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Diastereoselective synthesis of 3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones and their transformation into 3,4-oxolane-fused bicyclic β-lactams†

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cis-3-Acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones were prepared through a Staudinger [2+2]-cyclocondensation between acetoxyketene and the appropriate epoxyimines in a highly diastereoselective way. Subsequent potassium carbonate-mediated acetate hydrolysis, followed by intramolecular ring closure through epoxide ring opening, afforded stereodefined 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones as a novel class of C-fused bicyclic β-lactams. Selective benzylic oxidation of bicyclic *N*-(4-methoxybenzyl)-β-lactams with potassium persulfate and potassium dihydrogen phosphate provided the corresponding *N*-aroyl derivatives as interesting leads for further β-lactamase inhibitor development.

Introduction

In 1945, Alexander Fleming was awarded the Nobel Prize "for the discovery of penicillin and its curative effect in various infectious diseases", together with E. Chain and H. Florey.[1] Penicillin became available for use among the allied soldiers during World War II, considerably reducing the overall number of amputations and deaths, and ever since, β-lactam antibiotics have found widespread application in the treatment of infectious pathogens.[2] To date, this extraordinary class of strained compounds still comprises the most extensively used antibacterial agents and is considered to be a cornerstone of human health care.[3] However, the increasing bacterial resistance against classical β-lactam-based pharmaceuticals is truly alarming and imposes a continued search for novel types of β-lactam antibiotics and β-lactamase inhibitors.[4] In particular, the development of innovative new chemical entities is of paramount importance in medicinal chemistry in order to effectively address and eliminate microbial resistance.

Also from a synthetic point of view, the importance of β-lactams as versatile building blocks in organic chemistry has been universally recognized. Next to the generation of a wide variety of biologically interesting nitrogen-containing acyclic and heterocyclic target compounds by selective bond-cleavage and ring-rearrangement protocols,[5] the azetidin-2-one skeleton has been widely used as a template to construct cyclic attachments fused to the four-membered ring system using the β-lactam functionalizations as (stereo)directing elements.[5a,b,e–g,j,k] Among them, C-fused bicyclic β-lactams, in which the second ring is attached to the azetidin-2-one nucleus at the 3,4-position, have received considerably less attention as compared to their celebrated N-fused analogues,[5b,e–g,j,k] rendering their construction and further elaboration an interesting challenge and opportunity. A suitable strategy to access this class of heterocycles relates to the intramolecular displacement of a leaving group present in the β-lactam C4 side chain by a nucleophile attached to the C3 position. By applying this methodology, we have previously demonstrated the applicability of *cis*-3-benzyloxy-4-(2-bromo/mesyloxyethyl)-β-lactams for the efficient synthesis of 2-oxa-6-azabicyclo[3.2.0]heptan-7-one systems.[6] In continuation of our interest in the use of functionalized β-lactams as building blocks in heterocyclic chemistry,[5g,k] the present research is focused on the diastereoselective formation of *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)-β-lactams as eligible intermediates for the preparation of novel and polyvalent 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-one scaffolds.

4-Oxiranyl-substituted azetidin-2-ones have already been proven to be convenient precursors in the synthesis of bi- and tricyclic β-lactams, for example through reductive ring opening

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of the strained epoxide unit with titanocene(III) monochloride (Cp_2TiCl) and subsequent radical intramolecular cyclization.[7] However, as the reactivity of 4-oxiranylazetidin-2-ones reported in the literature is exclusively focused on the synthesis of traditional 1,4-fused (N-fused) polycyclic β-lactams,[7,8] this work comprises the first report on the deployment of 4-oxiranylazetidin-2-ones for the preparation of synthetically relevant 3,4-fused (C-fused) bicyclic β-lactams. Because of the pivotal position of C-fused bicyclic β-lactams in the search for alternative bioactive agents against class C β-lactamases,[3c,9] the premised 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones could also be considered as new anchor points in antibacterial drug design and discovery.

Results and discussion

In a first stage, the diastereoselective synthesis of *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4** was envisaged. The majority of literature procedures concerning the preparation of this type of substrates relies on an epoxidation step of the corresponding 4-alkenyl-β-lactams. In most cases, 3-chloroperbenzoic acid (*m*CPBA) is used as the oxidizing agent,[7a–d,f,g,8b,10] although also methods with hydrogen peroxide and sodium hydroxide (H_2O_2–NaOH)[8a] or magnesium monoperoxyphthalate (MMPP)[11] have been reported.

In that respect, imination of (*E*)-cinnamaldehyde **1** with isopropylamine was performed, followed by reaction of the resulting imine **2** with acetoxyacetyl chloride in the presence of Et_3N to give *cis*-3-acetoxy-1-isopropyl-4-(2-phenylethenyl)azetidin-2-one **3** in 48% yield after purification by column chromatography on silica gel (Scheme 1). The observed *cis*-diastereoselectivity in β-lactam **3** was assigned *via* the ^{1}H NMR spectrum, as the vicinal coupling constant of 4.7 Hz ($CDCl_3$) between the H3 and H4 proton is in accordance with values reported in the literature for *cis*-β-lactams.[7a–d,f,11,12] Subsequently, epoxidation of the double bond in the latter 4-alkenylazetidin-2-one **3** using 1.5 equiv. of *m*CPBA in dichloromethane afforded a 1/1 diastereomeric mixture of *cis*-3-acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-ones **4a** and **5a** after 90 hours at room temperature, which was purified in 83% yield by column chromatography on silica gel (Scheme 1). The relative stereochemistry of the two isomeric epoxides **4a** and **5a** could be easily deduced based on the vicinal coupling constants between the protons at C3 and C4 (of the β-lactam core), C1′ and C2′ (of the epoxide moiety), and C4 and C1′ in ^{1}H NMR ($CDCl_3$) (Fig. 1), which are in agreement with values reported in the literature for similar azetidin-2-ones.[7a,c,d] It should be noted that separation of the two isomers **4a** and **5a** by column chromatography on silica gel proved to be impossible; nonetheless, isolation of pure *cis*-3-acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-one **5a** was achieved by recrystallization from hexane/EtOAc (1/30), albeit in a very low yield (1%), to allow unequivocal assignment of its chemical structure.

