a** (10 mmol, 1 equiv) in THF/water (1:1, 200 mL) was added 2.28 g of p-TsOH·H_2O (12 mmol, 1.2 equiv) in a single portion. The resulting clear solution was heated under reflux for 4 h. The reaction mixture was allowed to cool to room temperature and was then neutralized with solid $NaHCO_3$. The mixture was extracted with EtOAc (3 × 40 mL), the organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure, yielding 2.93 g (9.8 mmol, 0.98 equiv) of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-((1*S*)-1,2-dihydroxyethyl)azetidin-2-one **6a**. In the next step, saturated aqueous sodium hydrogen carbonate (980 μL) was added to a solution of the diol (9.8 mmol) in dichloromethane (15 mL), maintaining the temperature below 25 °C. Solid sodium periodate (19.6 mmol) was added over a 10 min. period with vigorous stirring, and the reaction was allowed to proceed for 2 h while the temperature was maintained below 25 °C. The solid was removed by filtration, and the filtrate was washed with 25 mL of water, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Further purification, although not necessary to proceed to the next step, was performed by flash chromatography on silica gel or just by elution of the filtrate (obtained after drying with $MgSO_4$) over a silica gel column, followed by evaporation of the solvent in vacuo.

(3*R*,4*S*)-3-Benzyloxy-1-(2-chloroethyl)-4-((1*S*)-1,2-dihydroxyethyl)azetidin-2-one 6a. Colorless oil, 98% yield, TLC Rf 0.3 (EtOAc), $[\alpha]_D = +75°$ (*c* 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.20−2.30 and 2.88−2.96 (2H, 2 × m), 3.51−3.88 (6H, m), 3.90 (1H, t, $J = 5.0$ Hz), 4.15 (1H, m), 4.70 (1H, d, $J = 11.7$ Hz), 4.74 (1H, d, $J = 5.0$ Hz), 4.95 (1H, d, $J = 11.7$ Hz), 7.29−7.40 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 41.2, 43.4, 59.2, 63.9, 71.2, 73.3, 80.5, 128.1, 128.3, 128.6, 136.5, 168.4. **IR** (NaCl, cm^{-1}): $\nu_{C=O} = 1741$. **MS** (70 eV) *m*/*z* (%): 302/0 (M^++1, 100). Anal. Calcd for $C_{14}H_{18}ClNO_4$: C 56.10; H 6.05; N 4.67. Found: C 56.36; H 6.21; N 4.50.

(2*R*,3*R*)-3-Benzyloxy-1-(2-chloroethyl)-4-oxoazetidine-2-carbaldehyde 7a. White crystals, 94% yield, Mp: 54 °C, TLC Rf 0.4 (petroleum ether/ ethyl acetate 1/4), $[\alpha]_D = +133°$ (*c* 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.60−3.83 (4H, m), 4.38 (1H, d×d, $J = 5.1$ Hz, $J = 1.9$ Hz), 4.65 (1H, d, $J = 11.7$ Hz), 4.80 (1H, d, $J = 11.7$ Hz), 5.01 (1H, d, $J = 5.1$ Hz), 7.30−7.40 (5H, m), 9.58 (1H, d, $J = 1.9$ Hz). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 41.8, 43.5, 65.0, 73.5, 83.8, 128.3, 128.5, 128.7, 135.9, 166.5, 198.1. **IR** (NaCl, cm^{-1}): $\nu_{C=O} = 1761$ and 1733. **MS** (70 eV) *m*/*z* (%): 270/68 (M^++1, 90), 222 (100). Anal. Calcd for $C_{13}H_{14}ClNO_3$: C 58.32; H 5.27; N 5.23. Found: C 58.38; H 5.42; N 5.10.

Synthesis of 1-(2-Chloroethyl)-4-(hydroxymethyl)azetidin-2-ones 10. As a representative example, the synthesis of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-(hydroxymethyl)azetidin-2-one **10a** is described. In a 100 mL flask, 1.0 g (3.7 mmol, 1 equiv) of (2*R*,3*R*)-3-benzyloxy-1-(2-chloroethyl)-4-oxo-2-azetidinecarbaldehyde **7a** was dissolved in methanol (50 mL) and placed in an ice bath. Then, 0.28 g (7.5 mmol, 2 equiv) of $NaBH_4$ was added in portions, and the resulting mixture was kept at reflux temperature for 1 h. Water was added (50 mL), and the mixture was extracted 3 times with 40 mL of CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered over silicagel, and the solvent was evaporated in vacuo, yielding 0.89 g (3.3 mmol, 0.89 equiv) of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-(hydroxymethyl)azetidin-2-one **10a**.

