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Synthesis of 3,4-Fused Bicyclic β-Lactams and Their Transformation into Methyl *cis*-3-Aminotetrahydrofuran-2-carboxylates

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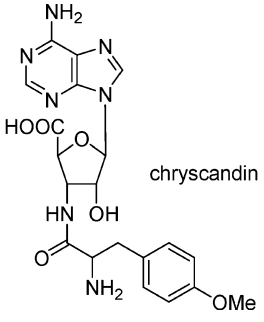
cis-3-Benzyloxy-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones were transformed into the corresponding 3-hydroxy-β-lactams through hydrogenolysis of the benzyl ether substituent, followed by formation of novel *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones by intramolecular nucleophilic substitution utilizing triethylamine in benzene. The conversion of the latter *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones into *cis*-3-aminotetrahydrofuran-2-carboxylates was accomplished by means of acidic methanolysis. In this paper, the first straightforward transformation of *cis*-azetidin-2-ones into *cis*-3-aminotetrahydrofuran-2-carboxylates via bicyclic β-lactams is reported.

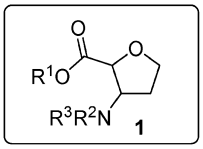
Introduction

Since the discovery of the antibiotic penicillin, β-lactams have maintained their fundamental role as antibacterial agents in medicinal chemistry.[1] However, the increasing bacterial resistance against β-lactam antibiotics imposes the search for novel types of azetidin-2-ones and β-lactamase inhibitors.[2] Besides their biological relevance as potential antibiotics, β-lactams have also acquired a prominent place in organic chemistry as synthons for further elaboration.[3,4] An important application of azetidin-2-ones involves the synthesis of β-amino acids through hydrolysis of the amide bond.[5–7] β-Amino acids comprise a valuable class of compounds because of their broad biological and synthetic applicability.[8] In particular, cyclic β-amino acids are present in a variety of natural products and are metabolically more stable toward hydrolysis than their α-amino counterparts, which is of importance for the preparation of modified peptides.[9]

Additionally, cyclic β-amino acids in which the amino group and the acid functionality are vicinally attached to an aliphatic ring represent an important challenge due to their biological utility.[10,11] Cispentacin,[12] an antifungal agent against various *Candida* strains and a subunit of the natural antibiotic amipurimycin,[13] comprises a relevant example and has attracted considerable attention to these five-membered β-amino acids.[14–17] Their oxaheterocyclic analogues, i.e. tetrahydrofurancarboxylic acid derivatives vicinally substituted with an amino group, are known to possess antimycotic activities.[18] Furthermore, the molecular structure of chryscandin, a peptidyl nucleoside antibiotic, accommodates a 3-aminotetrahydrofuran-2-carbocylic acid system as a central structural unit.[19] Consequently, the synthesis of oxolane β-amino acid derivatives such as **1** constitutes a relevant challenge in organic chemistry.



chryscandin



In continuation of our interest in the use of 4-(2-bromo-1,1-dimethylethyl)-β-lactams as versatile synthons,[20,21] the applicability of *cis*-3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)-β-lactams for the preparation of novel heterocyclic targets is investigated in this paper, leading to the synthesis of novel *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones and their conversion into the corresponding *cis*-3-aminotetrahydrofuran-2-carboxylates. The transfer of stereochemical information, introduced by stereoselective Staudinger synthesis of *cis*-β-lactams, through the reaction pathway enables the selective preparation of *cis*-3-aminotetrahydrofuran-2-carboxylates.

This is the first report on the transformation of azetidin-2-ones into biologically relevant 3-aminotetrahydrofuran-2-carboxylates via bicyclic β-lactams. Furthermore, the construction of 3,4-fused ("C-fused") bicyclic β-lactams com-

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prises an interesting synthetic challenge as an alternative for the conventional 1,4-fused bicyclic β-lactams, as very little information regarding this type of oxygen-containing 3,4-fused β-lactam systems can be found in the literature.[22]

Results and Discussion

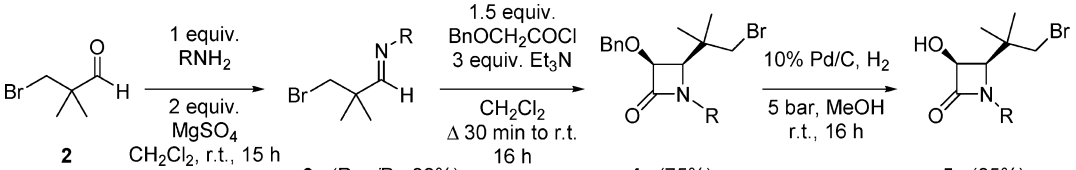
In the first step, *N*-alkyl- and *N*-aryl-β-bromoimines **3a**–**e** were synthesized through the condensation of 3-bromo-2,2-dimethylpropanal (**2**) with 1 equiv. of the corresponding amine in CH_2Cl_2 at room temperature in the presence of $MgSO_4$ (Scheme 1).[23] 3-Bromo-2,2-dimethylpropanal (**2**) was prepared according to a literature protocol involving oxidation of 3-bromo-2,2-dimethylpropan-1-ol with pyridinium chlorochromate mixed with silica in CH_2Cl_2 in 75% yield.[24] Subsequently, the obtained β-bromoimines **3a**–**e** were used as such for the Staudinger synthesis of β-lactams **4a**–**e** due to their hydrolytic instability, affording *cis*-3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **4a**–**e** in 66–75% yield upon treatment with 1.5 equiv. of benzyloxyacetyl chloride in CH_2Cl_2 in the presence of Et_3N at reflux for 30 min, followed by stirring at room temperature for 16 h (Scheme 1).[21] The *cis* selectivity could be deduced from the ^1H NMR spectra of β-lactams **4**, as the coupling constants between the 3-H and 4-H protons on the β-lactam ring varied between 5.3 and 6.1 Hz ($CDCl_3$).[25] Only for 3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)-1-(4-methoxyphenyl)-azetidin-2-one **(4e)** was a minor amount of the *trans* isomer formed during the reaction (*cis*/*trans* = 79:21, determined by ^1H NMR analysis), and separation of both isomers was performed by means of column chromatography on silica gel.