Because of the lack of diastereoselectivity and the cumbersome separation procedure associated with the latter method, an alternative approach for the preparation of *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4**/**5** was pursued. Next to the epoxidation of 4-alkenylazetidin-2-ones, two other methodologies for the synthesis of 4-oxiranylazetidin-2-ones are available in the literature, relying on either a ketene-imine cycloaddition[13] or an ester enolate–imine condensation of epoxyimines.[14]

To that end, (*E*)-*N*-[*trans*-(3-aryloxiran-2-yl)methylidene] amines **9** were prepared in 51–68% overall yield from

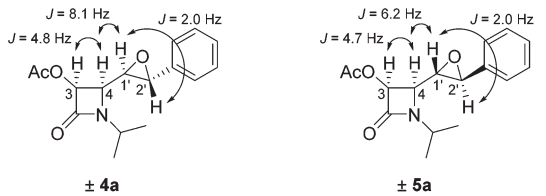
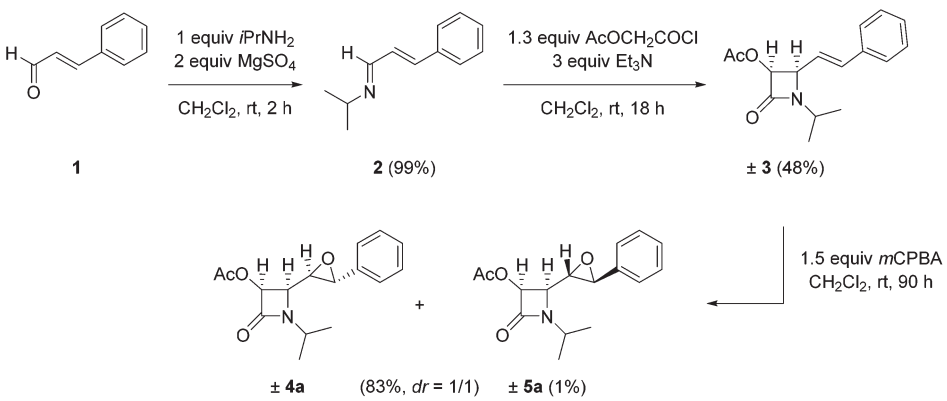


Fig. 1 Vicinal coupling constants between the protons at C3 and C4, C4 and C1′, and C1′ and C2′ of *cis*-3-acetoxy-4-(3-phenyloxiran-2-yl) azetidin-2-ones **4a** and **5a** in ^{1}H NMR ($CDCl_3$).



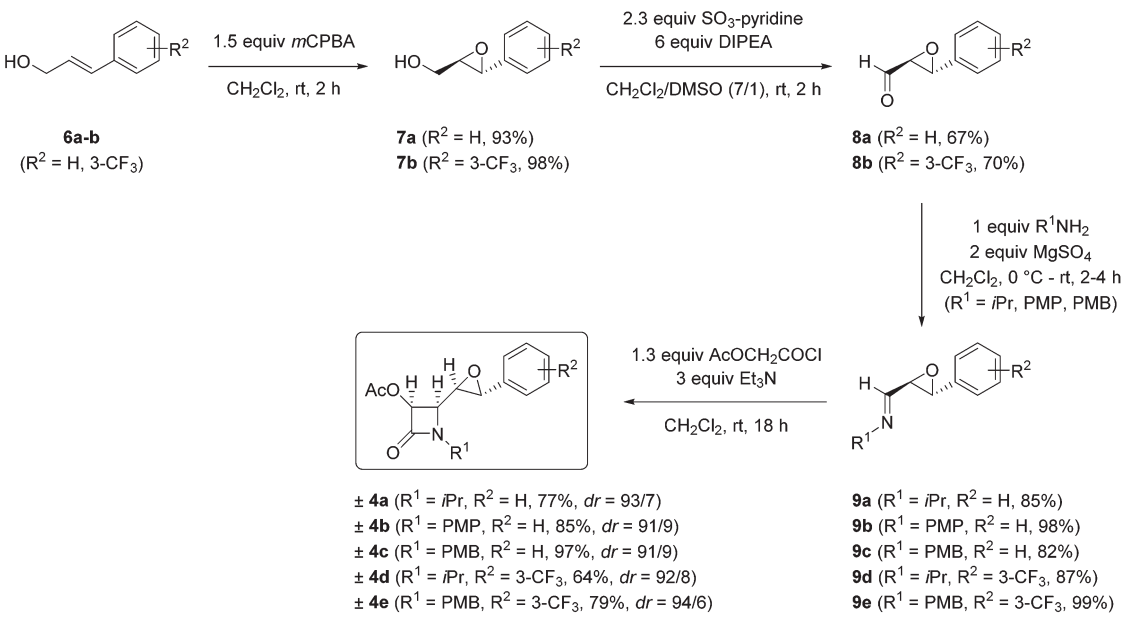
Scheme 1 Synthesis of *cis*-3-acetoxy-4-(3-phenyloxiran-2-yl)azetidin-2-ones **4a** and **5a** *via* epoxidation of *cis*-3-acetoxy-4-(2-phenylethenyl)azetidin-2-one **3**.

