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Electrophile-Induced Ring Expansions of β-Lactams toward γ-Lactams

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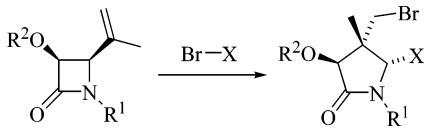


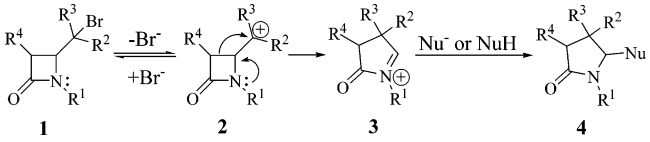
An efficient and straightforward route toward 3,4-*cis*-4-isopropenylazetidin-2-ones was developed from 4-(1-chloroalkyl)azetidin-2-ones. Starting from the latter β-lactams, a new synthesis of pyrrolidin-2-ones was achieved. When 4-isopropenylazetidin-2-ones were treated with bromine in dichloromethane, diastereoselective electrophile-induced ring expansions toward 5-bromopyrrolidin-2-ones were performed. Further oxidation of 3-benzyloxypyrrolidin-2-ones with bromine toward 3-bromopyrrolidin-2-ones was also established. When 4-isopropenyl-β-lactams were added to a mixture of NBS and $TMSN_3$, 5-azidopyrrolidin-2-ones were obtained in moderate to high yields.

Introduction

Recently, diastereoselective ring expansions of β-lactams toward γ-lactams via *N*-acyliminium intermediates have been described.[1−3] During these reactions, 4-(1-bromoalkyl)-2-azetidinones **1** were converted into the corresponding carbenium ions **2** via dissociation of the halide, and a subsequent ring transformation converted these electron-deficient species into *N*-acyliminium ions **3**, which are susceptible to attack of oxygen, nitrogen, and carbon nucleophiles. In this way, a variety of 5-hydroxy-, 5-alkoxy-, 5-allylamino-, 5-azido-, and 5-cyano-2-pyrrolidinones **4** were synthesized (Scheme 1). It was found that dehydrobromination of 4-(1-bromoalkyl)-2-azetidinones **1** constituted an important side reaction competing with the ring enlargements.

These new developments in the chemistry of 2-azetidinones encouraged us to investigate whether these ring expansions could be induced by attack of electrophiles onto 4-isopropenylazetidin-2-ones. In this way, a new pathway via *N*-acyliminium intermediates can give rise to the formation of a wide variety of γ-lactams, without the occurrence of side reactions (e.g., dehydrohalogenation reactions of 4-(1-bromoalkyl)-2-azetidinones **1**), which would be a great improvement concerning the synthetic use of the diastereoselective ring expansions of β-lactams toward γ-lactams.

SCHEME 1



Results and Discussion

4-(1-Chloroalkyl)azetidin-2-ones **6** were synthesized by cyclocondensation reactions of α-chloroisobutylideneamines **5**[4] with various ketenes, prepared in situ by dehydrohalogenation of the corresponding acetyl chlorides with triethylamine in benzene. This method is generally known as the Staudinger reaction (Scheme 2).[5−7] It was found that the obtained 3,4-*cis*-4-(1-chloroalkyl)azetidin-2-ones **6** underwent a clean dehydrochlorination at 160 °C in dry DMSO for 4 h, affording 3,4-*cis*-4-isopropenylazetidin-2-ones **7** in 62−82% yields. Working under dry conditions while performing the dehydrohalogenation step turned out to be important. In