The formation of ***trans*-4e** was unexpected, as it is well known that the use of Bose–Evans ketenes[26] generally results in the formation of *cis*-β-lactams (due to the electron-donating properties of the alkoxy or aryloxy substituent), regardless of the imine substituents. However, the presence of a minor amount of ***trans*-4e** can only be attributed to the nature of the nitrogen substituent, as all other parameters remained unchanged as compared to the synthesis of β-lactams **4a**–**d**. Apparently, the presence of an aromatic ring at the nitrogen atom accelerates the isomerisation of the Zwitterionic intermediate, resulting in the formation of the thermodynamically more stable *trans*-β-lactam. A few examples are known in the literature in which the formation of *trans*-1-aryl-3-methoxy-β-lactams has been reported under Staudinger reaction conditions, next to the corresponding *cis* isomers.[27] In particular, *N*-(4-methoxyphenyl)-imines are known to enhance the *trans* selectivity during Staudinger β-lactam synthesis.[28] Additionally, the influence of the electronic effect of the N-substituent on the stereoselectivity can also be deduced from the preferential formation of *trans*-1-methoxy- and -1-methylthio-β-lactams.[29]

Hydrogenolysis of the benzyl ether substituent in β-lactams **4** by using palladium on activated carbon in methanol at room temperature afforded *cis*-3-hydroxy-β-lactams **5a**–**e** after 16 h (Scheme 1). *cis*-β-Lactams **5a**–**c**,**e** were obtained in high purity (>95%) and were used as such in the next step, whereas β-lactam **5d** required purification by recrystallization from Et_2O. Apart from their synthetic utility, 3-hydroxy-β-lactams and their derivatives are of biological importance as for example inhibitors of the enzymes renin[30] and HIV-1 protease,[31] or as key fragments in phenylisoserine analogues (used in the synthesis of new taxane anticancer drugs).[32]

In the next part, the synthesis of 2-oxa-6-azabicyclo[3.2.0]heptan-7-ones, about which very little is known in the literature, was envisaged through cyclisation of 4-(2-bromo-1,1-dimethylethyl)-3-hydroxyazetidin-2-ones (**5**). Formation of the premised *cis*-2-oxa-6-azabicyclo[3.2.0]-heptan-7-ones (**6**) required the reaction with 10 equiv. of Et_3N in benzene under reflux for 16 h, resulting in novel bicyclic β-lactams **6a**–**e** in good yields (82–95%, Scheme 2). Experimental coupling constants of 3.9–4.0 Hz (^1H NMR, $CDCl_3$) were observed between the β-lactam protons at C-3 and C-4 in compounds **6a**–**e**, pointing to a *cis* configuration of the bicyclic framework.[22c,22d,22f,33] Remarkably, the methylene group of the tetrahydrofuran ring in compounds **6** appeared as a singlet in the ^1H NMR spectrum ($CDCl_3$) and not as the expected AB system. No precedents could be found in the literature in which similar observations were described.

Simultaneously, *trans*-3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)-1-(4-methoxyphenyl)azetidin-2-one (***trans*-4e**), obtained as the minor isomer after reaction of β-bromoimine **3e** with 1.5 equiv. of benzyloxyacetyl chloride and 3 equiv. of Et_3N, was transformed into the corresponding 3-hydroxy-β-lactam ***trans*-5e** upon hydrogenolysis (5 bar H_2, MeOH, room temp., 16 h) in 94% yield.



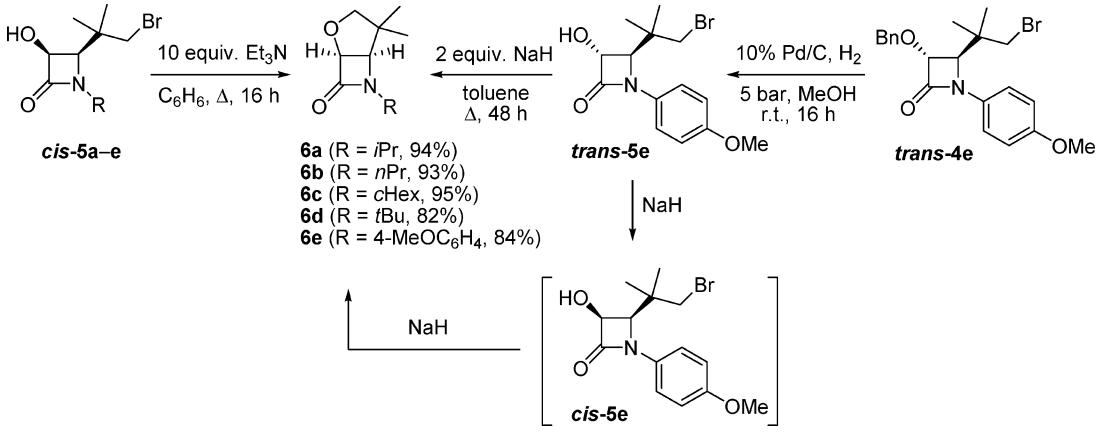
2

3a (R = *i*Pr, 82%)
3b (R = *n*Pr, 84%)
3c (R = *c*Hex, 84%)
3d (R = *t*Bu, 81%)
3e (R = 4-MeOC$_6$H$_4$, 98%)

4a (75%)
4b (67%)
4c (66%)
4d (66%)
4e (68%, *cis*/*trans* 79:21)

5a (85%)
5b (97%)
5c (93%)
5d (93%)
5e (88%)

Scheme 1.