(*E*)-3-arylprop-2-en-1-ols **6** in three successive steps, including (i) epoxidation with *m*CPBA in CH_2Cl_2, (ii) oxidation with SO_3-pyridine in CH_2Cl_2/DMSO (7/1) in the presence of Hünig's base and (iii) imination in CH_2Cl_2 under standard conditions (Scheme 2). Subsequently, epoxyimines **9** were used as substrates for a Staudinger β-lactam synthesis upon treatment with 1.3 equiv. of acetoxyacetyl chloride in CH_2Cl_2 in the presence of Et_3N, affording the corresponding racemic *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4** in high diastereomeric excess (dr = 91–94/6–9, determined by ^1H NMR in $CDCl_3$) and in 64–97% yield after purification by recrystallization from hexane/EtOAc (1/30) or column chromatography on silica gel. The excellent diastereoselectivity of this reaction could be rationalized by the imposed steric hindrance originating from the aryloxirane moiety during the Staudinger synthesis. The coupling constants between the protons at C4 and C1′ of the major isomers proved to be 7.8–8.2 Hz ($CDCl_3$), enabling its stereochemical assignment (Scheme 2).[7a] Structural diversity was introduced in these 4-epoxy-β-lactams **4** through variation of the *N*-β-lactam group (R^1 = iPr, PMP, PMB) and the aryloxirane substituent (R^2 = H, 3-CF_3).

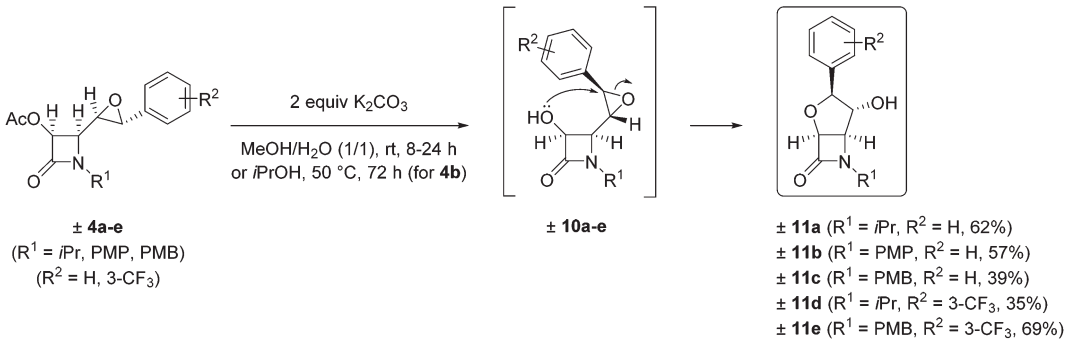
With *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4** in hand, the reactivity of these new building blocks toward the preparation of synthetically and biologically interesting 3,4-fused bicyclic β-lactams was investigated. The synthetic strategy proposed for this transformation consisted of deprotection of the alcohol moiety in 3-acetoxyazetidin-2-ones **4** through ester hydrolysis, followed by hydroxyl group-induced intramolecular ring closure by epoxide ring opening at the benzylic position, whether or not with the help of an additional Lewis acid to activate the oxirane ring.

To that end, *cis*-3-acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl) azetidin-2-one **4a** was used as a model substrate for *O*-deacetylation using a slightly modified literature procedure,[15] involving treatment with two equiv. of potassium carbonate in MeOH/H_2O (1/1) at room temperature. Interestingly, next to the expected *cis*-3-hydroxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-one **10a**, a small amount of 4-hydroxy-6-isopropyl-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11a** was observed in the reaction mixture after stirring for one hour without the use of a base or epoxide activator (**10a**/**11a** = 86/14). Additional stirring for seven more hours proved to be sufficient to drive the reaction to completion, giving rise to 4-hydroxy-6-isopropyl-3-phenyl-2-oxa-6-azabicyclo [3.2.0]heptan-7-one **11a**, which was eventually obtained in 62% yield and analytically pure form after additional purification by preparative HPLC. Subsequently, also *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4b–e** were smoothly converted into *rac*-3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **11b–e** as single diastereomers using similar reaction conditions (except for derivative **4b**, where iPrOH was used) in 35–69% yield and excellent purity after purification by preparative HPLC, recrystallization or column chromatography on silica gel (Scheme 3). It should be noted that complete conversion was obtained for all derivatives, leading to 'crude' isolated yields of 70–91%. The reported yields in Scheme 3 are those obtained after additional purification, which was performed to obtain analytically pure samples for structure characterization and biological evaluation purposes.

To examine the influence of the relative stereochemistry of *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4a** and **5a** on the kinetics of the above-described transformation, a 1/1 diastereomeric mixture of β-lactams **4a** and **5a** was dissolved in



Scheme 2 Diastereoselective synthesis of *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4** *via* Staudinger [2+2]-cyclocondensation between *in situ* prepared acetoxyketene and (*E*)-*N*-[*trans*-(3-aryloxiran-2-yl)methylidene]amines **9**.



