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Diastereoselective Ring Expansion of β-Lactams toward γ-Lactams via *N*-Acyliminium Intermediates

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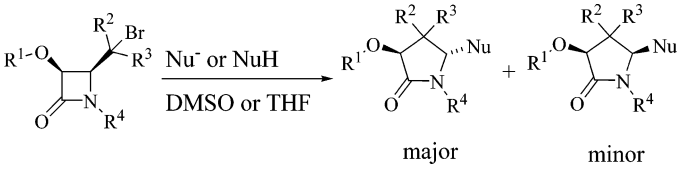
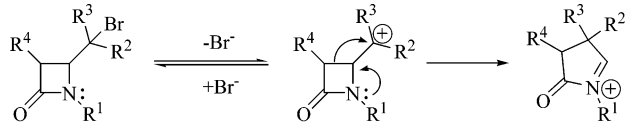


The diastereoselective synthesis of highly functionalized γ-lactams starting from 4-(1-bromoalkyl)-2-azetidinones via *N*-acyliminium intermediates is described. The carbenium ions, formed by dissociation of bromide from 4-(1-bromoalkyl)-2-azetidinones in polar medium, are converted via a ring expansion toward *N*-acyliminium ions, which are susceptible to attack of oxygen, nitrogen, and carbon nucleophiles. In this way, a variety of 5-hydroxy-, 5-alkoxy, 5-cyano-, 5-allylamino- and 5-azido-4,4-dimethyl-2-pyrrolidinones were synthesized. It was found that dehydrobromination of 4-(1-bromoalkyl)-2-azetidinones constituted an important side reaction when the title reactions were carried out in DMSO. When THF was used as a solvent, generally no dehydrobromination was observed, implying that higher yields of γ-lactams were obtained in THF compared to reactions performed in DMSO. Also substituents of the 4-(1-bromoalkyl)-2-azetidinones play an important role concerning the obtained diastereoselectivity and the degree of dehydrobromination.

Introduction

The pharmaceutical industry shows a lot of interest in 2-pyrrolidinones and their derivatives because of their biological properties, such as antifungal[1] and antidepressant[2] activities. In the present article, a new ring transformation of 4-(1-bromoalkyl)-2-azetidinones **1** into γ-lactams via transient iminium ions is described. In polar reaction medium, 4-(1-bromoalkyl)-2-azetidinones **1** were converted into the corresponding carbenium ions **2** via dissociation of the halide. A subsequent ring transformation converts these carbenium ions into *N*-acyliminium ions **3** (Scheme 1). Although the chemistry of β-lactams has been thoroughly investigated in the past, very little is known about this cation-induced intramolecular rearrangement toward five-membered rings. The present findings should allow the development of a wide variety of new pyrrolidinones, since the obtained *N*-acyliminium intermediates **3** can be used to introduce a variety of substituents at the α-carbon of the amine, even

SCHEME 1



though further optimization of the reaction conditions will be required in some cases.[3]

One example of a rearrangement of a very peculiar trisulfanylated β-lactam, i.e., 4-{bis(phenylsulfanyl)-methylene}-1-(4-methoxybenzyl)-3-(methylsulfanyl)-azetidin-2-one **4** toward the corresponding γ-lactam **5** via an intermediate *N*-acyliminium ion has been reported, but no information was given concerning the possibility and stereoselectivity of additions of nucleophiles at the *N*-acyliminium ion.[4] In addition, the *N*-acyliminium ion was created by protonation of the exocyclic double bond

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(1) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005−6018.

(2) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36−42.

(3) (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416. (c) Bienz, S.; Busacca, C.; Meyers, A. I. *J. Am. Chem. Soc.* **1989**, *111*, 1905−1907. (d) Meyers, A. I.; Bienz, S.; Hyok-Boong, K.; Wallace, R. H. *Helv. Chim. Acta* **1996**, *79*, 1026−1046.

(4) Ishibashi, H.; Nakaharu, T.; Nishimura, M.; Nishikawa, A.; Kameoka, C.; Ikeda, M. *Tetrahedron* **1995**, *51*, 2929−2938.