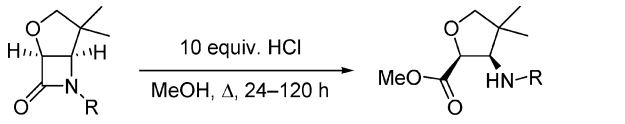
Scheme 2.

Attempted ring closure of the latter β-lactam ***trans*-5e** to the corresponding *trans*-2-oxa-6-azabicyclo[3.2.0]heptan-7-one upon treatment with 10 equiv. of Et_3N in benzene at reflux for 16 h failed and led to full recovery of the starting material. The use of 2 equiv. of sodium hydride in toluene under reflux for 48 h, however, resulted in complete transformation of ***trans*-5e** into the corresponding *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-one (**6e**) in 54% yield (after purification by column chromatography), pointing to an initial *trans*/*cis* isomerisation of the starting *trans*-β-lactam **5e**, followed by cyclization.

As mentioned before, very few examples are known in the literature regarding the synthesis of *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones. The radical-mediated ring closure of 3-benzyloxy-4-ethynylazetidin-2-ones has been described toward the corresponding "C-fused" bicyclic *cis*-β-lactams,[22c] and *cis*-6-allyl-4-(*tert*-butyldimethylsilanyloxy)-3-methyl-3-vinyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one has been prepared by a metal-catalyzed cyclization protocol.[22f] In a final example, a *cis*-4-(2-fluorophenyl)-3-hydroxy-β-lactam was transformed into a tricyclic β-lactam via an (η^6-arene)tricarbonylchromium(0) complex through a number of reaction steps.[22d] From a biological point of view, 3,4-fused bicyclic β-lactams are also of interest, e.g. as biologically active agents against class A and class C β-lactamases.[33a,33b]

Due to the release of ring-strain energy, hydrolytic ring cleavage of the amide functionality in azetidin-2-ones provides a convenient entry into the field of β-amino acid chemistry.[5–7,34] If cyclic β-amino acid derivatives are contemplated, hydrolysis of the corresponding bicyclic β-lactam framework comprises a suitable methodology.[7]

Because of the biological relevance of heterocyclic β-amino acid derivatives,[10,11] 2-oxa-6-azabicyclo[3.2.0]heptan-7-ones (**6**) can be regarded as useful synthetic precursors toward 3-aminotetrahydrofuran-2-carboxylic acids with a pre-determined stereochemistry. Thus, the synthesis of the desired 3-aminotetrahydrofuran-2-carboxylates **7a**–**e** was accomplished through ring opening of bicyclic *cis*-β-lactams **6a**–**e** by means of HCl in methanol.[35] In order to find suitable reaction conditions, a variety of different conditions (equiv., time, temperature) was evaluated by using 6-*tert*-butyl-4,4-dimethyl-2-oxa-6-azabicyclo[3.2.0]-heptan-7-one (**6d**) as the starting compound. Treatment of β-lactam **6d** with 4 or 8 equiv. of HCl in MeOH at 0 °C, followed by stirring for 16 h at room temp., resulted in complete recovery of the starting material. The addition of 4 equiv. of HCl at room temp., followed by stirring at ambient temperature for 6 h and subsequent heating under reflux for 18 h afforded a minor amount of tetrahydrofuran **7d** (15%) and mainly unreacted starting material. Finally, optimal conversion of β-lactam **6d** into 3-*tert*-butylamino-4,4-dimethyltetrahydrofuran-2-carboxylate **7d** was achieved by using 10 equiv. of HCl in methanol and reflux for 120 h (Scheme 3). Analogously, 3-aminotetrahydrofuran-2-carboxylates **7a**–**c**,**e** were prepared in good yields and purity upon treatment of *cis*-β-lactams **6a**–**c**,**e** with 10 equiv. of HCl in methanol at reflux temperature for 24–120 h (Scheme 3). In the ^1H NMR spectra, the methylene group of the tetrahydrofuran ring in compounds **7** appeared as an AB system with a coupling constant between 8.3 and 8.8 Hz ($CDCl_3$) (Figure 1).



Scheme 3.

Due to the high stereoselectivity in the Staudinger synthesis of *cis*-β-lactams **4** and transfer of this relative configuration through the reaction sequence, *cis*-3-aminotetrahydrofuran-2-carboxylates **7** were deduced as the final reaction products. Moreover, the experimental coupling constants between the protons at C-2 and C-3 in tetrahydrofurans **7** (6.2–8.3 Hz, $CDCl_3$) are in accordance with coupling constants of similar compounds described in the literature.[36,37] Nonetheless, coupling constants of 4.6–

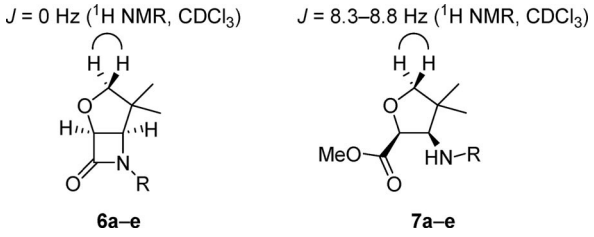


Figure 1. Geminal coupling constants in oxolanes **6** and **7**.