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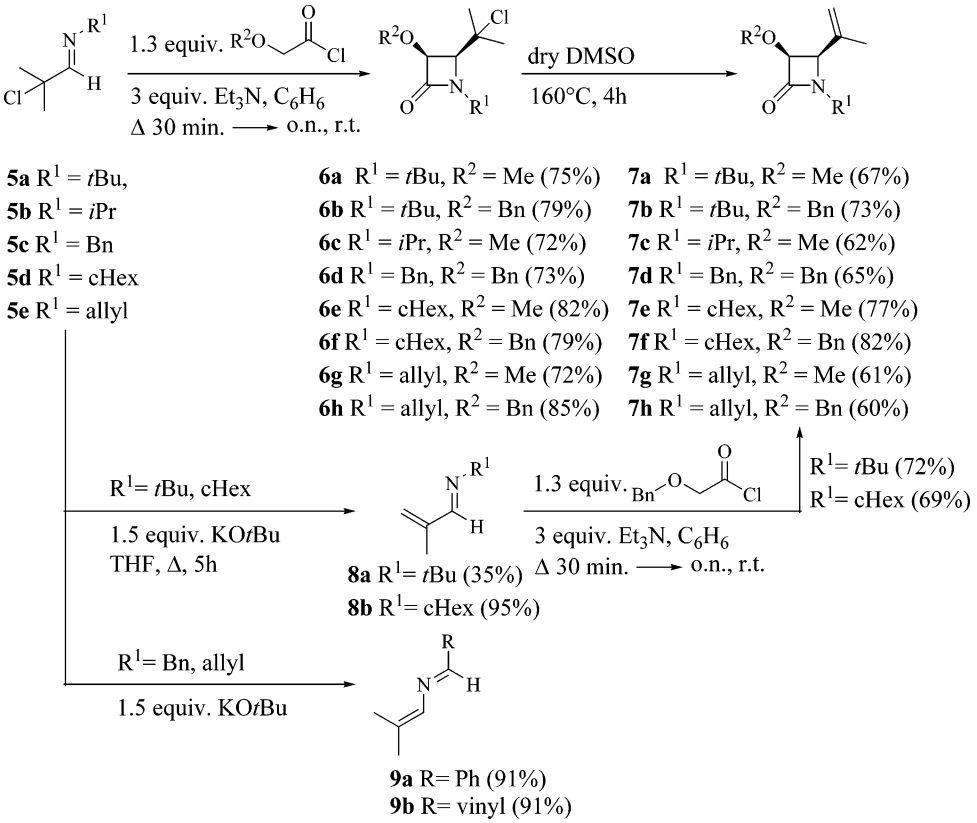
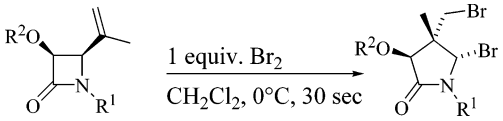
SCHEME 2



commercial DMSO that was not dry, ring expansions toward 5-hydroxy-γ-lactams were observed as side reactions. Performing the dehydrochlorination of 3,4-*cis*-4-(1-chloroalkyl)azetidin-2-ones **6** with 1 equiv of sodium azide suppressed these side reactions in commercial (not dried) DMSO, probably because of the water-withdrawing effects due to the solvation of this salt. Potassium tertiary butoxide could not be used as a base because dehydrohalogenation reactions were always accompanied by cis−trans isomerization reactions of the azetidin-2-ones **7** (via deprotonation−protonation at C3). Potassium carbonate also could not be used because of the release of water during the experiment via this reagent. Triethylamine, dissolved in DMSO, did not enhance the dehydrochlorination reactions and required high temperatures.

The cycloaddition of *N*-isobutenylideneamines **8** with ketenes is proposed as an alternative pathway towards the synthesis of 3,4-*cis*-4-isopropenylazetidin-2-ones. Although these reactions could be performed in comparable yields as the yields obtained after dehydrohalogenation of 3,4-*cis*-4-(1-chloroalkyl)azetidin-2-ones **6** (Scheme 2), some considerable drawbacks concerning this method should be stressed. A first synthesis toward *N*-isobutenylideneamines concerns the condensation of 2-methylacrylaldehyde with different amines. Because of the high reactive terminal double bond in 2-methylacrylaldehyde, these reactions toward α,β-unsaturated imines **8** proceed in low yields and show many side products.[4] A second synthesis toward *N*-isobutenylideneamines **8** is shown in Scheme 2. 1,2-Dehydrohalogention of α-chloroisobutylideneamines proceeds in low yields when volatile imines (e.g., **8a**) are obtained. Furthermore, *N*-benzyl α-chloroisobutylideneamine **5c** undergoes 1,4-dehydrohalogenation when treated with base to give 2-azadiene **9a** (in 91% yield).[8a] Also, *N*-allyl α-chloroisobutylideneamine **5e** suffered from 1,4-dehydrohalogenation when treated with potassium *t*-butoxide in ether.[8b] Because of this 1,4-dehydrohalogenation reaction, no N-benzylated or N-allylated 3,4-*cis*-4-isopropenylazetidin-2-ones can be synthesized starting from α-chloroisobutylideneamines.