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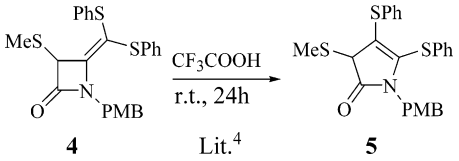
at C4 of β-lactam **4**, implying that no information is present concerning the cation induced intramolecular rearrangement of β-lactams **2** toward *N*-acyliminium intermediates **3** in neutral or basic conditions (Scheme 2). No other examples of conversions of β-lactams toward

SCHEME 2

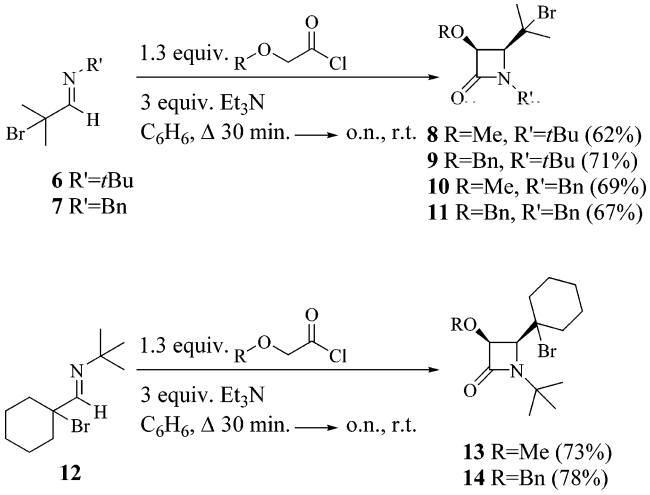


γ-lactams via *N*-acyliminium intermediates were found in the literature, pointing at the unexplored nature of this subject. The present report gives an account on this rearrangement from β-lactams to γ-lactams.

Results and Discussion

In the present report, new 4-(1-bromoalkyl)azetidin-2-ones **8**, **9**, **10**, **11**, **13**, and **14** were synthesized via a Staudinger reaction,[5,6] using different acetyl chlorides and *N*-(2-bromo-2-methylpropylidene)-2-methyl-2-propylamine **6**, *N*-(2-bromo-2-methylpropylidene)-2-benzylamine **7**, and *N*-((1-bromocyclohexyl)methylidene)-2-methyl-2-propylamine **12** (Scheme 3). The latter three

SCHEME 3



compounds were synthesized by bromination of the corresponding aldimines.[7,8] Examples of Staudinger reactions leading to 4-(1-bromoalkyl)azetidin-2-ones are not yet described in the literature, although the synthetic potential of this class of compounds is large and exemplified by ring opening reactions and ring transformations into aziridines and azetidines.[9] Only syntheses of these compounds via radical 4-*exo* cyclizations of bromoenamides and electrophile induced ring closure were reported.[10,11] A major advantage of the Staudinger reaction, compared to radical cyclization reactions, is the control of the relative stereochemistry of the substituents on the obtained β-lactams. This stereochemistry of β-lactams **8**, **9**, **10**, **11**, **13**, and **14** was determined based on the coupling constants between the protons at C3 and C4 of the azetidin-2-one rings. Since these coupling constants are reported to be 5−6 Hz for the cis derivatives and 0−2 Hz for the trans derivatives, the stereochemical outcome of this reaction was shown to be cis, based on observed coupling constants of 4.9 to 5.8 Hz between protons at C3 and C4 of **8**, **9**, **10**, **11**, **13**, and **14**.[12]

When the reactivity of β-lactam **8** toward hydrolysis was investigated by stirring it in a mixture of 20% water in DMSO (dimethyl sulfoxide) for 18 h at room temperature, a mixture of the dehydrobromination product **15** and the two stereoisomers **16** and **17** was isolated (Scheme 4). The integration in the ^{1}H NMR spectrum of the crude reaction mixture showed a ratio of 18/71/11 between **15**, **16**, and **17**, respectively. After flash chromatography, the obtained yields were consistent with this ratio (11%/54%/6% respectively). The stereochemistry of the two diastereomers was assigned based on the appearance of a W-coupling of 1.1 Hz between the two protons on the γ-lactam ring of one of the two diastereomers. 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 cis form **17**.[13−15]