(3*R*,4*S*)-3-Benzyloxy-1-(2-chloroethyl)-4-(hydroxymethyl)azetidin-2-one 10a. Colorless oil, 89% yield, $[\alpha]_D = +47°$ (*c* 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.38 (1H, broad s), 3.45

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(1H, d × d × d, J = 14.0 Hz, J = 7.2 Hz, J = 5.2 Hz), 3.64−3.69 (2H, m), 3.73−3.85 (1H, m), 3.88−3.93 (3H, m), 4.69 (1H, d, J = 11.6 Hz, 4.79 (1H, d, J = 4.4 Hz), 4.94 (1H, d, J = 11.6 Hz), 7.33−7.40 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 41.8, 42.3, 59.0, 59.7, 73.6, 81.8, 128.2, 128.4, 128.7, 136.4, 167.6. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$ = 1747. **MS** (70 eV) *m*/*z* (%): 272/0 (M^++1, 100). Anal. Calcd for $C_{13}H_{16}ClNO_3$: C 57.89; H 5.98; N 5.19. Found: C 58.10; H 5.84; N 4.99.

Synthesis of 4-Oxa-1-azabicyclo[4.2.0]octan-8-ones 11. As a representative example, the synthesis of (6*S*,7*R*)-7-benzyloxy-4-oxa-1-azabicyclo[4.2.0]octan-8-one **11a** is described. In a 100 mL flask, 0.89 g (3.3 mmol, 1 equiv) of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-(hydroxymethyl)azetidin-2-ones **10a** was dissolved in 10 mL of toluene. NaH (0.08 g (3.3 mmol, 1 equiv)) was added, and stirring was continued for 5 min at room temperature. Subsequently, the solvent was evaporated under reduced pressure and 30 mL of DMSO was added. The resulting reaction mixture was stirred overnight at 100 °C. Afterward, 50 mL of water was added, and the mixture was extracted 3 times with 40 mL of diethyl ether. The combined organic fractions were washed 3 times with 20 mL of water, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Further purification was performed by flash chromatography on silica gel, yielding 0.19 g (0.8 mmol, 0.25 equiv) of (6*S*,7*R*)-7-benzyloxy-4-oxa-1-azabicyclo[4.2.0]octan-8-one **11a**.

(6*R*,7*S*)-7-Benzyloxy-4-oxa-1-azabicyclo[4.2.0]octan-8-one 11a. Colorless oil, 25% yield, TLC Rf 0.2 (petroleum ether/ EtOAc 1/1), $[\alpha]_D$ = +24° (*c* 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.98 (1H, d × d × d×d, J = 13.5 Hz, J = 11.6 Hz, J = 4.7 Hz, J = 1.4 Hz), 3.38 (1H, t×d, J = 11.6 Hz, J = 3.6 Hz), 3.57 (1H, t, J = 9.9 Hz), 3.57−3.73 (3H, m), 3.79 (1H, d×d, J = 11.6 Hz, J = 4.7 Hz), 4.51 (1H, d, J = 11.6 Hz), 4.69 (1H, d×d, J = 4.1 Hz, J = 1.4 Hz), 4.82 (1H, d, J = 11.6 Hz), 7.32−7.40 (5H, m). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 38.6, 50.3, 65.7, 67.3, 73.7, 82.8, 128.3, 128.4, 128.6, 136.6, 167.7. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$ = 1758. **MS** (70 eV) *m*/*z* (%): 234 (M^++1, 40), 222 (100). Anal. Calcd for $C_{13}H_{15}ClNO_3$: C 66.94; H 6.48; N 6.00. Found: C 66.73; H 6.64; N 5.84.

Synthesis of 4-Imidoyl-β-lactams 12 and 14. As a representative example, the synthesis of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-((*E*)−(2-propenylimino)methyl)azetidin-2-one **12a** is described. In a 100 mL flask, 1.0 g (3.7 mmol, 1 equiv) of (2*R*,3*R*)-3-benzyloxy-1-(2-chloroethyl)-4-oxo-2-azetidinecarbaldehyde **7a** was dissolved in 50 mL of CH_2Cl_2, and 0.71 g (5.6 mmol, 1.5 equiv) of $MgSO_4$ was added. Subsequently, 0.21 g (3.7 mmol, 1 equiv) of allylamine was added, and the resulting mixture was stirred at room temperature for 1 h. $MgSO_4$ was filtered off, and the solvent was evaporated, yielding 1.11 g (3.6 mmol, 0.98 equiv) of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-((*E*)−(2-propenylimino)methyl)azetidin-2-one **12a**. Although the resulting imines are obtained in high purity, an additional purification can be performed by filtration of the imine (dissolved in a mixture of CH_2Cl_2/Et_3N (99/1)) over a column of silica gel (previously treated with a mixture of CH_2Cl_2/Et_3N (99/1)).

