Synthesis of 4-imidoyl-, 4-oxiranyl- and 4-propargyloxyphenyl-substituted β-lactam building blocks

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Abstract. In this study, the preparation of 4-imidoyl-, 4-oxiranyl- and 4-propargyloxyphenyl-substituted β-lactams as versatile building blocks in heterocyclic chemistry was realized. Efforts were made to deploy these polyvalent compounds for ensuing cyclization reactions *en route* to new bi- or polycyclic frameworks, which, in the case of a 3-chloro-4-propargyloxyphenyl-β-lactam substrate, enabled the preparation of an unprecedented β-lactam-fused benzotriazolo-oxazocane scaffold. The chemical structure of the latter polyheterocycle was unequivocally secured by means of X-ray analysis.

Key words. β-lactams • Staudinger synthesis • Epoxides • Imines • Alkynes

Introduction

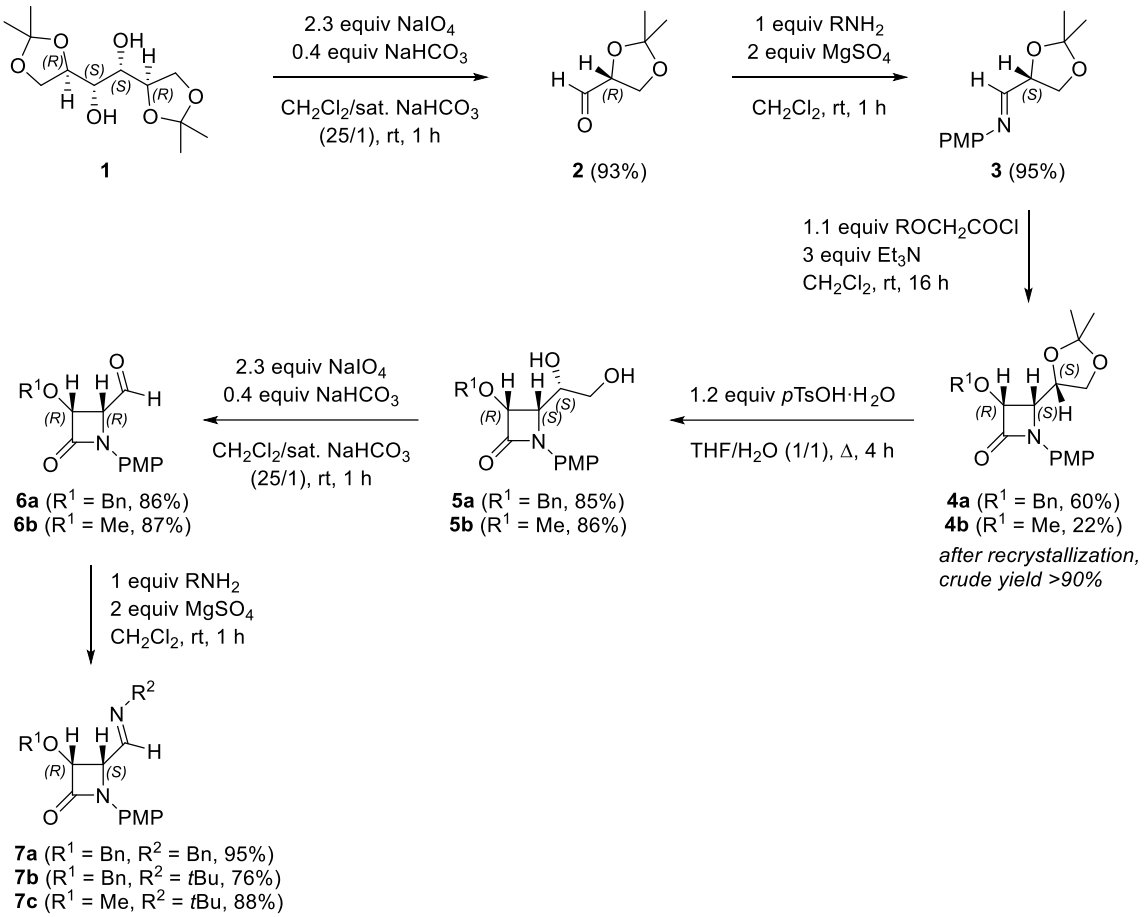
β-Lactams or azetidin-2-ones have established a strong reputation in organic chemistry because of their pronounced biological activities on the one hand and their synthetic utility on the other hand. These properties explain the high interest in β-lactam-based synthons, culminating in a plethora of new synthetic approaches developed during the past few decades.[1] A frequently deployed strategy in that respect relies on the initial construction of the β-lactam ring system, followed by the introduction of molecular complexity through further ring functionalization. The success of this approach originates from the relative stability of the β-lactam nucleus, allowing various synthetic manipulations without affecting the integrity of the four-membered ring system. The literature indeed reveals many examples of functional group transformations at reactive sites in the β-lactam side chains, enabling the preparation of diverse β-lactam-based building blocks for organic and medicinal chemistry purposes.