The results shown in Scheme 4 suggest a reaction mechanism in which dissociation of the bromide gives rise to the formation of a tertiary carbenium ion **18**, which is stabilized by the elimination of a proton toward β-lactam **15** or by an intramolecular rearrangement via opening of the C3−C4 bond toward the formation of a more stable *N*-acyliminium ion **19**. This additional stability can be explained by the relief of ring strain and by the fact that the positive charge is located in a polycentric molecular orbital (PCMO) in the case of the *N*-acyliminium ion **19**. Since the ring is flat, addition of a nucleophile to the *N*-acyliminium ion **19** is only directed by the methoxy substituent. Therefore, the attack of water on the intermediate **19** is favored at the opposite side of the methoxy group, to obtain the more stable trans stereoisomer **16**. This compound appears as the major compound, in addition to the other minor stereoisomer, i.e., *cis*-γ-lactam **17** (Scheme 4). It has to be noted that, next to this kinetic approach, the formation of *cis*- and *trans*-γ-lactams is also thermodynamically determined. This was proven by treating *trans*-γ-lactam **16** with a catalytic amount of hydrogen bromide (which is also released during the ring transformation of β-lactam **8** toward the γ-lactams **16** and **17**) in a mixture of 20% water in DMSO. After 5 min at

(5) Palomo, P.; Aizpura, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235.
(6) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631−7649.
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(10) (a) Clark, J. C.; Battle, G. M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 4409−4412. (b) Bryans, J. S.; Chessum, E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 4409−4412.
(11) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099−3114.
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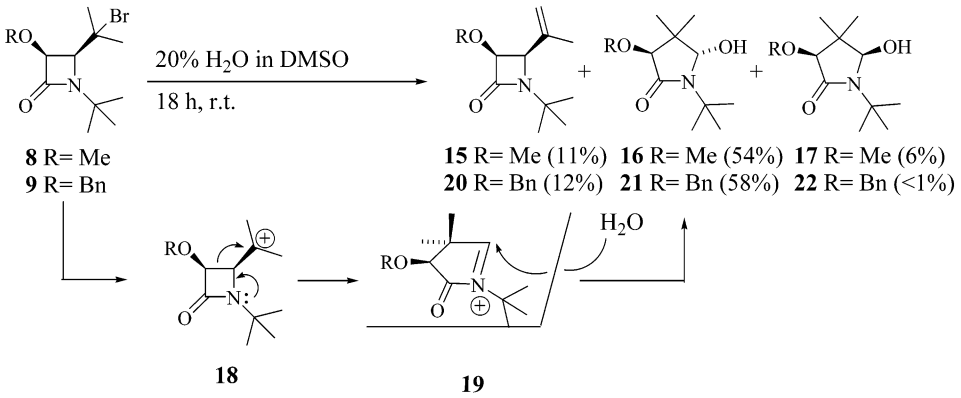
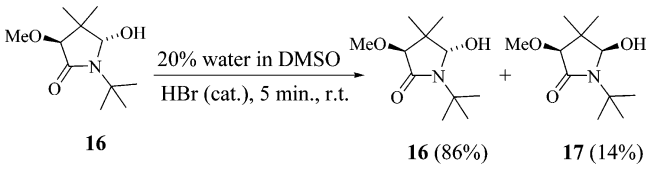
(15) Machocho, A.; Chhabra, S. C.; Viladomat, F.; Codina, C.; Bastida, J. *Phytochem.* **1999**, *51*, 1185−1191.

SCHEME 4



room temperature, the equilibrium between *trans*-γ-lactam **16** and *cis*-γ-lactam **17** was completely reestablished. On the basis of the integration signals of the ^{1}H NMR spectrum, a ratio of 86/14 between the *trans*- and the *cis*-isomers, respectively, was found (Scheme 5).

SCHEME 5



To enhance the stereocontrol, the same reaction was carried out with β-lactam **9**. The greater steric hindrance of the benzyloxy group compared to that of the methoxy group should direct the attack of the nucleophile even more into a trans stereochemistry. This strategy turned out to be successful. After reaction, the integration signals in the ^{1}H NMR spectrum of the crude reaction mixture showed a ratio of 19/76/5 between respectively **20**, **21**, and **22**. After chromatography, less than 1% of the cis stereoisomer **22**, 58% of *trans*-γ-lactam **21**, and 12% of the dehydrobromination product **20** was isolated. The determination of the stereochemistry was once more performed based on the appearance of a W-coupling of 1.1 Hz between the two protons on the ring of the γ-lactam **22** (Scheme 4). Similarities concerning the coupling constants between the hydroxyl proton and the proton at C5 also occurred. For both the cis derivatives **17** and **22**, coupling constants between 12 and 14 Hz were observed, whereas for the trans forms **16** and **21** coupling constants between 5 and 6 Hz were measured.