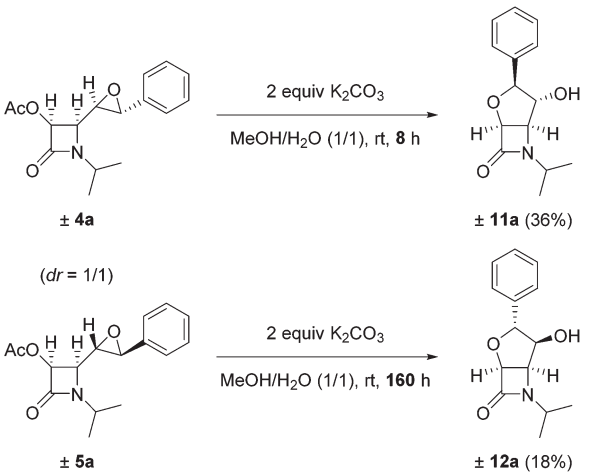
Scheme 3 Synthesis of 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **11**.

MeOH/H_2O (1/1) and treated with two equiv. of potassium carbonate. As expected, β-lactam **4a** was completely converted into 2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11a** after eight hours stirring at room temperature (according to LC-MS analysis). In contrast, β-lactam **5a** needed 20 times more time (160 h) to be rearranged into 2-oxa-6-azabicyclo[3.2.0]heptan-7-one **12a**, which is probably due to the steric hindrance exerted by the phenyl group during intramolecular epoxide ring opening (Scheme 4). Both isomers **11a** and **12a** were separated by preparative HPLC in 36% and 18% yield, respectively, to allow assessment of their structure and bioactivity.

Assuming a clean S_N2-type epoxide ring opening, the proposed relative stereochemistry of 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **11** and **12** is a direct result of the relative stereochemistry secured in the starting *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones **4a** and **5a**, which was deduced based on the vicinal coupling constants between the protons at C3 and C4 (of the β-lactam core), C1′ and C2′ (of the epoxide moiety), and C4 and C1′ in ^{1}H NMR ($CDCl_3$) (see above). Nonetheless, irrefutable proof for these relative configurations was eventually established by single crystal X-ray analysis of (1*S**,3*S**,4*R**,5*R**)-4-hydroxy-6-(4-methoxyphenyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11b** and (1*R**,3*S**,4*R**,5*S**)-4-hydroxy-6-isopropyl-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **12a** (Fig. 2).

In an initial attempt to debenzylate 3-aryl-4-hydroxy-6-(4-methoxybenzyl)-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **11c,e** by means of 3.4 equiv. of potassium persulfate in the presence of 6.8 equiv. of potassium dihydrogen phosphate in CH_3CN/H_2O (2/1) at reflux temperature,[16] the unprecedented selective oxidation of the benzylic position was observed, affording 3-aryl-4-hydroxy-6-(4-methoxybenzoyl)-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **13** in 46–69% yield after purification by preparative HPLC or column chromatography on silica gel (Scheme 5). Notably, benzylic oxidation of *N*-benzylated β-lactams, which is mentioned only sporadically in the literature using various methods and reagents,[17] provides a means to selectively transform the electron-donating 4-methoxybenzyl group on the β-lactam nitrogen atom in azetidin-2-ones **11c,e** into an electron-withdrawing functional group, which is considered to be beneficial in the framework of antibacterial activity studies.

Besides the synthetic novelty and relevance of the intramolecular epoxide ring opening as a valuable alternative toward the stereoselective preparation of C-fused bicyclic β-lactams, the new 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones can also be considered as useful building blocks for *e.g.* the synthesis of functional oxolane β-amino acids *via* amide bond hydrolysis.[6,18] Indeed, the tetrahydrofuran unit represents an important structural motif present in bioactive natural and synthetic molecules,[19] which explains the interest in efficient strategies for its construction. As mentioned in the introduction, tetrahydrofuran-based azetidin-2-ones can also be of interest as templates in the search for new β-lactamase inhibitors. Specifically, bridged monobactams (*i.e.*, C-fused bicyclic β-lactams) are considered to be potent, mechanism-based inhibitors of class C β-lactamases, which are able to stabilize the acyl-enzyme intermediate by blocking access of water to the enzyme-inhibitor ester bond.[9a] In spite of the fact that there are a few methods available in the literature for the synthesis of the 2-oxa-6-azabicyclo[3.2.0]heptan-7-one skeleton,[6,20] no details on their bioactivity are known. On the other hand, MK-8712, an aza-analogue of 2-oxa-6-azabicyclo[3.2.0]heptan-7-ones, has recently been found to overcome



Scheme 4 Comparison of the required reaction times for the synthesis of (1*S**,3*S**,4*R**,5*R**)-3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11a** and (1*R**,3*S**,4*R**,5*S**)-3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **12a**.