4.8 Hz between the protons at C-2 and C-3 have also been reported for *cis*-3-azidotetrahydrofuran-2-carboxylates, making a conclusive stereochemical assignment solely based on coupling constants precarious.[38]

Subsequently, NOESY experiments were performed on 3-aminotetrahydrofuran-2-carboxylates **7**. Although the latter experiments also pointed into the direction of the initially proposed *cis* stereochemistry, no irrefutable proof could be obtained. Finally, X-ray analysis of 3-aminotetrahydrofuran-2-carboxylate **7e** unambiguously settled the issue and revealed a *cis* relationship between the amino group and the ester moiety (Figure 2).

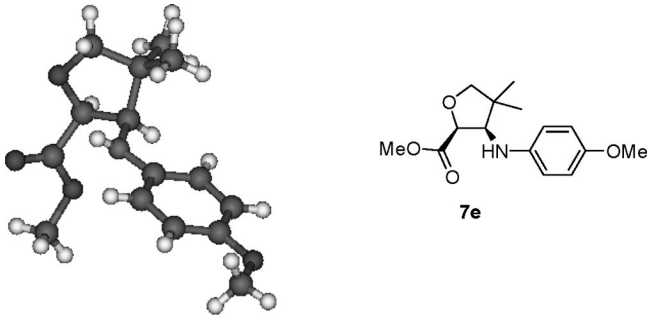


Figure 2. X-ray analysis of methyl *cis*-3-(4-methoxyphenylamino)-4,4-dimethyltetrahydrofuran-2-carboxylate (**7e**).

In addition to the above-described strategy, providing an entry into 2-oxa-6-azabicyclo[3.2.0]heptan-7-ones in which the oxygen atom is connected to the C-3 β-lactam carbon atom, an alternative approach was applied with the intention to produce the isomeric 2-oxa-7-azabicyclo[3.2.0]heptan-6-ones (in which the oxygen atom is connected to the C-4 β-lactam carbon atom). Based on a methodology reported in the literature,[39] cycloaddition of 2,3-dihydrofuran **8** with phenyl and benzyl isocyanate in a sealed tube at 100 °C afforded the corresponding 2-oxa-7-azabicyclo[3.2.0]heptan-6-ones **9a**–**b** (Scheme 4). The structural identity of bicyclic β-lactam **9a**, which was prepared in higher yield as compared to the above-mentioned literature protocol, was acknowledged through comparison of its spectroscopic data with those reported in the literature.[39c] In the ^{1}H NMR spectra, the coupling constants between the two protons at C-3 varied between 9.4 and 9.7 Hz ($CDCl_3$).

Attempts to open bicyclic β-lactams **9** toward the corresponding oxolanes **10** by using methanolic hydrogen chloride failed due to the presence of a labile hemiaminal moiety. Therefore, attempts were made to prepare the more stable 7-tosyl-2-oxa-7-azabicyclo[3.2.0]heptan-6-one as a substrate for acidic methanolysis upon treatment of 2,3-dihydrofuran with 1.05 equiv. of chlorosulfonyl isocyanate in diethyl ether under reflux for 8 h. However, only complex reaction mixtures were obtained. Finally, efforts were made to perform the cycloaddition of aryl isocyanates with 2,5-dihydrofuran in order to prepare 3-oxa-6-azabicyclo[3.2.0]-heptan-7-ones by applying the same reaction conditions (sealed tube, 100 °C, 5 d), albeit without any success.

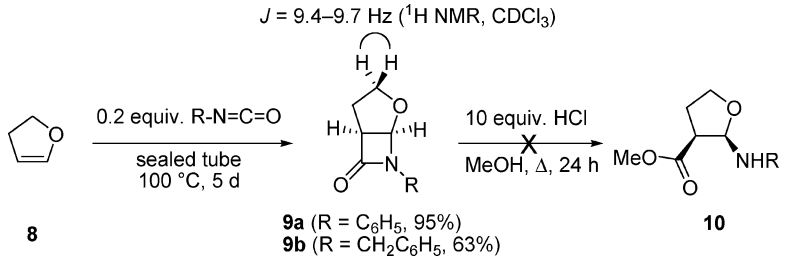
Conclusion

The synthesis of *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones as a novel class of C-fused bicyclic β-lactams is described starting from *cis*-3-hydroxy-β-lactams through intramolecular nucleophilic substitution. The latter 3,4-fused bicyclic β-lactams were converted into biologically relevant *cis*-3-aminotetrahydrofuran-2-carboxylates by methanolysis in acid medium. This approach comprises the first transformation of β-lactams into *cis*-3-aminotetrahydrofuran-2-carboxylates in good overall yields.

Experimental Section

General: See Supporting Information.

Synthesis of *cis*-3-Benzyloxy-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones 4a–e: As a representative example, the synthesis of *cis*-3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)-1-(4-methoxyphenyl)azetidin-2-one (**4e**) is described here. To a stirred solution of β-bromoimine **3e**[21] (1.85 g, 6.85 mmol) and Et_3N (2.08 g, 20.56 mmol) in CH_2Cl_2 (15 mL) was added benzyloxyacetyl chloride (1.90 g, 10.28 mmol), and the resulting solution was heated under reflux for 30 min. Afterwards, the mixture was cooled to room temperature and stirred for 12 h. Subsequently, the reaction mixture was poured into water (50 mL) under vigorous stirring and extracted



Scheme 4.

with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo to furnish a mixture of *cis*- and *trans*-3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)-1-(4-methoxyphenyl)azetidin-2-one (**4e**), in a *cis*/*trans* ratio of 79:21 (determined by ^{1}H NMR analysis). The two isomers were separated by means of column chromatography on silica gel (petroleum ether/EtOAc, 3:1) in 68% yield for ***cis*-4e** (1.95 g) and in 14% yield for ***trans*-4e** (0.40 g).