In this work, we focused on the synthesis of functionalized β-lactams bearing a C4 substituent with either an imino group, an oxirane moiety, or a carbon-carbon triple bond as a chemically reactive and responsive fragment, with the intention to deliver a convenient access to building blocks for further elaboration and exploration. In particular, the possibility to transform these β-lactam synthons into novel bi- or polycyclic scaffolds was considered to be a pertinent motivation to pursue this research.

Results and Discussion

The first envisioned building blocks concerned imine-based β-lactam substrates because of our in-house experience with similar systems.[2] In contrast to their celebrated oxygen counterparts (i.e. 4-formyl-β-lactams),[3] 4-imidoyl-β-lactams have received considerably less attention in the literature. Nonetheless, several interesting methods have been developed in which the reactivity of the imino group in 4-imidoyl-β-lactams has been exploited, for example for the preparation of *N*-fused bicyclic β-lactams employing a protocol where the imination of 4-formyl-1-(haloalkyl)azetidin-2-ones and subsequent sodium borohydride-assisted reduction yielded the anticipated bicyclic β-lactams.[3c, 3h] In addition, the stereoselective reaction between a set of similar 4-imidoyl-β-lactams and cyanide-based reagents has been reported to furnish a variety of new compounds including functionalized γ-lactams, succinimide derivatives, and diamino-β-lactam derivatives in optically pure forms.[4]

With the intention to provide building blocks for diverse applications, such as *C*-fused β-lactam synthesis, a number of new 3-alkoxy-4-imidoyl-β-lactams were prepared in this work (**Scheme 1**). To that end, the commercially available D-mannitol diacetonide **1** was transformed into (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **2** via oxidative cleavage using sodium periodate in a CH_2Cl_2/$NaHCO_3$ solution, followed by imination upon treatment with different primary amines to deliver the corresponding imines **3** in high yields. Utilization of these (1,3-dioxolan-4-yl)methanimines **3** for a subsequent Staudinger β-lactam synthesis approach with different alkoxyketenes (derived from the corresponding acid chlorides through the action of Et_3N in CH_2Cl_2) furnished *cis*-4-(1,3-dioxolan-4-yl)azetidin-2-ones **4**. The *cis*-diastereoselectivity could be easily deduced from the ^1H NMR spectra ($CDCl_3$), showing a vicinal coupling constant between the protons of C3 and C4 of the β-lactam between 4.4 and 5.6 Hz, which is in accordance with values reported in the literature.[3f, 5] Cyclic acetals **4** were then hydrolyzed using *p*-toluenesulfonic acid in a THF/H_2O solution to give diols **5** in good yields. Malaprade oxidation of the latter glycols with $NaIO_4$ delivered β-lactam aldehydes **6**, which served as eligible substrates for the preparation of the contemplated new 4-imidoyl-β-lactams **7** in high yields upon treatment with different primary amines (**Scheme 1**).