SCHEME 3



7a R^1 = *t*Bu, R^2 = Me
7b R^1 = *t*Bu, R^2 = Bn
7c R^1 = *i*Pr, R^2 = Me
7d R^1 = Bn, R^2 = Bn
7e R^1 = cHex, R^2 = Me
7f R^1 = cHex, R^2 = Bn

10a R^1 = *t*Bu, R^2 = Me, purity >98%
10b R^1 = *t*Bu, R^2 = Bn, purity >95%
10c R^1 = *i*Pr, R^2 = Me, purity >91%
10d R^1 = Bn, R^2 = Bn, purity >83%
10e R^1 = cHex, R^2 = Me, purity >81%
10f R^1 = cHex, R^2 = Bn, purity >78%

The capability of electrophiles to induce ring expansions of 4-isopropenylazetidin-2-ones **7** toward pyrrolidin-2-ones was investigated by reacting the β-lactams **7** with 1 equiv of bromine in dichloromethane at 0 °C. Immediately after adding bromine, the solvent was evaporated and 5-bromopyrrolidin-2-ones **10** were obtained (Scheme 3). Due to the high reactivity of the resulting compounds **10**, no further purification was possible, as they led to decomposition products. The stereochemical

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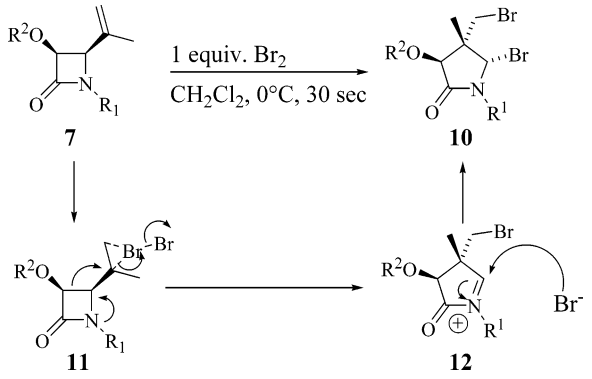
SCHEME 4



course of the reaction is highly selective, as only compounds with a 3,4-trans and 4,5-cis relationship were obtained.

The mechanism of this ring expansion of β-lactams **7** can be explained by an initial activation of the carbon−carbon double bond of the 4-isopropenyl group, when treated with bromine (Scheme 4). A subsequent ring expansion converts compounds **11** into *N*-acyliminium ions **12**, which are susceptible to attack of bromide, affording the corresponding 5-bromopyrrolidin-2-ones **10**.

The stereochemistry of the 5-bromopyrrolidin-2-ones **10** was determined based on both nOe experiments (Figure 1) and the δ-values of the protons at C3. The former technique indicated clearly the cis relationship between the proton at C3 and the bromomethyl group, and between the methyl group at C4 and the proton at C5, as nOe effects of more than 2% were observed between these groups in both cases.