***cis*-3-Benzyloxy-4-(2-bromo-1,1-dimethylethyl)-1-(4-methoxyphenyl)-azetidin-2-one (*cis*-4e):** White translucent crystals (obtained after column chromatography). Yield 68%. M.p. 92.9–93.9 °C. R_f = 0.40 (petroleum ether/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H), 1.21 (s, 3 H), 3.25 (d, J = 9.9 Hz, 1 H), 3.63 (d, J = 9.9 Hz, 1 H), 3.78 (s, 3 H), 4.50 (d, J = 5.5 Hz, 1 H), 4.76 (d, J = 11.6 Hz, 1 H), 4.86 (d, J = 5.5 Hz, 1 H), 5.01 (d, J = 11.6 Hz, 1 H), 6.85–6.90 and 7.28–7.40 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 and 24.40 (CH_3), 38.6 (C), 44.7 (CH_2), 55.4 (CH_3), 63.0 (CH), 73.6 (CH_2), 81.4 (CH), 114.3 (CH), 121.8 (CH), 127.7 (CH), 128.0 (CH), 128.5 (CH), 129.8 (C), 137.0 (C), 157.2 (C), 166.4 (C) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 1246, 1510, 1746 cm^{-1}. MS: m/z (%) = 418/420 (100) $[M + H]^+$. $C_{21}H_{24}BrNO_3$ (418.32): calcd. C 60.29, H 5.78, N 3.35; found C 59.94, H 5.41, N 3.43.

Synthesis of *cis*-4-(2-Bromo-1,1-dimethylethyl)-3-hydroxyazetidin-2-ones 5a–e: As a representative example, the synthesis of *cis*-4-(2-bromo-1,1-dimethylethyl)-1-*tert*-butyl-3-hydroxyazetidin-2-one (**5d**) is described here. Palladium on activated carbon (0.16 g, 10% Pd) was added to a solution of β-lactam **4d** (1.64 g, 4.46 mmol) in methanol (30 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. Filtration of the heterogeneous mixture through Celite® and evaporation of the solvent in vacuo afforded *cis*-4-(2-bromo-1,1-dimethylethyl)-1-*tert*-butyl-3-hydroxyazetidin-2-one (**5d**), which was purified by recrystallisation from diethyl ether in 93% yield (1.15 g).

***cis*-4-(2-Bromo-1,1-dimethylethyl)-1-*tert*-butyl-3-hydroxyazetidin-2-one (5d):** White crystals (recrystallization from Et_2O). Yield 93%. M.p. 157.4–158.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.27 (s, 3 H), 1.39 (s, 9 H), 3.40 (d, J = 9.9 Hz, 1 H), 3.97 (d, J = 5.5 Hz, 1 H), 3.99 (d, J = 9.9 Hz, 1 H), 4.87 (dd, J = 5.5, J = 5.5 Hz, 1 H), 5.39 (d_{br}, J = 5.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (CH_3), 26.6 (CH_3), 29.0 (CH_3), 37.2 (C), 44.5 (CH_2), 54.1 (C), 66.2 (CH), 73.7 (CH), 172.3 (C) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 1700, 2972, 3225 cm^{-1}. MS: m/z (%) = 278/280 (100) $[M + H]^+$. $C_{11}H_{20}BrNO_2$ (278.19): calcd. C 47.49, H 7.25, N 5.04; found C 47.11, H 7.43, N 4.90.

Synthesis of *cis*-4,4-Dimethyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones 6a–e: As a representative example, the synthesis of *cis*-6-*tert*-butyl-4,4-dimethyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one (**6d**) is described here. To *cis*-4-(2-bromo-1,1-dimethylethyl)-1-*tert*-butyl-3-hydroxyazetidin-2-one (**5d**) (0.70 g, 2.52 mmol) in benzene (20 mL) was added Et_3N (2.54 g, 25.19 mmol). This mixture was heated under reflux for 16 h, after which the solvent was removed under reduced pressure. Dry diethyl ether was added, and the precipitated triethylammonium bromide was removed by filtration. Evaporation of the solvent yielded the bicyclic *cis*-β-lactam **6d** in 90% crude yield. Purification by column chromatography (petroleum ether/EtOAc, 3:1) gave 6-*tert*-butyl-4,4-dimethyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one (**6d**, 0.41 g, 82%) in pure form.

***cis*-*tert*-Butyl-4,4-dimethyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one (6d):** White translucent crystals (obtained after column chromatography). Yield 82%. R_f = 0.17 (petroleum ether/EtOAc, 3:1). M.p. 72.2–73.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 and 1.16 (2 s, 2 × 3 H), 1.37 (s, 9 H), 3.63 (s, 2 H, OCH_2), 3.71 (d, J = 3.9 Hz, 1 H), 4.97 (d, J = 3.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5 and 24.3 (CH_3), 28.3 (CH_3), 39.5 (C), 53.4 (C), 66.1 (CH), 77.7 (CH_2), 84.9 (CH), 167.3 (C) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 1722, 2959 cm^{-1}. MS: m/z (%) = 198 (100) $[M + H]^+$. $C_{11}H_{19}NO_2$ (197.27): calcd. C 66.97, H 9.71, N 7.10; found C 67.11, H 9.57, N 7.10.