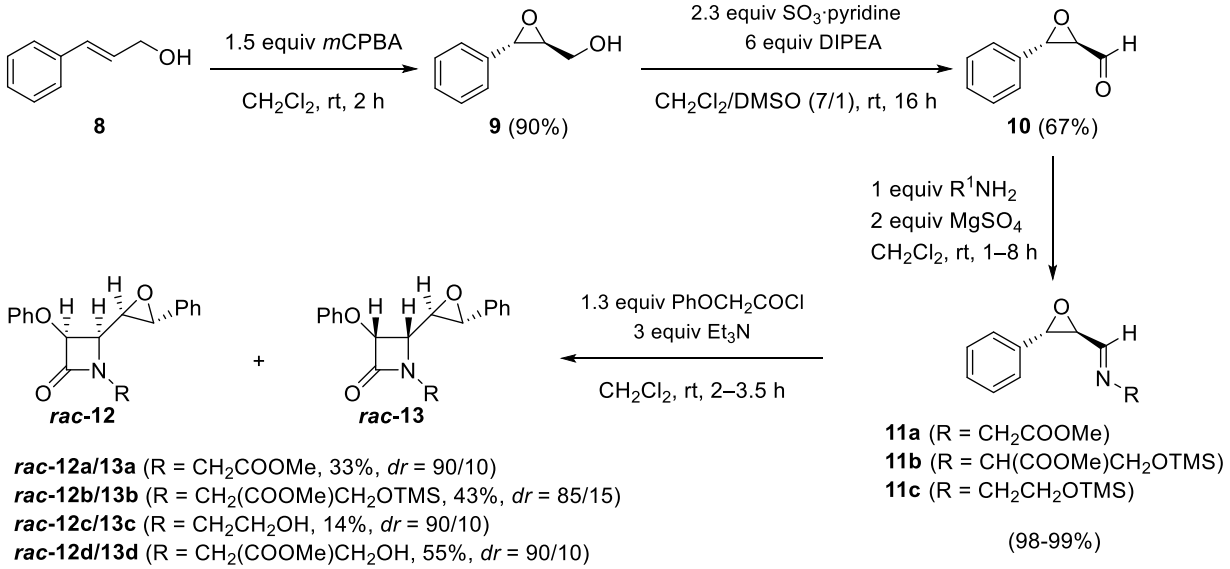


Scheme 1. Stepwise synthesis of 4-imidoyl-β-lactams **7** starting from D-mannitol diacetonide **1**.

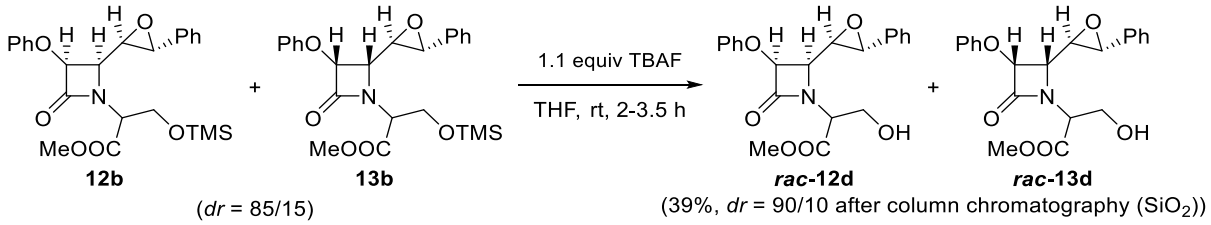
Next, these β-lactam-substituted imines **7** were subjected to strong bases in order to effect deprotonation, followed by quenching with a leaving group-bearing electrophile. The presence of such a leaving group could allow for cyclization in a later stage through reaction with the nucleophilic imine nitrogen atom. In a previous preliminary screening, 4-(3*R*,4*S*)-4-[(benzylimino)methyl]-3-benzyloxy-1-butylazetidin-2-one[6] was treated with one equivalent of different bases, such as NaH, KHMDS, LiHMDS and LDA at -78 °C and quenched with methyl iodide after one hour. ^{1}H NMR analysis ($CDCl_3$) of the crude reaction mixtures showed only the presence of the starting 4-imidoyl-β-lactam. However, when five equivalents of LDA were added, up to 80% C3 deprotonation was observed. Based on the latter result, 4-imidoyl-β-lactam **7a** was treated with five equivalents of LDA and subsequently treated with 1-bromo-2-chloroethane to install the desired leaving group-bearing substituent at the C3 position. Spectroscopic analysis, however, showed a complex reaction mixture, which was also the case when methyl iodide was used as the quenching agent. Therefore, it was decided to evaluate the use of smaller excesses of LDA (1.3–2 equivalents) in combination with different electrophiles (methyl iodide, allyl bromide, D_2O) at different temperatures (-84 °C – reflux temperature, THF). In addition, also the use of the lithium ion-complexating agent hexamethylphosphoramide and the addition of sodium iodide for a Finkelstein reaction in the case of allyl bromide were tested. Although under certain reaction conditions C3 deprotonation and functionalization was observed to some extent, no reproducible results could be obtained, and therefore we shifted the focus of this work toward other types of building blocks.