The latter attribution technique was based on the observation that δ-values of protons at C3 of 3-alkoxy-4,4-dimethylpyrrolidin-2-ones are mainly influenced by the cis−trans stereochemistry of the substituents at C3 and C5.[1] The 3,5-cis derivatives showed a δ-value for the proton at C3 around 3.3 ppm ($CDCl_3$), while this proton in 3,5-trans isomers appeared around 3.9 ppm ($CDCl_3$). To compare these data with the present new results, γ-lactam **10a** (obtained as the reaction mixture) was poured into water and extracted with dichloromethane, affording a mixture of 3,5-*cis*- and 3,5-*trans*-5-hydroxypyrrolidin-2-ones **(3*S**,4*R**,5*R**)-13** and **(3*S**,4*R**,5*S**)-13** in a 1:4 ratio, respectively (Scheme 5). One of the two stereoisomers showed a W-coupling of 1.1 Hz between the two protons of the γ-lactam ring. Since this long range coupling exists only when the bonds between the two protons form a W-pattern in the same plane, this W-coupling can only appear in the 3,5-cis form **(3*S**,4*R**,5*R**)-13.**[9−11] It was found that C3 protons of 3,5-*cis*- and 3,5-*trans*-3-alkoxy-4-bromomethyl-4-methylpyrrolidin-2-ones **(3*S**,4*R**,5*R**)-13** and **(3*S**,4*R**,5*S**)-13** showed equal δ-values as C3 protons of 3,5-*cis*- and 3,5-*trans*-3-alkoxy-4,4-dimethylpyrrolidin-2-ones, respectively. In this way, it was proven that the C3 and C5 substituents of the 5-bromopyrrolidin-2-ones **10** were

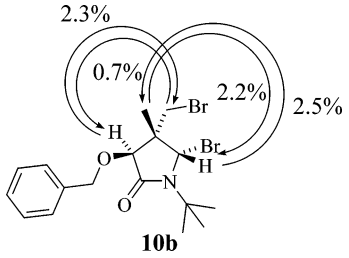


FIGURE 1. nOe effects observed in compound **10b**.

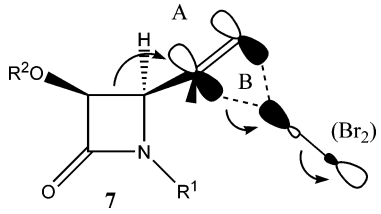


FIGURE 2. Reaction of 4-isopropenylazetidin-2-ones **7** with bromine.

trans oriented, according to the δ-values around 3.9 ppm of the C3 protons of these compounds ($CDCl_3$). These findings, in combination with the performed nOe experiments, shown in Figure 1, proved the exact stereochemistry of pyrrolidin-2-ones **10** as shown in Scheme 4.

To explain the high diastereoselectivity observed in the title reaction, the following proposition can be made. On the basis of allylic strain concepts,[12] it can be predicted that the double bond of 4-isopropenylazetidin-2-ones **7** will be syn or eclipsed with the C4−H bond, as shown in Figure 2. Attack of bromine at this double bond will occur via the B-plane, because in this way a better orbital overlap toward the ring expansion is possible. Rearrangement via this mechanism gives rise to the formation of *N*-acyliminium ion **12**. These results are in accordance with literature data where the same relative C3,C4 stereochemistry was obtained after an intramolecular ring expansion of 3-methoxy-4-(2-methyl-2-oxiranyl)azetidin-2-ones toward γ-lactams.[13] In the second step of the reaction, the outcome can be explained by external ion pair return concepts. After ring expansion, the bromide will attack from the same side where the bromomethyl group is formed, because it is at this side that the bromide is formed after the ring expansion. The same concepts concerning external ion pair return were already proven to be responsible for the stereochemical control of "memory effects".[14−22] This term is used in reactions of carbocations in which the latter "remember" how they were formed before they go on to give the second step. Also in these cases, counterions attacked the rearranged carbocations from the side from which they were expelled (during ionization).

When 4-isopropenylazetidin-2-ones **7b** and **7d** were used to perform electrophile-induced ring expansions, addition of 5 equiv of bromine instead of 1 equiv gave