Synthesis of *cis*-3-Aminotetrahydrofuran-2-carboxylates 7a–e: As a representative example, the synthesis of methyl *cis*-3-(*tert*-butylamino)tetrahydrofuran-2-carboxylate (**7d**) is described here. 6-*tert*-Butyl-4,4-dimethyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one (**6d**) (0.40 g, 2.03 mmol) was dissolved in methanol (25 mL) containing 10 equiv. of HCl gas. The HCl gas was obtained by adding sulfuric acid to a solution of sodium chloride in hydrogen chloride, and utilizing sulfuric acid as drying trap. The mixture was heated under reflux for 120 h, after which the solvent was removed under reduced pressure. Saturated sodium hydrogen carbonate solution (15 mL) was added to the reaction mixture, followed by extraction with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (petroleum ether/EtOAc, 4:1) furnished methyl *cis*-3-(*tert*-butylamino)tetrahydrofuran-2-carboxylate (**7d**, 0.32 g) in 68% yield.

Methyl *cis*-3-(*tert*-Butylamino)tetrahydrofuran-2-carboxylate (7d): Colorless liquid. Yield 68%. R_f = 0.28 (petroleum ether/EtOAc, 17:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 and 1.04 (2 s, 2 × 3 H), 1.05 (s, 9 H), 3.21 (d, J = 8.3 Hz, 1 H), 3.57 (d, J = 8.3 Hz, 1 H), 3.74 (s, 3 H), 3.82 (d, J = 8.3 Hz, 1 H), 4.52 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 and 25.3 (CH_3), 30.1 (CH_3), 41.1 (C), 50.0 (C), 51.5 (CH_3), 63.6 (CH), 79.8 (CH_2), 80.5 (CH), 172.5 (C) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 1084, 1198, 1466, 1748, 2958 cm^{-1}. MS: m/z (%) = 230 (100) $[M + H]^+$. $C_{12}H_{23}NO_3$ (229.32): calcd. C 62.85, H 10.11, N 6.11; found C 62.71, H 10.34, N 5.98.

Synthesis of 2-Oxa-7-azabicyclo[3.2.0]heptan-6-ones 9a–b: As a representative example, the synthesis of 2-oxa-7-aza-7-phenylbicyclo[3.2.0]heptan-6-one (**9a**) is described here. A mixture of 2,3-dihydrofuran (**8**, 2.76 g, 39.43 mmol) and phenyl isocyanate (0.94 g, 7.90 mmol) in a sealed Teflon® tube was heated at 100 °C and stirred for 5 d. The resulting mixture was subjected to concentration. 7-Phenyl-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (**9a**, 1.49 g) was obtained in 95% yield without further purification (purity > 95% based on ^{1}H NMR).

7-Phenyl-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (9a): Yellow crystals. Yield 99%. M.p. 48.9–49.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (dddd, J = 13.2, J = 12.1, J = 8.8, J = 8.3 Hz, 1 H), 2.27 (dd, J = 13.2, J = 5.5 Hz, 1 H), 3.78 (dd, J = 8.8, J = 3.3 Hz, 1 H), 3.93 (ddd, J = 12.1, J = 9.7, J = 5.5 Hz, 1 H), 4.24 (dd, J = 9.7, J = 8.3 Hz, 1 H), 5.90 (d, J = 3.3 Hz, 1 H), 7.08–7.13 and 7.29–7.51 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4 (CH_2), 55.8 (CH), 66.9 (CH_2), 85.8 (CH), 116.9 (CH), 124.4 (CH), 129.2 (CH), 136.9 (C), 165.2 (C) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 1072, 1381, 1743 cm^{-1}. MS: m/z (%) = 190 (100) $[M + H]^+$. $C_{11}H_{11}NO_2$ (189.21): calcd. C 69.83, H 5.86, N 7.40; found C 69.61, H 5.92, N 7.23.

Supporting Information (see footnote on the first page of this article): Spectroscopic data of compounds ***trans*-4e**, ***cis*-5a–c,e**, ***trans*-5e**, **6a–c,e** and **7a–c,e**. X-ray structural information on compound **7e**.

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[1] a) R. B. Morin, M. Gorman (Eds.), *Chemistry and Biology of β-Lactam Antibiotics*, Academic Press, New York, **1982**, vols. 1–3; b) G. I. Georg, V. T. Ravikumar, in *The Organic Chemistry of β-Lactams* (Ed.: G. I. Georg), VCH, New York, **1993**, chapter 6, pp. 295; c) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223; d) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Curr. Med. Chem.* **2004**, *11*, 1837; e) N. De Kimpe in *Comprehensive Heterocyclic Chemistry II* (Ed.: A. Padwa), Elsevier, Oxford, **1996**, vol. 1B, p. 507; f) G. S. Singh, M. D'hooghe, N. De Kimpe in *Comprehensive Heterocyclic Chemistry III* (Eds.: A. Katritzky, C. Ramsden, E. Scriven, R. Taylor), Elsevier, Oxford, **2008**, vol. 2, p. 1.

[2] a) H. C. Neu, *Science* **1992**, *257*, 1064; b) J. Davies, *Science* **1994**, *264*, 375.

[3] I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377.

[4] a) I. Ojima, *Acc. Chem. Res.* **1995**, *28*, 383; b) J. F. Fisher, S. O. Meroueh, S. Mobashery, *Chem. Rev.* **2005**, *105*, 395; c) B. Alcaide, P. Almendros, *Synlett* **2002**, 381; d) G. S. Singh, *Tetrahedron* **2003**, *59*, 7631; e) S. France, A. Weatherwax, A. E. Taggi, T. Lectka, *Acc. Chem. Res.* **2004**, *37*, 592; f) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437; g) N. Fu, T. T. Tidwell, *Tetrahedron* **2008**, *64*, 10465; h) M. T. Aranda, P. Perez-Faginas, R. Gonzalez-Muniz, *Curr. Org. Synth.* **2009**, *6*, 325; i) A. R. A. S. Deshmukh, B. M. Bhawal, D. Krishnaswamy, V. V. Govande, B. A. Shinkre, A. Jayanthi, *Curr. Med. Chem.* **2004**, *11*, 1889.