Upon trying to extend the scope of the reaction with different nucleophiles, the ratio of the elimination product and the two diastereomers turned out to be nucleophile dependent. A summary of these results is given in Table 1. The ratios between the different products, shown by the integration signals in the ^{1}H NMR spectra of the crude reaction mixtures, are also given in this table. When the rearrangement of β-lactam **9** toward γ-lactam **23a** was carried out in DMSO and methanol, no traces of the cis derivative **24a** were observed after flash chromatography. The diastereoselectivity of this reaction can again be explained in terms of steric hindrance between methanol and the benzyloxy group. When potassium cyanide, allylamine, or sodium azide were used as nucleophiles, lower yields were obtained. Under basic reaction conditions more dehydrobromination product **20** was formed compared to the yields of **20** in neutral reaction conditions.

In all cis forms presented in Table 1, no W-coupling appeared in the ^{1}H NMR spectrum ($CDCl_3$). In these cases the stereochemistry was determined based on the δ-value of the proton at C3 of all γ-lactams. In the case of γ-lactam **22**, where the stereochemistry was determined based on the appearance of a W-coupling, the proton at C3 appeared at a δ-value of 3.31 ppm, whereas the proton at C3 of the trans derivative **21** appeared at a δ-value of 3.97 ppm. Also in the case of lactams **17** and **16**, this difference in δ-value was similar. Since in all sets of stereoisomers there was always a stereoisomer present with a δ-value for the proton at C3 close to 3.3 ppm and another stereomer with a δ-value for the proton at C3 close to 3.9 ppm, the proper stereochemistry could be assigned to the isomers.[16]

When the title reaction was carried out with 4-(1-bromocyclohexyl)azetidin-2-ones **13** and **14**, the spiro compounds **26** and **27** were formed. In these cases, more dehydrobromination was observed compared to the reactions with 4-(1-bromo-1-methylethyl)azetidin-2-ones **8** and **9**, probably because of the higher ring strain of the corresponding *N*-acyliminium intermediates (Scheme 6). The integration signals in the ^{1}H NMR spectra of the crude reaction mixtures showed a ratio of 73/22/5 between respectively **25a**, **26a**, and **27a**, and a ratio of 77/20/3 between respectively **25b**, **26b**, and **27b**. Again, the stereochemistry was determined based on the appearance of a W-coupling in γ-lactams **27a** and **27b**.

(16) The δ-value of the proton at C3 is indeed a reliable indicator for the stereochemistry, since it can only be influenced by the difference in ring structure between cis substituted lactams and trans substituted derivatives. The influence of different substituents at C5 on the δ-value of the C3-proton can hardly be that pronounced that it would shift the signal in a range of 0.6 ppm, since the inductive influence over four bonds is negligible.[17] Also from a steric point of view the influence of the substituent at C5 will be small because the C5-substituent and the C3-proton do not approach each other. Since it was already clear that the trans diastereomer was formed in larger yield than the cis stereoisomer, the yields indicated also that the isomers with a δ-value around 3.3 ppm were the cis isomers, because they were always the minor products in the reaction mixtures (see the mechanism described above).

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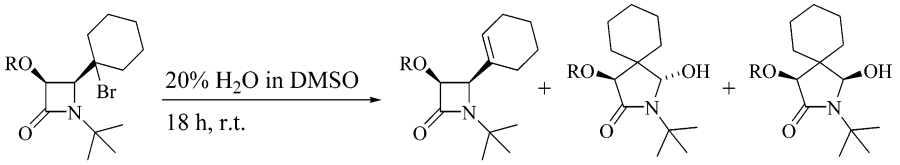
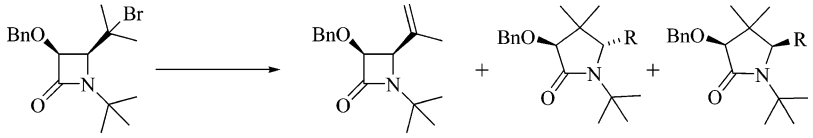
SCHEME 6



13 R=Me
14 R=Bn

25a R=Me (60%) **26a** R=Me (17%) **27a** R=Me (4%)
25b R=Bn (61%) **26b** R=Bn (19%) **27b** R=Bn (2%)

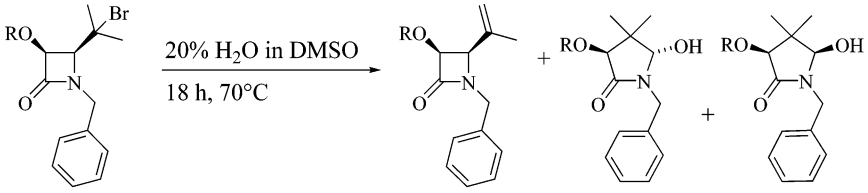
TABLE 1. Reaction of 4-(1-Bromo-1-methylethyl)azetidin-2-one 9 with Different Nucleophiles