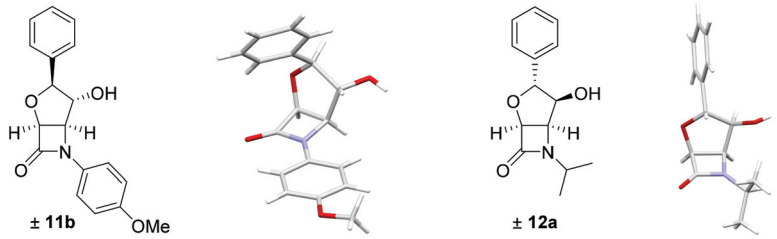
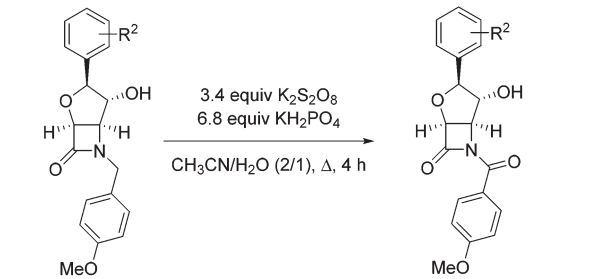


Fig. 2 Molecular structure of (1*S**,3*S**,4*R**,5*R**)-4-hydroxy-6-(4-methoxyphenyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11b** and (1*R**,3*S**,4*R**,5*S**)-4-hydroxy-6-isopropyl-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **12a**.



± 11c,e (R^1 = **PMB**) (R^2 = H, 3-CF_3)

± 13a (R^2 = H, 46%)
± 13b (R^2 = 3-CF_3, 69%)

Scheme 5 Synthesis of 3-aryl-4-hydroxy-6-(4-methoxybenzoyl)-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **13**.

class C β-lactamase-mediated resistance and has been selected for preclinical development.[21]

In order to provide some preliminary data on their β-lactamase inhibitory potential, 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **11a–e**, **12a** and **13a–b** were incubated with β-lactamase from *Enterobacter cloacae*, after which the residual enzymatic activity was measured by following the rate of nitrocefin hydrolysis, which is an excellent substrate for class C enzymes.[22] Although none of the tested compounds showed a better activity than the reference compound tazobactam, an interesting profile was observed for 3-aryl-4-hydroxy-6-(4-methoxybenzoyl)-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **13a–b** (residual activities of 58.7 ± 12.4% and 44.3 ± 13.8%, respectively, after incubation with 500 μM; 16.2 ± 10.6% residual activity for tazobactam), revealing opportunities for further β-lactamase inhibitor development (Table 1). These results point to a pronounced effect of the β-lactam *N*-substituent, supporting the literature consensus on the necessity of an electron-withdrawing group at nitrogen.[23] It is evident that additional optimization studies are required in the future to further unravel the β-lactamase inhibitory potential of this new class of oxazabicyclic scaffolds.

Table 1 Residual enzymatic activities after incubation of 500 μM 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **11a–e**, **12a** and **13a–b** with β-lactamase from *Enterobacter cloacae*

Compd	R^1	R^2	Residual activity[a] (%)
11a	iPr	H	99.3 ± 5.8
11b	PMP	H	108.8 ± 11.3
11c	PMB	H	95.1 ± 12.9
11d	iPr	3-CF_3	113.7 ± 17.7
11e	PMB	3-CF_3	87.1 ± 14.6
12a	iPr	H	96.6 ± 13.3
13a	*p*-Anisoyl	H	58.7 ± 12.4
13b	*p*-Anisoyl	3-CF_3	44.3 ± 13.8

[a] Reference compound = tazobactam (16.2 ± 10.6% residual activity).

Conclusions

In summary, two methodologies for the preparation of 4-oxiranyl-β-lactams were investigated, in which the Staudinger [2+2]-cyclocondensation between acetoxyketene and the appropriate epoxyimines delivered the desired *cis*-3-acetoxy-4-(3-aryloxiran-2-yl)azetidin-2-ones in a highly diastereoselective way. These β-lactams were subsequently used as eligible substrates for the synthesis of the novel class of 3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones employing an 'intramolecular ring closure through epoxide ring opening' strategy. This protocol afforded versatile building blocks for further elaboration and offers a valuable alternative for the preparation of 3,4-fused bicyclic β-lactams, which have received much less attention as compared to their celebrated 1,4-fused analogues. Finally, a selective benzylic oxidation of *N*-(4-methoxybenzyl)-β-lactams was realized, which provided 3-aryl-4-hydroxy-6-(4-methoxybenzoyl)-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones with potential β-lactamase inhibitory activity, revealing opportunities for further medicinal chemistry studies toward the development of novel antibacterial agents.

Experimental

General methods

Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification. Melting points were measured using a Kofler bench, type WME Heizbank of Wagner & Munz. ^{1}H NMR spectra were recorded at 400 MHz (Bruker Avance III-400) in deuterated solvents with TMS as internal standard. ^{19}F NMR spectra were recorded at 376 MHz (Bruker Avance III-400). ^{13}C NMR spectra were recorded at 100 MHz (Bruker Avance

III-400). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory with a Perkin-Elmer Spectrum BX FT-IR spectrophotometer. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series Time of Flight.