In the second approach, the introduction of a reactive oxirane moiety in the C4 β-lactam side chain was proposed in order to allow for intramolecular ring-opening reactions. In previous studies, 3-hydroxy-4-(oxiran-2-yl)-β-lactams have been transformed into *C*-fused bicyclic β-lactams through nucleophilic attack of the C3 oxygen atom onto the three-membered oxacycle.[5a] With the intention to provide a route to *N*-fused β-lactam systems, the synthesis of 4-(oxiran-2-yl)-β-lactams bearing an N-substituent in which a carbon or oxygen anionic center could be created through deprotonation, was suggested. *In concreto*, a (methoxycarbonyl)methyl group and an (*O*-silyl-protected) 2-hydroxy-1-(methoxycarbonyl)ethyl group were selected for installation at the β-lactam nitrogen atom (**Scheme 2**).

Their synthesis commenced with a *m*CPBA-mediated Prilezhaev epoxidation of the commercially available cinnamyl alcohol **8**, which was subsequently oxidized to the corresponding aldehyde **10** via a Parikh-Doering oxidation. The introduction of the epoxide was realized prior to Staudinger β-lactam synthesis because previous in-house research studies showed that performing the epoxidation of the aldehyde counterpart before the β-lactam formation is more beneficial in terms of the diastereoselectivity and yield of the desired 4-(oxiran-2-yl)-β-lactams.[5a] Aldehyde **10** was then reacted with glycine methyl ester, methyl *O*-(trimethylsilyl)serinate or 2-[(trimethylsilyl)oxy]ethan-1-amine to render imines **11a-c** in quantitative yields. Staudinger synthesis using imines **11a-c** and phenoxyacetyl chloride resulted in the corresponding *cis*-4-(oxiran-2-yl)-β-lactams **12/13** in high diastereoselectivity (*dr* = 90/10). During purification of β-lactams **12b,c/13b,c** by means of column chromatography (SiO_2), (partial) deprotection of the trimethylsilyl-protected hydroxy groups was observed. Treatment of the diastereomeric mixture of TMS-protected β-lactams **12b/13b** with tetra-*n*-butylammonium fluoride (TBAF) resulted in deprotected β-lactams **12d/13d** in low to moderate yield (**Scheme 3**). The relative stereochemistry of major diastereomers **12** could be deduced based on the vicinal coupling constants between the C3 and C4 protons of the β-lactam core, the protons of C1' and C2' of the oxirane moiety, and the protons of C4 and C1' in ^{1}H NMR ($CDCl_3$), which are in agreement with the values reported in the literature for similar β-lactams (**Figure 1**).[5, 7]



Scheme 2. Synthesis of 4-oxiranyl-β-lactams **12** starting from cinnamyl alcohol **8**.



Scheme 3. Deprotection of TMS-protected 3-hydroxypropanoates **12b/13b**.

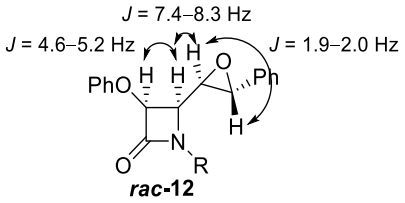
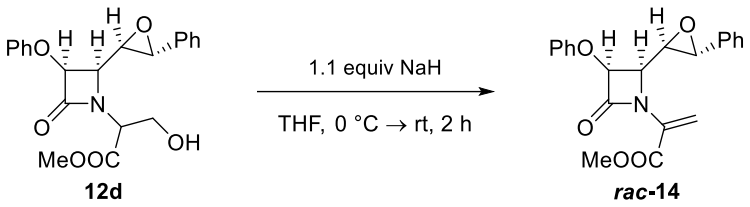


Figure 1. Vicinal coupling constants between the protons at C3 and C4, C4 and C1', and C1' and C2' of *cis*-3-phenoxy-4-(3-phenyloxiran-2-yl)azetidin-2-ones **12** in ^{1}H NMR ($CDCl_3$).