9 **20** **23a-d** **24a-d**

R	reaction conditions	% elimination product **20**	trans stereomer **23**	cis stereomer **24**	ratios of **20/23/24** based on ^{1}H NMR
MeO	20% MeOH in DMSO, 18 h, rt	5	**23a** (73%)	**24a** (0%)	5/95/0
C≡N	10 equiv of KCN, DMSO, 18 h, rt	25	**23b** (22%)	**24b** (20%)	47/26/27
$NHCH_2CH{=}CH_2$	10 equiv of allylamine, DMSO, 18 h, rt	31	**23c** (28%)	**24c** (2%)	50/47/3
N_3	10 equiv of NaN_3, DMSO, 18 h, rt	23	**23d** (24%)	**24d** (10%)	41/41/18

SCHEME 7



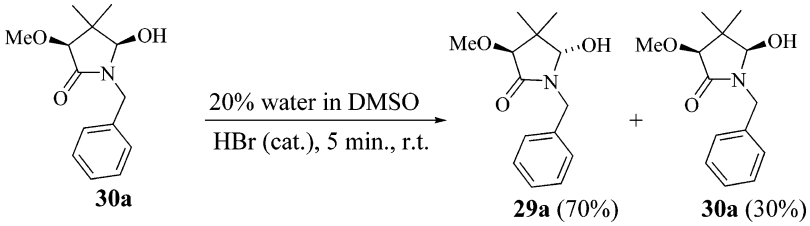
10 R=Me
11 R=Bn

28a R=Me (38%) **29a** R=Me (29%) **30a** R=Me (10%)
28b R=Bn (28%) **29b** R=Bn (42%) **30b** R=Bn (4%)

The influence of the substituents at nitrogen of 4-(1-bromoalkyl)azetidin-2-ones was investigated by stirring *N*-benzyl(1-bromo-1-methylethyl)azetidin-2-ones **10** and **11** for 18 h in a mixture of 20% water in DMSO at room temperature. After workup, the starting materials were recovered. Only after heating at 70 °C did the *N*-benzylated β-lactams react to form the corresponding γ-lactams (Scheme 7). The ^{1}H NMR spectrum of the crude reaction mixtures showed a ratio of 46/37/17 between **28a**, **29a**, and **30a**, respectively, and a ratio of 37/52/11 between **28b**, **29b**, and **30b**, respectively. More dehydrobromination had occurred during these reactions, compared to the reactions performed with *N*-*tert*-butylated β-lactams, probably because of the higher reaction temperature. The difference in reactivity between both types of β-lactams can be explained by pointing at the electron-withdrawing capacities of benzyl substituents compared to the electron-donating *tert*-butyl groups. It seems that the investigated ring transformations proceed faster when the nucleophilicity of the nitrogen atom of 4-(1-bromoalkyl)azetidin-2-ones is higher. The fact that *N*-benzylated 4-(1-bromoalkyl)azetidin-2-ones did not undergo elimination reactions at room temperature, whereas the corresponding *N*-*tert*-butylated β-lactams did, suggests that the nitrogen lone pair influences the dissociation of the bromide from 4-(1-bromoalkyl)azetidin-2-ones.

Also in the latter cases, where an electron-withdrawing group was present at nitrogen, the equilibrium between *cis*- and *trans*-γ-lactams was also thermodynamically determined. When γ-lactam **30a** was treated with a catalytic amount of hydrogen bromide in a mixture of 20% water in DMSO, the equilibrium between *trans*-γ-lactam **29a** and *cis*-γ-lactam **30a** was completely reestablished after the mixture was stirred for 5 min at room temperature (Scheme 8).