Synthesis of *cis*-3-acetoxy-1-isopropyl-4-(2-phenylethenyl) azetidin-2-one 3

To an ice-cooled solution of (*E*)-*N*-(3-phenylprop-2-en-1-ylidene)isopropylamine **2** (4.33 g, 25 mmol, 1 equiv.) and triethylamine (7.59 g, 75 mmol, 3 equiv.) in anhydrous CH_2Cl_2 (50 mL), acetoxyacetyl chloride (4.44 g, 33 mmol, 1.3 equiv.) in anhydrous CH_2Cl_2 (10 mL) was added dropwise. After stirring for 18 hours at room temperature, CH_2Cl_2 (30 mL) was added and the resulting mixture was washed with a saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL). Drying of the organic phase with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude *cis*-3-acetoxy-1-isopropyl-4-(2-phenylethenyl)azetidin-2-one **3**, which was purified in 48% (3.28 g) yield by column chromatography on silica gel (hexane/EtOAc 3/1).

cis-3-Acetoxy-1-isopropyl-4-(2-phenylethenyl)azetidin-2-one 3

Yellow oil. R_f = 0.14 (hexane/EtOAc 3/1). Yield 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, d, J = 6.7 Hz), 1.29 (3H, d, J = 6.7 Hz), 2.05 (3H, s), 3.90 (1H, septet, J = 6.7 Hz), 4.52 (1H, d × d, J = 8.8, 4.7 Hz), 5.73 (1H, d, J = 4.7 Hz), 6.09 (1H, d × d, J = 16.0, 8.8 Hz), 6.69 (1H, d, J = 16.0 Hz), 7.28–7.39 (5H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.1, 20.4, 21.7, 44.8, 59.1, 76.1, 123.5, 126.6, 128.5, 128.8, 135.8, 136.3, 163.9, 169.4. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1742, 1711; ν_{max} = 1372, 1222, 1105, 1043, 1021, 975, 931, 751, 693. MS (70 eV): *m*/*z* (%) 274 (M^+ + 1, 13). HRMS (ESI) Calcd for $C_{16}H_{20}NO_3^+$ 274.1438 $[M + H]^+$, found 274.1439.

Synthesis of (3*S**,4*R**,2′*S**,3′*S**)-3-acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-one 5a

To an ice-cooled solution of *cis*-3-acetoxy-1-isopropyl-4-(2-phenylethenyl)azetidin-2-one **3** (3.11 g, 12 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (40 mL), 3-chloroperbenzoic acid (3.55 g, 18 mmol, 1.5 equiv.) was added in small portions. The resulting mixture was stirred for 90 hours at room temperature, after which a saturated aqueous Na_2SO_3 solution (40 mL) was added. After additionally stirring for 15 minutes at room temperature, the reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). Drying of the organic phase with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded an equimolar mixture of (3*S**,4*R**,2′*R**,3′*R**)-3-acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-one **4a** and (3*S**,4*R**,2′*S**,3′*S**)-3-acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-one **5a**, which was purified in 83% (2.88 g) yield by column chromatography on silica gel (hexane/EtOAc 3/1). Separation of the two isomers **4a** and **5a** by column chromatography on silica gel proved to be impossible, however, isolation of (3*S**,4*R**,2′*S**,3′*S**)-3-acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-one **5a** could be achieved in 1% (35 mg) yield by recrystallization from hexane/EtOAc (1/30).

(3*S**,4*R**,2′*S**,3′*S**)-3-Acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl) azetidin-2-one 5a

White crystals. Recrystallization from hexane/EtOAc (1/30). Mp 110 °C. Yield 1%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, d, J = 6.7 Hz), 1.30 (3H, d, J = 6.7 Hz), 2.05 (3H, s), 3.05 (1H, d × d, J = 6.2, 2.0 Hz), 3.83 (1H, d, J = 2.0 Hz), 3.91 (1H, septet, J = 6.7 Hz), 3.92 (1H, d × d, J = 6.2, 4.7 Hz), 5.78 (1H, d, J = 4.7 Hz), 7.27–7.29 (2H, m), 7.34–7.39 (3H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.0, 20.3, 21.5, 44.9, 56.2, 56.8, 59.6, 74.4, 125.4, 128.7, 135.6, 164.0, 169.6. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1759, 1744; ν_{max} = 1401, 1212, 1116, 1020, 892, 759, 703. MS (70 eV): *m*/*z* (%) 290 (M^+ + 1, 27). HRMS (ESI) Calcd for $C_{16}H_{20}NO_4^+$ 290.1387 $[M + H]^+$, found 290.1385.

Synthesis of (*E*)-*N*-[*trans*-(3-aryloxiran-2-yl)methylidene]amines 9

As a representative example, the synthesis of (*E*)-*N*-[*trans*-(3-phenyloxiran-2-yl)methylidene]isopropylamine **9a** is described. To a solution of *trans*-(3-phenyloxiran-2-yl)formaldehyde **8a** [24] (1.48 g, 10 mmol, 1 equiv.) and $MgSO_4$ (2.41 g, 20 mmol, 2 equiv.) in anhydrous CH_2Cl_2 (20 mL), isopropylamine (0.59 g, 10 mmol, 1 equiv.) was added. After stirring for 2 hours at room temperature, $MgSO_4$ was removed by filtration. Evaporation of the solvent *in vacuo* afforded (*E*)-*N*-[*trans*-(3-phenyloxiran-2-yl)methylidene]isopropylamine **9a** in 85% (1.61 g) yield and high purity (>95% based on ^{1}H NMR spectroscopy), which was used as such in the next reaction step.

(*E*)-*N*-[*trans*-(3-Phenyloxiran-2-yl)methylidene]isopropylamine 9a

Orange oil. Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, d, J = 6.3 Hz), 1.22 (3H, d, J = 6.3 Hz), 3.45 (1H, septet, J = 6.3 Hz), 3.56 (1H, d × d, J = 7.1, 1.9 Hz), 3.96 (1H, d, J = 1.9 Hz), 7.28–7.37 (6H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 23.82, 23.83, 57.9, 61.2, 61.9, 125.7, 128.58, 128.61, 135.7, 158.4. IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1666; ν_{max} = 2968, 1459, 1158, 1126, 958, 854, 753, 696, 617. MS (70 eV): *m*/*z* (%) 190 (M^+ + 1, 20).