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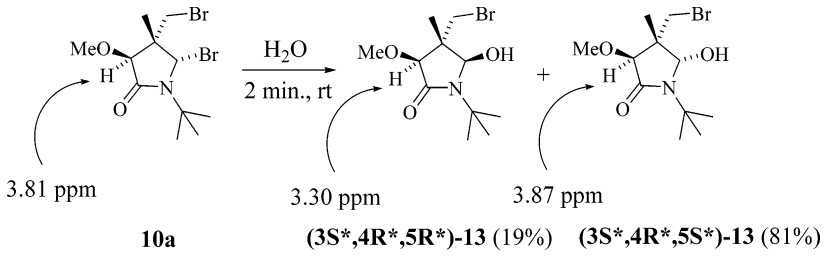
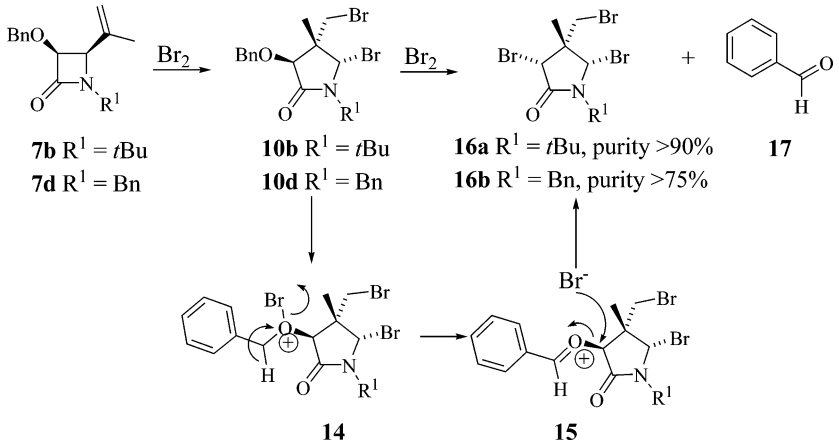
SCHEME 5



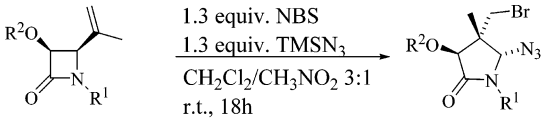
SCHEME 6



unexpected results when the reaction mixture was stirred for 4 h at 0 °C. After the ring expansion, a further reaction toward 3-bromopyrrolidin-2-ones **16** was observed, together with the formation of benzaldehyde. The mechanism of this reaction can be explained by attack of oxygen at bromine, followed by a dehydrobromination of the resulting oxonium ion **14** and a second-order nucleophilic substitution of "benzaldehyde" by bromide (Scheme 6).[23–25]

In a second approach toward electrophile-induced ring expansions, 4-isopropenylazetidin-2-ones **7** were added to a mixture of 1.3 equiv of *N*-bromosuccinimide (NBS), 1.3 equiv of azidotrimethylsilane ($TMSN_3$) and dichloromethane and nitromethane in a ratio of 3:1 by volume at room temperature.[26] Azidobromination of the starting compounds gave 5-azidopyrrolidin-2-ones in moderate to high yields (Scheme 7). The stereochemistry of the resulting γ-lactams **18** was determined in the same way as described for the 5-bromopyrrolidin-2-ones **10**.

SCHEME 7



7a R^1 = tBu, R^2 = Me	**18a** R^1 = tBu, R^2 = Me (87%)
7c R^1 = iPr, R^2 = Me	**18b** R^1 = iPr, R^2 = Me (65%)
7d R^1 = Bn, R^2 = Bn	**18c** R^1 = Bn, R^2 = Bn (48%)
7e R^1 = cHex, R^2 = Me	**18d** R^1 = cHex, R^2 = Me (43%)
7f R^1 = cHex, R^2 = Bn	**18e** R^1 = cHex, R^2 = Bn (63%)

When the same reactions were performed with trimethylsilyl cyanide instead of azidotrimethylsilane or with *N*-iodosuccinimide (NIS) instead of NBS, starting materials **7** were recovered.