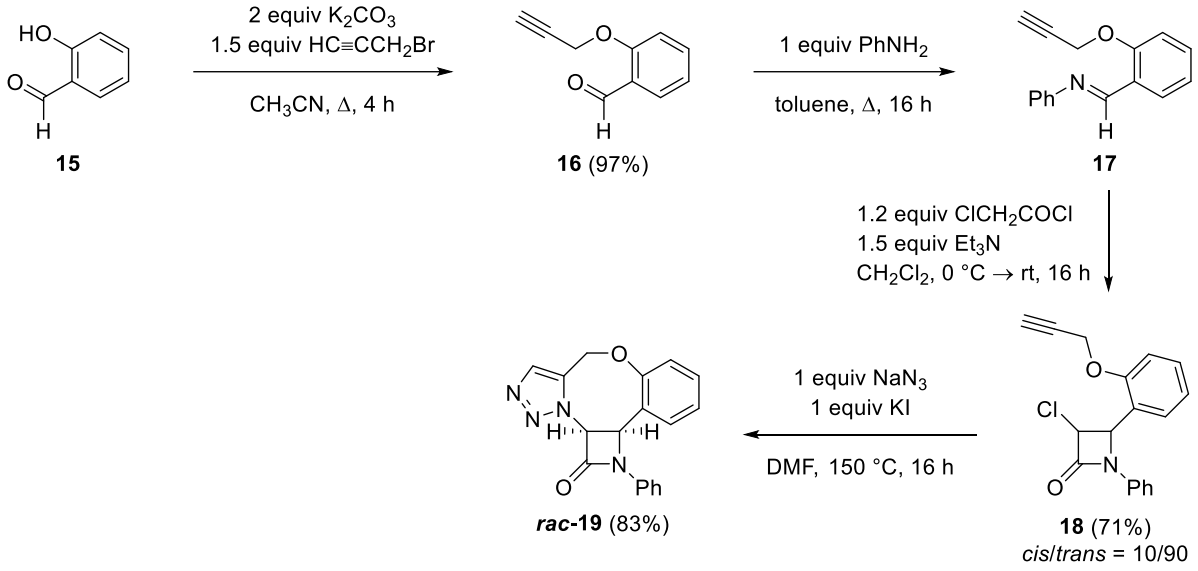
Once in hand, these *cis*-4-(oxiran-2-yl)-β-lactams **12** were treated with strong bases in order to realize α-deprotonation (for methoxycarbonylmethyl-substituted derivative **12a**) or alcohol deprotonation (for 2-hydroxyethyl-substituted derivatives **12c,d**), followed by carbanion- or alkoxide-induced intramolecular epoxide ring opening, respectively. A first cyclisation attempt was made using 4-(methoxycarbonyl)methylazetidin-2-one **12a**. Treatment of the latter compound with different bases (NaH, LiHMDS, KHMDS, LDA) at different temperatures and with the additions of different reagents (HMPA, $BF_3{\cdot}Et_2O$, $MgBr_2$) only resulted in recuperation of the starting compound **12a** or the formation of complex reaction mixtures, with no indication of the desired bicyclic β-lactam system. Therefore, we switched toward methyl propanoate **12d**, as deprotonation of the hydroxy group might generate an alkoxide which could open the epoxide moiety at C4. In that respect, 1.1 equivalents of sodium hydride were added at 0 °C and the reaction mixture was allowed to warm to room temperature, giving rise to acrylate **14** instead of the envisioned bicyclic azetidin-2-one as a result of water elimination (**Scheme 4**). In order to avoid α-carbonyl deprotonation, we evaluated 1-(2-hydroxyethyl)azetidin-2-one **12c** as a substrate for the formation of the corresponding bicyclic β-lactam. In that respect, azetidin-2-one **12c** was treated with 1.05 equivalents of sodium hydride at 0 °C for four hours. LC-MS analysis indicated partial conversion of the starting product to two different end products in a ratio of 14/29/57 (**12c**/product 1/product 2). The first product had a mass twice of that of the starting material **12c**, which was suggestive of an undesired intermolecular reaction that might have occurred leading to the formation of a dimeric system. The second product had a mass equal to that of the starting substrate, which indicated that an intramolecular reaction had occurred. After a thorough analysis of the spectral data, however, it could not be unequivocally demonstrated whether the desired bicyclic β-lactam was formed, or an intramolecular conversion led to the formation of a lactone. Data from the literature seemed more likely to point to the formation of a lactone structure (based on ^{13}C NMR and IR analysis), but further research is required to confirm its structural identity. It is also possible that the reaction might not have been able to proceed optimally,

partly due to the large amount of dimeric product that was formed, and so there is room for further optimization of this unexplored reactivity.



Scheme 4. Formation of acrylate **14** by treatment of propanoate **12d** with sodium hydride.