(*E*)-*N*-[*trans*-(3-Phenyloxiran-2-yl)methylidene]-4-methoxyphenylamine 9b [13,25]

(*E*)-*N*-[*trans*-(3-phenyloxiran-2-yl)methylidene]-4-methoxybenzylamine 9c

Orange oil. Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (1H, d × d, J = 7.0, 1.9 Hz), 3.80 (3H, s), 3.98 (1H, d, J = 1.9 Hz), 4.61 (1H, d, J = 13.9 Hz), 4.63 (1H, d, J = 13.9 Hz), 6.87–6.90 (2H, m), 7.19–7.40 (7H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 55.3, 57.9, 62.0, 64.3, 114.1, 125.7, 128.60, 128.63, 129.4, 130.3, 135.7, 158.9, 161.6. IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1666; ν_{max} = 1509, 1240, 1180, 1031, 856, 844, 810, 760, 697. MS (70 eV): *m*/*z* (%) 268 (M^+ + 1, 42). HRMS (ESI) Calcd for $C_{17}H_{18}NO_2^+$ 268.1332 $[M + H]^+$, found 268.1330.

(*E*)-*N*-{*trans*-{3-[3-(Trifluoromethyl)phenyl]oxiran-2-yl}methylidene}isopropylamine 9d

Orange oil. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, d, J = 6.3 Hz), 1.22 (3H, d, J = 6.3 Hz), 3.46 (1H, septet, J = 6.3 Hz), 3.54 (1H, d × d, J = 7.0, 1.9 Hz), 4.03 (1H, d, J = 1.9 Hz), 7.34 (1H, d, J = 7.0 Hz), 7.47–7.49 (2H, m), 7.56–7.59 (2H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.82 (s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 23.8, 57.2, 61.3, 62.1, 122.7 (q, J = 3.8 Hz), 123.9 (q, J = 272.3 Hz), 125.4 (q, J = 3.7 Hz), 128.9, 129.2, 131.1 (q, J = 31.7 Hz), 137.0, 157.7. IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1665; ν_{max} = 1327, 1163, 1121, 1071, 801, 700. MS (70 eV): m/z (%) 258 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{13}H_{15}F_3NO^+$ 258.1100 $[M + H]^+$, found 258.1102.

(*E*)-*N*-{*trans*-{3-[3-(Trifluoromethyl)phenyl]oxiran-2-yl}methylidene}-4-methoxybenzylamine 9e

Orange oil. Yield 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58–3.60 (1H, m), 3.80 (3H, s), 4.05 (1H, s(broad)), 4.62 (1H, d, J = 13.8 Hz), 4.65 (1H, d, J = 13.8 Hz), 6.86–6.90 (2H, m), 7.20–7.24 (2H, m), 7.39 (1H, d, J = 6,9 Hz), 7.47–7.50 (2H, m), 7.55–7.59 (2H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.79 (s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 55.3, 57.2, 62.1, 64.2, 114.1, 122.7 (q, J = 3.7 Hz), 123.9 (q, J = 273.0 Hz), 125.4 (q, J = 3.7 Hz), 128.8, 129.2, 129.4, 130.1, 131.1 (q, J = 32.7 Hz), 136.9, 158.9, 160.8. IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1666; ν_{max} = 1511, 1328, 1246, 1164, 1121, 1119, 1070, 1034, 802, 700. MS (70 eV): m/z (%) 336 (M^+ + 1, 22). HRMS (ESI) Calcd for $C_{18}H_{17}F_3NO_2^+$ 336.1206 $[M + H]^+$, found 336.1207.

Synthesis of (3*S,4*R**,2′*R**,3′*R**)-3-acetoxy-4-(3-aryloxiran-2-yl) azetidin-2-ones 4**

As a representative example, the synthesis of (3*S**,4*R**,2′*R**,3′*R**)-3-acetoxy-4-{3-[3-(trifluoromethyl)phenyl]oxiran-2-yl}-1-(4-methoxybenzyl)azetidin-2-one **4e** is described. To an ice-cooled solution of (*E*)-*N*-{*trans*-{3-[3-(trifluoromethyl)phenyl]oxiran-2-yl}methylidene}-4-methoxybenzylamine **9e** (1.68 g, 5 mmol, 1 equiv.) and triethylamine (1.52 g, 15 mmol, 3 equiv.) in anhydrous CH_2Cl_2 (20 mL), acetoxyacetyl chloride (0.89 g, 7 mmol, 1.3 equiv.) in anhydrous CH_2Cl_2 (5 mL) was added dropwise. After stirring for 18 hours at room temperature, CH_2Cl_2 (15 mL) was added and the resulting mixture was washed with a saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). Drying of the organic phase with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude (3*S**,4*R**,2′*R**,3′*R**)-3-acetoxy-4-{3-[3-(trifluoromethyl)phenyl]oxiran-2-yl}-1-(4-methoxybenzyl)azetidin-2-one **4e**, which was purified in 79% (1.72 g) yield by column chromatography on silica gel (hexane/EtOAc 2/1).