Conclusions

Dehydrochlorination of 3,4-*cis*-4-(1-chloroalkyl)azetidin-2-ones **6** constitutes an efficient and straightforward pathway toward 3,4-*cis*-4-isopropenylazetidin-2-ones **7**. Starting from the latter β-lactams, a new synthesis of pyrrolidin-2-ones was achieved. When 4-isopropenylazetidin-2-ones **7** were treated with bromine in dichloromethane, diastereoselective electrophile-induced ring expansions toward 5-bromopyrrolidin-2-ones **10** were performed. Further oxidation of 3-benzyloxypyrrolidin-2-ones toward 3-bromopyrrolidin-2-ones **16** was also established. When 4-isopropenyl β-lactams **7** were added to a mixture of NBS and $TMSN_3$, 5-azidopyrrolidin-2-ones **18** were obtained in moderate to high yields. These new

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findings in the chemistry of 2-azetidinones emphasize the synthetic potential of diastereoselective ring expansions of β-lactams toward γ-lactams.

Experimental Section

α-Chloroisobutylideneamines **5** were synthesized via a known procedure.[3]

1. Synthesis of 3,4-*cis*-4-(1-Chloroalkyl)azetidin-2-ones 6. As a representative example, the synthesis of 3,4-*cis*-4-(1-chloro-1-methylethyl)-1-*tert*-butyl-3-methoxy-azetidin-2-one **6a** is described. A solution of *N*-(2-chloro-2-methylpropylidene)-2-methyl-2-propylamine **5** (1.61 g, 10 mmol) and triethylamine (3.03 g, 30 mmol) in benzene (50 mL) was heated. A solution of methoxyacetyl chloride (1.41 g, 13 mmol) in benzene (30 mL) was added dropwise to this refluxing solution. The resulting solution was kept at reflux temperature for 30 min and was subsequently stirred overnight at room temperature. The reaction mixture was diluted with chloroform (70 mL) and washed with a saturated sodium bicarbonate solution and brine. After the solvent was dried ($MgSO_4$) and evaporated, the crude reaction product was obtained. Further purification was performed by flash chromatography (1.75 g, 7.5 mmol). For spectral data, see also ref 7.

(3*S,4*S**)-4-(1-Chloro-1-methylethyl)-1-*tert*-butyl-3-methoxyazetidin-2-one 6a:** White crystals, 75% yield, mp 77 °C, TLC R_f 0.30 (petrol ether/ethyl acetate, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 1.70 and 1.71 (6H, 2 × s), 3.53 (3H, s), 4.14 (1H, d, J = 5.5 Hz), 4.33 (1H, d, J = 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 29.7, 28.7, 54.7, 59.7, 68.4, 71.6, 82.0, 168.7. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1737, ν_{max} = 2987, 1458. MS (70 eV) *m/z* (%): 236/4 (M^+ + 1, 100); 180/78 (85). Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99. Found: C, 56.64; H, 8.76; N, 5.75.

2. Synthesis of 3,4-*cis*-4-Isopropenylazetidin-2-ones 7. As a representative example, the synthesis of 3,4-*cis*-4-isopropenyl-1-isopropyl-3-methoxyazetidin-2-one **7c** is described. 3,4-*cis*-4-(1-Chloro-1-methylethyl)-1-isopropyl-3-methoxyazetidin-2-one **6c** (2.20 g, 10 mmol) was heated at 160 °C for 4 h in dry DMSO (30 mL). After cooling to room temperature, the solution was poured into water (50 mL) and extracted three times with ether (30 mL). The combined organic fractions were washed three times with water (30 mL) and dried ($MgSO_4$). After evaporation of the solvent in vacuo the crude reaction mixture was obtained, which was further purified by flash chromatography (1.36 g, 6.2 mmol). For spectral data, see also ref 1.

(3*S,4*R**)-*cis*-4-Isopropenyl-1-isopropyl-3-methoxyazetidin-2-one 7c:** 62% yield, TLC R_f 0.15 (petrol ether/ethyl acetate, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 and 1.29 (6H, 2 × d, J = 6.6 Hz), 1.84 (3H, d × d, J = 0.8 Hz, J = 1.4 Hz), 3.44 (3H, s); 3.76 (1H, sept, J = 6.6 Hz), 4.25 (1H, d, J = 5.0 Hz), 4.48 (1H, d, J = 5.0 Hz), 5.09−5.11 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 20.1, 20.7, 45.0, 58.8, 62.2, 84.3, 116.2, 141.7, 166.9. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1756; ν_{max} = 3079, 2975, 2934, 2835, 1454, 1385, 1369. MS (70 eV) *m/z* (%): 184 (M^+ + 1, 85); 110 (100). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.43; H, 9.31; N, 7.49.