In the third approach to develop new β-lactam building blocks allowing for subsequent cyclizations, 4-propargyloxyphenyl-substituted β-lactams were proposed, as the presence of a triple bond could allow for functionalization and cyclization utilizing electrophilic additions or cycloaddition reactions (**Scheme 5**). In our work, salicylaldehyde **15** was selected as the starting material to effect *O*-propargylation upon treatment with propargyl bromide in the presence of potassium carbonate to facilitate the formation of the propargylated analog **16** under reflux conditions. This aldehyde **16** was subsequently converted to imine **17** by reacting it with one equivalent of aniline under reflux conditions in toluene. Imine **17** was then used in combination with 2-chloroacetyl chloride in a Staudinger β-lactam synthesis to form a diastereomeric mixture of 3-chloro-4-propargyloxyphenyl-β-lactam **18** (*cis*/*trans* = 10/90), which was then used without purification for further reaction trials. Several attempts were made for the C3-chloro group to be replaced by an azido group upon treatment with sodium azide, which seemed infeasible at lower temperatures using a variety of solvents, and even so at temperatures as high as 150 °C (CAUTION). Eventually, when employing DMF as a solvent at a temperature of 150 °C, complete conversion of 3-chloro-β-lactam **18** was observed. Although the original plan was to isolate the resulting 3-azido-β-lactam after the displacement in order to facilitate the formation of triazole **19** *via* azide-alkyne Click chemistry, spectral analysis of the isolated compound (after purification by column chromatography on silica gel) indicated the *in situ* formation of the desired polycycle **19**.



Scheme 5. Synthesis of 3-chloro-β-lactam **18** and transformation toward tetracyclic β-lactam **19**.

In that respect, analysis of the IR spectra did provide some initial evidence, showing the disappearance of the alkyne absorption at 2118 cm^{-1} and the C-H stretching vibration at 3269 cm^{-1}, which served as a preliminary indication of a chemical transformation of the alkyne moiety. The NMR analysis was also in line with the formation of compound **19**. Nonetheless, polycycle **19** was further crystallized and single crystal X-ray analysis unequivocally established its unprecedented molecular framework (**Figure 2**).

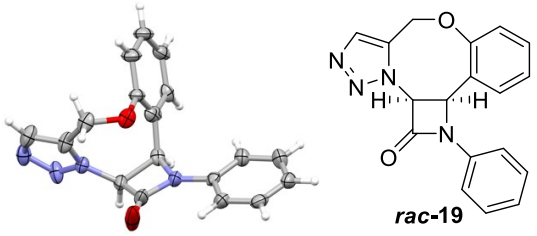


Figure 2. Molecular structure of β-lactam-fused benzotriazolooxazocane scaffold **19**, showing thermal displacement ellipsoids at the 50% probability level.

Conclusion

In summary, the synthesis of new 4-imidoyl-, 4-oxiranyl- and 4-propargyloxyphenyl-substituted β-lactams as versatile building blocks in heterocyclic chemistry was realized, and efforts were made to deploy these compounds for ensuing cyclization reactions *en route* to new bi- or polycyclic scaffolds. Whereas employment of both 4-imidoyl- and 4-oxiranyl-β-lactams did not result in bicyclic structures in this work, synthetic elaboration of a 3-chloro-4-propargyloxyphenyl-β-lactam substrate enabled the preparation of an unexplored β-lactam-fused benzotriazolo-oxazocane framework. The chemical structure of the latter polyheterocycle was unambiguously proven by means of single crystal X-ray

analysis, paving the way for further chemical and biological investigation of this new heterocyclic scaffold in the future.