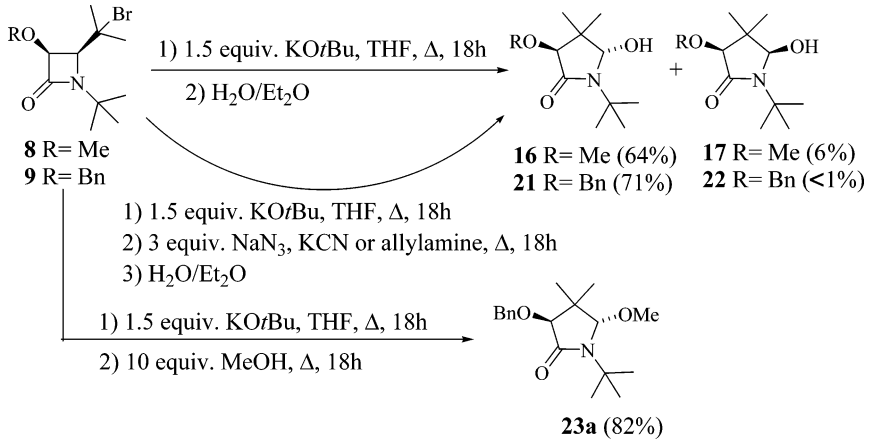
SCHEME 8



30a

29a (70%) **30a** (30%)

SCHEME 9



An unexpected result was obtained when β-lactam **8** was stirred with potassium *tert*-butoxide (KO*t*Bu) in THF for 18 h. The aim of the reaction was to obtain the 1,2-dehydrobromination product **15** via dehydrobromination with KO*t*Bu. Instead, it appeared that no elimination had taken place after workup with water, as only γ-lactams **16** and **17** were formed. When the same reaction was performed with β-lactam **9**, again no elimination product was formed. When methanol was added as a reagent after the reaction of β-lactam **8** in THF in the presence of KO*t*Bu, 5-methoxy-γ-lactam **23a** was obtained in 82% yield.

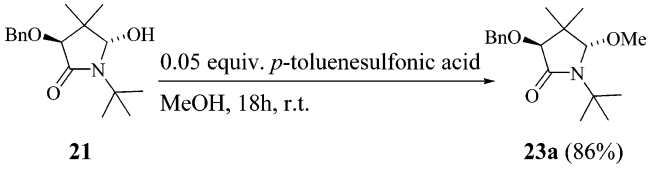
Since no formation of the elimination products **15** and **20** occurred, higher yields of γ-lactams **16**, **17**, **21**, **22**, and **23a** were found after flash chromatography when ring transformations of β-lactams **8** and **9** were carried out with KO*t*Bu in THF compared to the yields obtained in DMSO. The disadvantage of the reactions carried out in THF is that not all nucleophiles, such as sodium azide, potassium cyanide, and allylamine, reacted with the intermediate *N*-acyliminium ion. After workup with water, γ-lactams **21** and **22** were formed in these cases. In the cases of sodium azide and potassium cyanide, this may be due to the poor solubility of these inorganic salts in THF. In the case of allylamine, the nucleophilic nature and/or the polarity of this reagent may influence the outcome of this reaction. A summary of the reactions performed in THF with β-lactams **8** and **9** is given in Scheme 9.

The fact that no reaction occurred at all when no KO*t*Bu was present, with or without extraction in water with ether as a workup procedure, indicates the necessity of the presence of KO*t*Bu for the formation of the intermediate *N*-acyliminium ions. 4-Isopropenylazetidin-2-one **20** was refluxed for 18 h in THF in the presence of 1.5 equiv of KO*t*Bu. In this way it was investigated whether dehydrobromination was an intermediate step in the reaction mechanism to obtain γ-lactams via *N*-acyliminium intermediates. After reaction, the ^{1}H NMR spectrum of the reaction mixture did not contain any trace of γ-lactams **21** or **22**, so the possibility of an intermediate 4-isopropenylazetidin-2-one or a 4-(1-cyclohexen-1-yl)azetidin-2-one in the ring transformations of β-lactams **8**, **9**, **10**, **11**, **13**, and **14** to γ-lactams **16**, **17**, **21**, **22**, **23a**−**d**, **24b**−**d**, **26a**,**b**, **27a**,**b**, **29a**,**b**, and **30a**,**b** can be excluded.

When 4-(1-bromocyclohexyl)azetidin-2-ones **13** and **14** were treated with 1.5 equiv of KO*t*Bu in THF for 18 h at reflux temperature, complex reaction mixtures were obtained after workup with water. In the ^{1}H NMR spectra of the crude reaction mixtures, slight amounts of the dehydrobromination products **25a** and **25b** were detected, and no signals of the pyrrolidinones **26** and **27** were present. The slower reaction rate of 4-(1-bromocyclohexyl)azetidin-2-ones **13** and **14** toward ring expansion (because of the strained reaction intermediates) compared to 4-(1-bromo-1-methylethyl)azetidin-2-ones **8** and **9** can be suggested as an explanation for the different reactivity of β-lactams **13** and **14** in THF. Complex reaction mixtures were also obtained when *N*-benzylated β-lactams **10** and **11** were treated with 1.5 equiv of KO*t*Bu in THF for 18 h at reflux temperature.