3. Synthesis of 5-Bromopyrrolidin-2-ones 10. As a representative example, the synthesis of 5-bromo-4-(bromomethyl)-1-*tert*-butyl-3-methoxy-4-methylpyrrolidin-2-one **10a** is described. 3,4-*cis*-4-Isopropenyl-3-methoxy-1-*tert*-butylazetidin-2-one **7a** (0.12 g, 0.6 mmol) was cooled at 0 °C in dichloromethane (10 mL). Under continuous stirring, bromine (0.10 g, 0.6 mmol) was added. Immediately after the addition of bromine the solvent was evaporated, obtaining 3-benzyloxy-5-bromo-4-(bromomethyl)-1-*tert*-butyl-4-methylpyrrolidin-2-one **10a** in 100% yield with a purity of more than 95%. Mass spectra were taken, but because of the use of aqueous solvents during this technique, the corresponding mother ions of the 5-hydroxypyrrolidin-2-ones were always detected.

(3*S,4*R**,5*S**)-5-Bromo-4-(bromomethyl)-1-*tert*-butyl-3-methoxy-4-methylpyrrolidin-2-one 10a:** Purity >98% (^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, s), 1.50 (9H, s), 3.64 (1H, d, J = 10.3 Hz), 3.70 (3H, s), 3.81 (1H, s), 4.03 (1H, d, J = 10.3 Hz), 5.83 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1, 26.8, 40.5, 47.8, 56.3, 78.7, 83.2, 173.9. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1680; ν_{max} = 2977, 1458.

4. Synthesis of 5-Hydroxypyrrolidin-2-ones (3*S,4*R**,5*R**)-13 and (3*S**,4*R**,5*S**)-13.** 3,4-*cis*-4-Isopropenyl-3-methoxy-1-*tert*-butylazetidin-2-one **10a** (0.12 g, 0.5 mmol) was cooled at 0 °C in dichloromethane (10 mL). Under continuous stirring, bromine (0.08 g, 0.5 mmol) was added. Immediately after the addition of bromine, the mixture was poured into water (50 mL), and the mixture was extracted two times with dichloromethane (20 mL). After drying ($MgSO_4$) of the combined organic fractions and evaporation of the solvent in vacuo, a mixture of 19% 3,5-cis substituted 4-(bromomethyl)-5-hydroxy-1-*tert*-butyl-3-methoxy-4-methylpyrrolidin-2-one **(3*S**,4*R**,5*R**)-13** and 81% 3,5-trans substituted 4-(bromomethyl)-5-hydroxy-1-*tert*-butyl-3-methoxy-4-methylpyrrolidin-2-one **(3*S**,4*R**,5*R**)-13** was obtained. NMR spectra were obtained from the reaction mixture.

(3*S,4*R**,5*R**)-4-(Bromomethyl)-1-*tert*-butyl-5-hydroxy-3-methoxy-4-methylpyrrolidin-2-one (3*S**,4*R**,5*R**)-13:** ^{1}H NMR (300 MHz, $CDCl_3$): **δ** 1.23 (3H, s); 1.47 (9H, s); 2.65 (1H, d, J = 12.4 Hz); 3.30 (1H, d, J = 1.1 Hz); 3.56 (1H, d, J = 10.5 Hz); 3.59 (3H, s); 3.84 (1H, d, J = 10.5 Hz); 4.94 (1H, d × d, J = 12.4 Hz, J = 1.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): **δ** 14.0, 27.9, 38.8, 45.4, 54.5, 59.5, 84.3, 87.8, 172.1. IR (NaCl, cm^{-1}): **$\nu_{C=O}$** = 1690; **ν_{OH}** = 3335. MS (70 eV) *m/z* (%): 296/4 (M^+ + 1, 100).