Experimental Section

General part

^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 400 and 100 MHz, respectively, using a Bruker Avance III-400 spectrophotometer, equipped with ^{1}H/BB z-gradient probe (BBO, 5 mm). The samples were dissolved in deuterated solvents (with tetramethylsilane as internal standard). All spectra were processed using TOPSPIN 3.2 and acquired through the standard sequences available in the Bruker pulse program library. ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and referenced to the residual solvent peak ($CDCl_3$ δ_H = 7.26, δ_C = 77.16). Coupling constants (*J*) are reported in hertz (Hz). Peaks were assigned with the aid of 2D spectra (COSY, HSQC, HMBC). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory on a PerkinElmer Spectrum BX FT-IR or Shimadzu IRAffinity-1S WL FT-IR spectrophotometer. Only selected absorbances (ν_{max}, cm^{-1}) are reported. Optical rotations were defined using a Jasco P-2000 polarimeter, using methanol as a solvent and blank measurement. HPLC and HPLC-MS analyses were performed on an Agilent 1200 series HPLC system fitted with a Supelco Ascentis® Express C18 column (I.D. x L 4.6 mm x 30 mm, particle size 2.7 µm) and connected to a UV-VIS detector and an Agilent 1100 series LC/MSD-type SL mass spectrometer (ESI, 4000 V) using a mass-selective single-quadrupole detector. A mixture of acetonitrile/water (5 mM NH_4OAc) was used as the eluent. Automated preparative HPLC separations were executed with an Agilent 1100 Series apparatus with a UV detector, using a Zorbax® Eclipse XDB-C18 column (I.D. x L 21.2 mm x 150 mm), characterized by a 5 µm particle size. The eluent mixtures consisted of water and acetonitrile. Melting points were measured using a Kofler heating bench system of Wagner & Munz (type WME, accuracy ± 1 °C).

Synthesis of 4-(*tert*-butylimino)methyl-1-(4-methoxyphenyl)azetidin-2-one 7b,c

As a representative example, the synthesis of β-lactam **7b** is described. To a solution of 156 mg (0.5 mmol) (3*R*,4*S*)-3-benzyloxy-4-formyl-1-(4-methoxyphenyl)azetidin-2-one **6a** in 10 mL dichloromethane, 129 mg (1 mmol; 2 eq.) magnesium sulphate, as drying agent, and 53 µL (0.5 mmol; 1 eq.) *tert*-butylamine were added. After stirring for one hour at room temperature, filtration of the drying agent and removal of the solvent *in vacuo*, 139 mg (76%) (3*R*,4*S*)-3-benzyloxy-4-(*tert*-butylimino)methyl-1-(4-methoxyphenyl)azetidin-2-one **7b** was obtained with no need for purification.

Synthesis of 3-phenoxy-4-(3-phenyloxiran-2-yl)azetidin-2-ones 12

The synthesis of methyl 2-[(3*S**,4*R**)-2-oxo-3-phenoxy-4-((2*R**,3*R**)-3-phenyloxiran-2-yl)azetidin-1-yl]acetate **12a** is described as a representative example. In a 100 mL flask 1.10 g (5 mmol) of methyl 2-{[(*E*)-((2*R**,3*R**)-3-phenyloxiran-2-yl)methylene]amino}acetate **11a** was dissolved in 20 mL of dry dichloromethane, followed by the addition of 2.09 mL (15 mmol; 3 eq.) triethylamine. The reaction mixture was cooled to 0 °C using an ice bath, after which 1.11 g (6.5 mmol; 1.3 eq.) phenoxyacetyl chloride, dissolved in 10 mL of dry dichloromethane, was added dropwise. The reaction mixture was stirred for three hours at room temperature, after which it was diluted with 12 mL of

dichloromethane. Then the reaction mixture was washed with 15 mL of saturated $NaHCO_3$ solution, followed by 15 mL of brine. The aqueous phase was extracted three more times with 10 mL dichloromethane and the combined organic phase was dried over $MgSO_4$. After filtering the drying agent, evaporation of the solvent and purification by column chromatography (SiO_2) eluting with petroleum ether/ethyl acetate (3/1), 0.58 g (33%) 2-[2-oxo-3-phenoxy-4-(3-phenyloxiran-2-yl)azetidin-1-yl]acetate **12a**/**13a** was obtained with a diastereomeric ratio of 90/10.

In the synthesis of 3-phenoxy-4-(3-phenyloxiran-2-yl)azetidin-2-ones **12b,c** the deprotection of the TMS-protected hydroxy group took place during column chromatography. However, only partial deprotection was observed in the case of propanoate **12b**, and an additional deprotection step was needed. To that end, 456 mg of propanoate **12b** (1 mmol) was dissolved in 10 mL dry tetrahydrofuran in a flame-dried 25 mL flask under an argon atmosphere, followed by cooling the reaction mixture to 0 °C using an ice bath. Subsequently, 1.1 mL (1.1 mmol; 1.1 eq.) TBAF solution (1.0 M in tetrahydrofuran) was slowly added dropwise. After stirring at room temperature for two hours, the reaction mixture was diluted with 20 mL dichloromethane and quenched with 10 mL of water. Then it was washed with 20 mL brine and the aqueous phase was extracted three times with 20 mL of dichloromethane. The combined organic phase was dried over $MgSO_4$. After filtration of the drying agent, removal of the solvent *in vacuo* and purification by means of column chromatography (SiO_2) using petroleum ether/ethyl acetate (3/1) as the eluent, 150 mg (39%) of methyl 3-hydroxy-2-[3-phenoxy-4-(3-phenyloxiran-2-yl)-2-oxoazetidin-1-yl]propanoate **12d**/**13d** was obtained in a diastereomeric ratio of 90/10.