As a final proof, γ-lactam **21** was treated with a catalytic amount of *p*-toluenesulfonic acid in methanol (Scheme 10).[18] After workup, *trans*-3-(benzyloxy)-1-*tert*-

SCHEME 10



butyl-5-methoxy-4,4-dimethyl-2-pyrrolidin-2-one **23a** was isolated. This result confirms the structure of the γ-lactams formed starting from β-lactams **8** and **9** via ring transformation of *N*-acyliminium intermediates.

Conclusions

A new synthesis of 2-pyrrolidinones was developed starting from β-lactams. Dissociation of the bromide in 4-(1-bromoalkyl)-2-azetidinones in polar medium gave rise to the formation of tertiary carbenium ions, which rearranged toward *N*-acyliminium ions. These intermediates are susceptible to attack of oxygen, nitrogen, and carbon nucleophiles, resulting in different highly functionalized 2-pyrrolidinones. When DMSO was used as a solvent, dehydrobromination of the 4-(1-bromoalkyl)-2-

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azetidinones occurred as an important side reaction, but these reactions were successful with all tested nucleophiles (water, methanol, sodium azide, potassium cyanide, and allylamine). When THF was used as a solvent, ring transformations occurred with water and methanol as nucleophiles and in the presence of KO*t*Bu, but they were unsuccessful with sodium azide, potassium cyanide, and allylamine as nucleophiles. In THF no dehydrobromination of 4-(1-bromo-1-methylethyl)-1-*tert*-butylazetidin-2-ones was observed. As a consequence, successful ring expansions in THF were obtained in higher yields compared to reactions performed in DMSO. It was found that the diastereocontrol of the investigated ring transformation is dependent on both the reacting nucleophile and the substituents on the 4-(1-bromoalkyl)-2-azetidinones. The substituents at N and C4 of the 4-(1-bromoalkyl)-2-azetidinones also have an important influence on the degree of dehydrobromination.

Experimental Section

N-(2-Bromo-2-methylpropylidene)-2-methyl-2-propylamine **6,** *N*-(2-bromo-2-methylpropylidene)-2-benzylamine **7**, and *N*-((1-bromocyclohexyl)methylidene)-2-methyl-2-propylamine **12** were synthesized via a known procedure.[7,8]

1. Synthesis of Azetidin-2-ones 8, 9, 10, 11, 13, and 14. As an example, the synthesis of *cis*-4-(1-bromo-1-methylethyl)-1-*tert*-butyl-3-methoxy-azetidin-2-one **8** is described. A solution of *N*-(2-bromo-2-methylpropylidene)-2-methyl-2-propylamine **6** (1.86 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 drying (magnesium sulfate) and evaporation of the solvent, the crude reaction product was obtained. Further purification was performed by flash chromatography (compounds **8**, **9**, **10**, and **11**) or recrystallization from diethyl ether (compounds **13** and **14**).

***cis*-4-(1-Bromo-1-methylethyl)-1-*tert*-butyl-3-methoxyazetidin-2-one 8:** white crystals, 62% yield, TLC R_f 0.2 (petroleum ether/ethyl acetate 4/1); mp 65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (9H, s), 1.91 and 1.95 (6H, 2 × s), 3.54 (3H, s), 4.30 (1H, d, J = 5.8 Hz), 4.34 (1H, d, J = 5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 29.9, 31.0, 54.8, 59.9, 67.2, 69.4, 82.8, 169.0; IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1733, ν_{max} = 2977, 1463; MS (70 eV) *m/z* (%) 280/78 (M^+ + 1, 10), 216 (100). Anal. Calcd for $C_{11}H_{20}BrNO_2$: C 47.49; H 7.25; N 5.04. Found: C 47.66; H 7.12; N 4.90.