(3*S,4*R**,5*S**)-4-(Bromomethyl)-1-*tert*-butyl-5-hydroxy-3-methoxy-4-methylpyrrolidin-2-one (3*S**,4*R**,5*S**)-13:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, s), 1.46 (9H, s), 2.60 (1H, d, J = 4.00 Hz), 3.55 (1H, d, J = 9.5 Hz), 3.66 (3H, s), 3.84 (1H, s), 3.84 (1H, d, J = 9.5 Hz), 4.89 (1H, d, J = 4.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 27.8, 39.0, 46.4, 54.5, 60.5, 82.8, 85.5, 173.6. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1690; ν_{OH} = 3335. MS (70 eV) *m/z* (%): 296/4 (M^+ + 1, 100).

5. Synthesis of 5-Bromopyrrolidin-2-ones 16. As a representative example, the synthesis of 3,5-dibromo-4-(bromomethyl)-1-*tert*-butyl-4-methylpyrrolidin-2-one **16a** is described. 3,4-*cis*-3-Benzyloxy-4-isopropenyl-1-*tert*-butylazetidin-2-one **7b** (0.16 g, 0.5 mmol) was cooled at 0 °C in dichloromethane (10 mL). Under continuous stirring, bromine (0.4 g, 2.5 mmol) was added. After 4 h at room temperature, the solvent was evaporated, affording 3,5-dibromo-4-(bromomethyl)-1-*tert*-butyl-4-methylpyrrolidin-2-one **16a** in 100% yield with a purity of more than 90%. Mass spectra were taken, but because of the use of aqueous solvents during this technique, the corresponding mother ions of the 5-hydroxypyrrolidin-2-ones were always detected.

(3*R,4*R**,5*S**)-3,5-Dibromo-4-(bromomethyl)-1-*tert*-butyl-4-methylpyrrolidin-2-one 16a:** Purity >90% (^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, s), 1.51 (9H, s), 3.71 (1H, d, J = 10.5 Hz), 3.98 (1H, d, J = 10.5 Hz), 4.38 (1H, s), 5.77 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 26.8, 40.4, 48.3, 56.8, 74.8, 80.3, 176.4. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1692; ν_{max} = 2978; 1453; 1370.

6. Synthesis of 5-Azidopyrrolidin-2-ones 18. As a representative example, the synthesis of 5-azido-4-(bromomethyl)-1-*tert*-butyl-3-methoxy-4-methylpyrrolidin-2-one **18a** is described. In a mixture of dichloromethane and nitromethane at a ratio of 3:1 (30 mL), NBS (1.16 g, 6.5 mmol) and $TMSN_3$ (0.64 g, 6.5 mmol) were added. After being stirred at room temperature for 1 h, 3,4-*cis*-1-*tert*-butyl-4-isopropenyl-3-methoxyazetidin-2-one **7a** (1.59 g, 5 mmol) was added, and the mixture was stirred overnight at room temperature. After pouring in water (50 mL), the water was extracted twice with dichloromethane (20 mL). The resulting organic fractions were dried ($MgSO_4$), and after evaporation of the solvent, the crude

reaction mixture was obtained. Further purification was performed by flash chromatography (1.39 g, 4.4 mmol).

(3*S,4*R**,5*S**)-5-Azido-4-(bromomethyl)-1-*tert*-butyl-3-methoxy-4-methylpyrrolidin-2-one 18a:** 87% yield, TLC R_f 0.15 (petrol ether/ethyl acetate, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, s), 1.47 (9H, s), 3.55 (1H, d, J = 10.2 Hz), 3.64 (3H, s), 3.66 (1H, s), 3.83 (1H, d, J = 10.2 Hz), 4.78 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 27.7, 38.4, 47.4, 54.7, 60.4, 80.5, 82.4, 173.1. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1714; ν_{N3} = 2108. MS (70 eV) *m/z* (%): 321/19 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{19}BrN_4O_2$: C, 41.39; H, 6.00; N, 25.03. Found: C, 41.53; H, 6.14; N, 24.97.

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Supporting Information Available: General information and all spectroscopic data for compounds **6b**, **6d**, **7e**−**h**, **10b**−**f**, **16b**, and **18b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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