Synthesis of methyl 2-[(3*S,4*R**)-2-oxo-3-phenoxy-4-((2*R**,3*R**)-3-phenyloxiran-2-yl)azetidin-1-yl]acrylate (14)**

In a 100 mL flame-dried flask, 383 mg (1 mmol) of β-lactam **12d** was dissolved in 40 mL dry tetrahydrofuran, and 26 mg (1.1 mmol; 1.1 eq.) of sodium hydride was added to the ice cooled mixture (0 °C). After stirring the reaction mixture for one hour and an additional hour at room temperature, complete conversion of the starting material **12** was observed based on LC-MS analysis. The reaction mixture was washed with 20 mL of brine and the aqueous phase was extracted with 20 mL ethyl acetate (3 x). After filtering off the drying agent, removal of the solvent *in* vacuo and purification by preparative HPLC, 7.3 mg (2%) methyl 2-[(3*S**,4*R**)-2-oxo-3-phenoxy-4-((2*R**,3*R**)-3-phenyloxiran-2-yl)azetidin-1-yl]acrylate **14** was obtained.

Synthesis of 1-phenyl-2a,12b-dihydro-7*H*-azeto[3,2-*e*]benzo[*g*][1,2,3]triazolo[5,1-*c*][1,4]oxazocin-2(1*H*)-one (19)

187 mg (0.6 mmol) of 3-chloro-β-lactam **18** (*cis*/*trans* = 10/90) was treated with 39 mg (0.6 mmol; 1 eq.) sodium azide and 100 mg (0.6 mmol; 1 eq.) potassium iodide at 150 °C using DMF as the solvent. After stirring overnight, the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and washed with water. Drying of the organic phase with $MgSO_4$, followed by filtration of the drying agent and removal of the solvent *in vacuo* resulted in crude polycycle **19**. Pure 1-phenyl-2a,12b-dihydro-7*H*-azeto[3,2-*e*]benzo[*g*][1,2,3]triazolo[5,1-*c*][1,4]oxazocin-2(1*H*)-one **19** was obtained after purification by column chromatography (SiO_2) in a yield of 83%.

Acknowledgements

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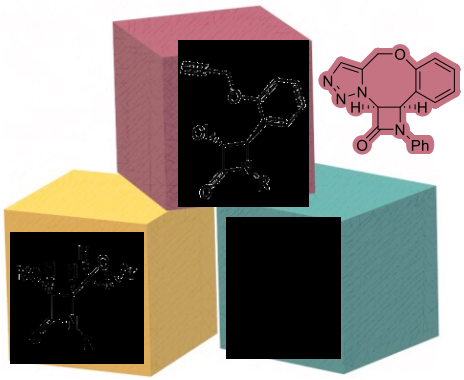

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[6] Compound from previous, unpublished work. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J* = 7.3 Hz); 1.29 (2H, ~sextet, *J* = 7.4 Hz); 1.42–1.50 (2H, m); 3.18 (1H, d x t, *J* = 14.1, 7.1 Hz); 3.31 (1H, d x t, *J* = 14.1, 7.5 Hz); 4.26 (1H, d x d, *J* = 6.8, 4.7 Hz); 4.58 (1H, d, J_{AB} = 11.7 Hz); 4.63 (1H, d, J_{AB} = 13.9 Hz); 4.67 (1H, d, J_{AB} = 13.9 Hz); 4.70 (1H, d, J_{AB} = 11.7 Hz); 4.82 (1H, d, *J* = 4.7 Hz); 7.23–7.34 (10H, m); 7.77 (1H, br d, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3); 20.1 (CH_2); 29.8 (CH_2); 41.0 (CH_2); 61.1 (CH); 65.2 (CH_2); 73.0 (CH_2); 83.0 (CH); 127.3 (CH); 128.0 (CH); 128.1 (CH); 128.5 (CH); 128.7 (CH); 136.5 (C_q); 138.0 (C_q); 162.4 (HC=N)); 166.9 (C=O).

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