[5] W. R. Vaughan, D. I. McCane, *J. Org. Chem.* **1955**, *20*, 143.

[6] a) M. S. Manhas, S. G. Amin, A. K. Bose, *Heterocycles* **1976**, *5*, 669; b) M. S. Manhas, V. R. Hegde, D. R. Wagle, A. K. Bose, *J. Chem. Soc. Perkin Trans. 1* **1985**, *10*, 2045.

[7] a) G. Stajer, E. A. Szabo, F. Fülöp, G. Bernath, P. Sohar, *J. Heterocycl. Chem.* **1983**, *20*, 1181; b) Z. Szakonyi, F. Fülöp, G. Bernath, F. Evanics, F. G. Riddell, *Tetrahedron* **1998**, *54*, 1013; c) S. Gyonfalvi, Z. Szakonyi, F. Fülöp, *Tetrahedron: Asymmetry* **2003**, *14*, 3965; d) L. Kiss, E. Forro, T. A. Martinek, G. Bernath, N. De Kimpe, F. Fülöp, *Tetrahedron* **2008**, *64*, 5036.

[8] a) E. Juaristi (Ed.), *Enantioselective Synthesis of β-Amino Acids*, Wiley-VCH, New York, **1997**; b) A. F. Abdel-Magid, J. H. Cohen, C. A. Maryanoff, *Curr. Med. Chem.* **1999**, *6*, 955; c) J. S. Ng, R. S. Topgi, *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 314.

[9] a) L. Kiss, E. Forró, T. A. Martinek, G. Bernáth, N. De Kimpe, F. Fülöp, *Tetrahedron* **2008**, *64*, 5036; b) E. Forró, F. Fülöp, *Mini-Rev. Org. Chem.* **2004**, *1*, 93; c) M. Palkó, L. Kiss, F. Fülöp, *Curr. Med. Chem.* **2005**, *12*, 3063.

[10] a) A. Kuhl, M. G. Hahn, M. Dumić, J. Mittendorf, *Amino Acids* **2005**, *29*, 89; b) J. A. Miller, S. T. Nguyen, *Mini-Rev. Org. Chem.* **2005**, *2*, 39.

[11] a) S. Mangelinckx, M. D'hooghe, S. Peeters, N. De Kimpe, *Synthesis* **2009**, 1105; b) S. Mangelinckx, A. Žukauskaitė, V. Buinauskaitė, A. Šačkus, N. De Kimpe, *Tetrahedron Lett.* **2008**, *49*, 6896; c) L. Kiss, S. Mangelinckx, F. Fülöp, N. De Kimpe, *Org. Lett.* **2007**, *9*, 4399; d) N. Giubellina, S. Mangelinckx, K. W. Törnroos, N. De Kimpe, *J. Org. Chem.* **2006**, *71*, 5881; e) S. Mangelinckx, N. De Kimpe, *Synlett* **2005**, 1521.

[12] K. Tomatsu, T. Oki, M. Hirano, K. Numamta, H. Kamei, *J. Antibiot.* **1989**, *42*, 1756.

[13] T. Goto, Y. Toya, T. Ohgi, T. Kondo, *Tetrahedron Lett.* **1982**, *23*, 1271.

[14] E. Nativ, P. Rona, *Isr. J. Chem.* **1972**, *10*, 55.

[15] S. G. Davis, I. Osomu, A. S. Walters Iain, *Synlett* **1993**, 461.

[16] V. K. Aggarwal, S. Roseblade, R. Alexander, *Org. Biomol. Chem.* **2003**, *1*, 684.

[17] a) G. Benedek, M. Palkó, E. Wéber, T. A. Martinek, E. Forró, F. Fülöp, *Eur. J. Org. Chem.* **2008**, 3724; b) E. Forró, F. Fülöp, *Tetrahedron: Asymmetry* **2008**, *19*, 1005; c) L. Kiss, E. Forró, G. Bernath, F. Fülöp, *Synthesis* **2005**, 1265; d) E. Abraham, S. G. Davies, A. J. Docherty, K. B. Ling, P. M. Roberts, A. J. Russell, J. E. Thomson, S. M. Toms, *Tetrahedron: Asymmetry* **2008**, *19*, 1356; e) F. Fülöp, *Chem. Rev.* **2001**, *101*, 2181.

[18] F. Kunisch, J. Mittendorf, M. Plempel Eur. Pat. Appl. **1993**, EP 538688 A1, *Chem. Abstr.* **1993**, *119*, 139065.

[19] M. Yamashita, Y. Tsurumi, J. Hosoda, T. Komori, M. Kohsaka, H. Imanaka, *J. Antibiot.* **1984**, *37*, 1279.

[20] a) W. Van Brabandt, Y. Dejaegher, R. Van Landeghem, N. De Kimpe, *Org. Lett.* **2006**, *8*, 1101; b) W. Van Brabandt, R. Van Landeghem, N. De Kimpe, *Org. Lett.* **2006**, *8*, 1105; c) E. Leemans, M. D'hooghe, Y. Dejaegher, K. W. Törnroos, N. De Kimpe, *J. Org. Chem.* **2008**, *73*, 1422.

[21] Y. Dejaegher, N. De Kimpe, *J. Org. Chem.* **2004**, *69*, 5974.