(3*R*,4*S*)-3-Benzyloxy-1-(2-chloroethyl)-4-((*E*)−(N−(2-propenylimino))methyl)-azetidin-2-one 12a. Colorless oil, 98% yield, $[\alpha]_D$ = 43° (*c* 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.51−3.73 (4H, m), 4.10 (2H, d × d, J = 6.1 Hz, J = 1.4 Hz), 4.36 (1H, d × d, J = 6.1 Hz, J = 5.0 Hz), 4.61 (1H, d, J = 11.7 Hz), 4.73 (1H, d, 11.7 Hz), 4.89 (1H, d, J = 5.0 Hz), 5.07−5.22 (2H, m), 5.89−6.02 (1H, m), 7.28−7.38 (5H, m), 7.69 (1H, d × t, J = 6.1 Hz, J = 1.4 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 41.2, 43.0, 61.5, 63.3, 73.1, 83.3, 116.7, 128.0, 128.2, 128.5, 134.9, 136.4, 161.4, 167.0. **IR** (NaCl, cm^{-1}): $\nu_{C=O}$ = 1761, ν_{max}= 2912, 2873, 1643, 1497. **MS** (70 eV) *m*/*z* (%): 307/9 (M^++1, 100). Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C 62.64; H 6.24; N 9.13. Found: C 62.40; H 6.39; N 9.29.

Synthesis of 1,4-Diazabicyclo[4.2.0]octan-8-ones 13 and 1,5-Diazabicyclo[5.2.0]nonan-9-ones 15. As a representative example, the synthesis of (6*S*,7*R*)-4-allyl-7-benzyloxy-1,4-diazabicyclo[4.2.0]-octan-8-one **13a** is described. Depending on the steric hindrance of the imidoyl substituent of the 4-imidoyl-β-lactams **12** and **14**, slightly different reaction conditions were required, presented in Table 1. In a 100 mL flask, 1.11 g (3.6 mmol, 1 equiv) of (3*R*,4*S*)-3-benzyloxy-1-(2-chloroethyl)-4-((*E*)−(2-propenylimino)methyl)-azetidin-2-one **12a** was dissolved in 40 mL of methanol and placed in an ice bath. 0.27 g (7.2 mmol, 2 equiv) of $NaBH_4$ was added, and the mixture was warmed and kept at reflux temperature for 1 h. Water (50 mL) was added, and the resulting mixture was extracted 3 times with 30 mL of CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), and the solvent was evaporated in vacuo. Further purification was performed by flash chromatography on silica gel (CH_2Cl_2/MeOH 95/5).

(6*S*,7*R*)-4-Allyl-7-benzyloxy-1,4-diazabicyclo[4.2.0]octan-8-one 13a. Colorless oil, 81% yield, TLC Rf 0.2 (CH_2Cl_2/MeOH 95/5), $[\alpha]_D$ = +25° (*c* 1, CH_2Cl_2).**^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.00 (1H, d × d × d, J = 11.6 Hz, J = 11.3 Hz, J = 4.1 Hz), 2.13 (1H, d × d, J = 11.4 Hz, J = 10.4 Hz), 2.67 (1H, d × d, J = 11.4 Hz, J = 4.4 Hz), 2.72 (1H, d × d, J = 11.3 Hz, J = 4.4 Hz), 2.91 (1H, d × d × d×d, J = 13.1 Hz, J = 11.6 Hz, J = 4.4 Hz, J = 1.1 Hz), 2.96−3.05 (2H, m), 3.54 (1H, d × t, J = 10.2 Hz, J = 4.3 Hz), 3.73 (1H, d × d, J = 13.1 Hz, J = 4.1 Hz), 4.53 (1H, d, J = 11.8 Hz), 4.69 (1H, d×d, J = 4.3 Hz, J = 1.1 Hz), 4.79 (1H, d, J = 11.8 Hz), 5.14−5.21 (2H, m), 5.71−5.84 (1H, m), 7.26−7.35 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.9, 51.7, 51.8, 52.2, 61.7, 73.4, 82.7, 118.5, 128.2, 128.2, 128.5, 134.3, 136.8, 167.6. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1760. MS (70 eV) *m*/*z* (%): 273 (M^++1, 100). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C 70.56; H 7.40; N 10.29. Found: C 70.32; H 7.58; N 10.38.

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Supporting Information Available: General information and all spectroscopic data for compounds **2**, **3b**−**c**, **4**, **5a**−**b**, **6b**−**c**, **7b**−**c**, **8a**−**b**, **9a**−**b**, **10b**, **11b**, **12b**−**e**, **13b**−**e**, **14a**−**e**, and **15a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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