2. Synthesis of Pyrrolidin-2-ones from Azetidin-2-ones 8, 9, 10, 11, 13, and 14. 2.1. Reaction of Azetidin-2-ones 8, 9, 10, 11, 13, and 14 in DMSO. As an example, the synthesis of *cis*-1-*tert*-butyl-4-isopropenyl-3-methoxyazetidin-2-one **15**, *trans*-1-*tert*-butyl-5-hydroxy-3-methoxy-4,4-dimethylpyrrolidin-2-one **16**, and *cis*-1-*tert*-butyl-5-hydroxy-3-methoxy-4,4-dimethyl-pyrrolidin-2-one **17** is described (see also Table 1). Water (10 mL) was added to a mixture of *cis*-4-(1-bromo-1-methylethyl)-1-*tert*-butyl-3-methoxyazetidin-2-one **8** (1.39 g, 5 mmol) and DMSO (40 mL). The resulting solution was stirred overnight. Subsequently, water (50 mL) was added to the reaction mixture and the solution was extracted three times with diethyl ether (20 mL). The combined organic fractions were washed three times with water and dried with magnesium sulfate. After evaporation of the solvent, the crude reaction mixture was obtained. Further purification was performed by flash chromatography.

***cis*-1-*tert*-Butyl-4-isopropenyl-3-methoxyazetidin-2-one 15:** white crystals, 16% yield; TLC R_f 0.3 (petroleum ether/ethyl acetate 3/1); mp 52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (9H, s), 1.86 (3H, d × d, J = 1.4 Hz, J = 0.8 Hz), 3.43 (3H, s), 4.29 (1H, d, J = 5.1 Hz), 4.40 (1H, d, J = 5.1 Hz), 5.08−5.11 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 27.8, 54.3, 58.7, 62.7, 83.4, 116.1, 142.6, 166.8; IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1737, ν_{max} = 2974, 2835, 1454, 1375. MS (70 eV); *m/z* (%) 198 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{19}NO_2$: C 66.97; H 9.71; N 7.10. Found: C 67,11; H 9.88; N 6.96.

***trans*-1-*tert*-Butyl-5-hydroxy-3-methoxy-4,4-dimethylpyrrolidin-2-one 16:** white crystals, 54% yield; TLC R_f 0.1 (petroleum ether/ethyl acetate 4/1); mp 105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 and 1.22 (6H, 2 × s), 1.45 (9H, s), 2.65 (1H, d, J = 5.4 Hz), 3.66 (3H, s), 3.78 (1H, s), 4.75 (1H, d, J = 5.37 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.0, 27.9, 42.2, 54.1, 60.4, 84.6, 87.6, 174.4; IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1678, ν_{max} = 3392, 2972, 1426; MS (70 eV); *m/z* (%) 216 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{21}NO_3$: C 61.37; H 9.83; N 6.51. Found: C 61.42; H 9.70; N 6.37.

2.2. Reaction of Azetidin-2-ones 8 and 9 with KO*t*Bu in THF. As an example, the synthesis of *trans*-1-*tert*-butyl-5-hydroxy-3-methoxy-4,4-dimethylpyrrolidin-2-one **16** and *cis*-1-*tert*-butyl-5-hydroxy-3-methoxy-4,4-dimethylpyrrolidin-2-one **17** is described (see also Scheme 9). A mixture of *cis*-4-(1-bromo-1-methylethyl)-1-*tert*-butyl-3-methoxyazetidin-2-one **8** (1.39 g, 5 mmol) and KO*t*Bu (0.84 g, 7.5 mmol) in THF (40 mL) was refluxed overnight. Subsequently, water (50 mL) was added to the reaction mixture which was extracted three times with diethyl ether (20 mL). The combined organic fractions were washed three times with water and dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude reaction mixture was obtained. Further purification was performed by flash chromatography and pyrrolidin-2-ones **16** and **17** were obtained in 64% and 6% yield, respectively.

3. Synthesis of *trans*-3-Benzyloxy-1-*tert*-butyl-5-methoxy-4,4-dimethylpyrrolidin-2-one 23a from Pyrrolidin-2-one 21. *trans*-3-Benzyloxy-1-*tert*-butyl-5-hydroxy-4,4-dimethylpyrrolidin-2-one **21** (0.58 g, 2 mmol) was treated with *p*-toluenesulfonic acid (0.04 g, 0.2 mmol) in methanol (30 mL). The solution was stirred at room temperature for 18 h. Subsequently, water (50 mL) was added to the reaction mixture, which was extracted three times with diethyl ether (20 mL). The combined organic fractions were washed three times with water and dried ($MgSO_4$). After filtration and evaporation of the solvent, pyrrolidin-2-one **23a** was obtained in 86% yield.

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Supporting Information Available: General information and all spectroscopic data for compounds **9**, **10**, **11**, **13**, **14**, **17**, **20**, **21**, **22**, **23a**−**d**, **24b**−**d**, **25a**,**b**, **26a**,**b**, **27a**,**b**, **28a**,**b**, **29a**,**b**, and **30a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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