[22] a) Y. Nagao, T. Kumagai, S. Takao, T. Abe, M. Ochiai, Y. Inoue, T. Taga, E. Fujita, *J. Org. Chem.* **1986**, *51*, 4737; b) B. Alcaide, G. Esteban, Y. Martin-Cantalejo, J. Plumet, J. Rodriguez-Lopez, A. Monge, V. Perez-Garcia, *J. Org. Chem.* **1994**, *59*, 7994; c) B. Alcaide, I. M. Rodriguez-Campos, J. Rodriguez-Lopez, A. Rodriguez-Vicente, *J. Org. Chem.* **1999**, *64*, 5377; d) P. Del Buttero, C. Baldoli, G. Molteni, T. Pilati, *Tetrahedron: Asymmetry* **2000**, *11*, 1927; e) Y. Yang, F. Wang, F. D. Rochon, M. M. Kayser, *Can. J. Chem.* **2005**, *83*, 28; f) B. Alcaide, P. Almendros, T. Martinez del Campo, *Angew. Chem. Int. Ed.* **2007**, *46*, 6684; g) B. Alcaide, P. Almendros, A. Luna, M. R. Torres, *Org. Biomol. Chem.* **2008**, *6*, 1635.

[23] a) P. Sulmon, N. De Kimpe, R. Verhé, L. De Buyck, N. Schamp, *Synthesis* **1986**, 192; b) P. Sulmon, N. De Kimpe, N. Schamp, B. Tinant, J.-P. Declercq, *Tetrahedron* **1988**, *44*, 3653.

[24] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *31*, 2647.

[25] a) K. D. Barrow, T. M. Spotswood, *Tetrahedron Lett.* **1965**, *37*, 3325; b) J. Decazes, J. L. Luche, H. B. Kagan, *Tetrahedron Lett.* **1970**, *11*, 3365.

[26] a) G. I. Georg, V. T. Ravikumar in *The Organic Chemistry of β-Lactams* (Ed.: G. I. Georg), VCH, New York, **1993**, p. 295–368 and references cited therein; b) X. Huang, J. X. Xu, *Heteroat. Chem.* **2003**, *14*, 564.

[27] L. M. Monleón, M. Grande, J. Anaya, *Tetrahedron* **2007**, *63*, 3017.

[28] L. Jiao, Y. Liang, J. Xu, *J. Am. Chem. Soc.* **2006**, *128*, 6060.

[29] a) O. Miyata, Y. Fujiwara, I. Ninomiya, T. Naito, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2167; b) D. A. Evans, E. B. Sjogren, *Tetrahedron Lett.* **1986**, *27*, 3119; c) N. V. Shah, L. D. Cama, *Heterocycles* **1987**, *25*, 221.

[30] S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner, F.-S. Han, *J. Med. Chem.* **1987**, *30*, 976.

[31] J. R. Huff, *J. Med. Chem.* **1987**, *34*, 2305.

[32] a) I. Ojima, I. Habus, M. Zhao, G. I. Georg, L. R. Jayasinghe, *J. Org. Chem.* **1991**, *56*, 1681; b) G. I. Georg, Z. S. Cheruvallath, R. H. Himes, M. R. Mejillano, C. T. Burke, *J. Med. Chem.* **1992**, *35*, 4230; c) A. R. A. S. Deshmukh, B. M. Bhawal, D. Krishnaswamy, V. V. Govande, B. A. Shinkre, A. Jayanthi, *Curr. Med. Chem.* **2004**, *11*, 1889.

[33] a) C. Hubschwerlen, P. Angehrn, K. Gubernator, M. G. P. Page, J.-L. Specklin, *J. Med. Chem.* **1998**, *41*, 3972; b) R. Charnas, K. Gubernator, I. Heinze, C. Hubschwerlen, Eur. Pat. Appl. EP. 508234 A2, 1992, *Chem. Abstr.* **1993**, *119*, 117025.

[34] B. Alcaide, P. Almendros, *Synlett* **2002**, *3*, 381.

[35] W. R. Vaughan, D. I. McCane, *J. Org. Chem.* **1955**, *20*, 143.

[36] P. Dauban, A. Chiaroni, C. Riche, R. H. Dodd, *J. Org. Chem.* **1996**, *61*, 2488.

[37] U. Jahn, D. Rudakov, *Synlett* **2004**, 1207.

[38] a) M. P. Watterson, L. Pickering, M. D. Smith, S. J. Hudson, P. R. Marsh, J. E. Mordaunt, D. J. Watkin, C. J. Newman, G. W. J. Fleet, *Tetrahedron: Asymmetry* **1999**, *10*, 1855; b) Y. Vera-Ayoso, P. Borrachero, F. Cabrera-Escribano, M. Gómez-Guillén, *Tetrahedron: Asymmetry* **2005**, *16*, 889.

[39] a) Y. Taguchi, A. Oishi, T. Tsuchiya, I. Shibuya, Y. Nagawa, *Nippon Kagaku Kaishi* **1995**, 459–463; *Chem. Abstr.* **1995**, *123*, 82997; b) Y. Taguchi, A. Oishi, I. Shibuya, T. Tsuchiya, Eur. Pat. Appl. EP 671398 A2, **1995**, *Chem. Abstr.* **1995**, *124*, 29747; c) Y. Taguchi, T. Tsuchiya, A. Oishi, I. Shibuya, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1667; d) C. Garcia-Martinez, Y. Taguchi, A. Oishi, K. Hayamizu, *Tetrahedron: Asymmetry* **1998**, *9*, 955; e) Z. Szakonyi, F. Fülöp, G. Bernáth, F. Evanics, F. G. Riddell, *Tetrahedron* **1998**, *54*, 1013.

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