(3*S,4*R**,2′*R**,3′*R**)-3-Acetoxy-1-isopropyl-4-(3-phenyloxiran-2-yl)azetidin-2-one 4a**

White crystals. Recrystallization from hexane/EtOAc (1/30). Mp 110 °C. Yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, d, J = 6.7 Hz), 1.40 (3H, d, J = 6.7 Hz), 1.74 (3H, s, $CH_3C{=}O$), 2.95 (1H, d × d, J = 8.1, 2.0 Hz), 3.59 (1H, d × d, J = 8.1, 4.8 Hz), 3.68 (1H, d, J = 2.0 Hz), 4.07 (1H, septet, J = 6.7 Hz), 5.67 (1H, d, J = 4.8 Hz), 7.23–7.25 (2H, m), 7.29–7.38 (3H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 19.9, 20.0, 21.5, 44.3, 56.8, 59.2, 61.3, 74.8, 125.3, 128.61, 128.63, 135.6, 163.3, 170.0. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1747, 1711; ν_{max} = 1400, 1216, 1130, 1107, 1024, 923, 895, 797, 761, 701. MS (70 eV): m/z (%) 290 (M^+ + 1, 15). HRMS (ESI) Calcd for $C_{16}H_{20}NO_4^+$ 290.1387 $[M + H]^+$, found 290.1385.

(3*S,4*R**,2′*R**,3′*R**)-3-Acetoxy-1-(4-methoxyphenyl)-4-(3-phenyloxiran-2-yl)azetidin-2-one 4b**

White crystals. Recrystallization from hexane/EtOAc (1/30). Mp 147 °C. Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (3H, s), 3.11 (1H, d × d, J = 7.8, 1.9 Hz), 3.78 (1H, d, J = 1.9 Hz), 3.82 (3H, s), 4.00 (1H, d × d, J = 7.8, 5.0 Hz), 5.89 (1H, d, J = 5.0 Hz), 6.94 (2H, d, J = 9.0 Hz), 7.23–7.26 (2H, m), 7.32–7.38 (3H, m), 7.60 (2H, d, J = 9.0 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.1, 55.5, 56.2, 60.5, 61.0, 75.0, 114.6, 118.8, 125.4, 128.7, 128.8, 130.5, 135.3, 157.0, 160.5, 170.0. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1745, 1704; ν_{max} = 1514, 1246, 1216, 1195, 1108, 1096, 826, 760. MS (70 eV): m/z (%) 354 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{20}H_{20}NO_5^+$ 354.1336 $[M + H]^+$, found 354.1337.

(3*S,4*R**,2′*R**,3′*R**)-3-Acetoxy-1-(4-methoxybenzyl)-4-(3-phenyloxiran-2-yl)azetidin-2-one 4c**

Yellow oil. R_f = 0.17 (hexane/EtOAc 2/1). Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (3H, s), 2.90 (1H, d × d, J = 8.0, 2.0 Hz), 3.45 (1H, d × d, J = 8.0, 4.8 Hz), 3.55 (1H, d, J = 2.0 Hz), 3.82 (3H, s), 4.33 (1H, d, J = 14.7 Hz), 4.66 (1H, d, J = 14.7 Hz), 5.68 (1H, d, J = 4.8 Hz), 6.89–6.93 (2H, m), 7.16–7.19 (2H, m), 7.30–7.35 (5H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.0, 45.1, 55.3, 55.5, 59.9, 60.5, 75.8, 114.3, 125.3, 126.8, 128.57, 128.61, 130.2, 135.5, 159.5, 163.6, 169.9. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1762, 1747; ν_{max} = 1512, 1239, 1218, 1176, 1028, 754, 698. MS (70 eV): m/z (%) 368 (M^+ + 1, 51). HRMS (ESI) Calcd for $C_{21}H_{22}NO_5^+$ 368.1492 $[M + H]^+$, found 368.1499.

(3*S,4*R**,2′*R**,3′*R**)-3-Acetoxy-4-{3-[3-(trifluoromethyl)phenyl] oxiran-2-yl}-1-isopropylazetidin-2-one 4d**

Yellow oil. R_f = 0.37 (hexane/EtOAc 1/1). Yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, d, J = 6.7 Hz), 1.40 (3H, d, J = 6.7 Hz), 1.78 (3H, s), 2.92 (1H, d × d, J = 8.2, 1.8 Hz), 3.60 (1H, d × d, J = 8.2, 4.8 Hz), 3.77 (1H, d, J = 1.8 Hz), 4.07 (1H, septet, J = 6.7 Hz), 5.66 (1H, d, J = 4.8 Hz), 7.46–7.51 (3H, m), 7.58–7.60 (1H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.78 (s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 19.9, 20.0, 21.5, 44.4, 56.2, 59.1, 61.4, 74.9, 122.1 (q, J = 3.7 Hz), 123.8 (q, J = 271.9 Hz), 125.3 (q, J = 3.7 Hz), 128.6, 129.2, 131.3 (q, J = 32.3 Hz), 137.0, 163.1, 170.1. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1764, 1748; ν_{max} = 1329, 1220, 1193, 1166, 1109, 1089, 1068, 1026, 894, 804. MS (70 eV): m/z (%) 358 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{17}H_{19}F_3NO_4^+$ 358.1261 $[M + H]^+$, found 358.1249.

(3*S,4*R**,2′*R**,3′*R**)-3-Acetoxy-4-{3-[3-(trifluoromethyl)phenyl] oxiran-2-yl}-1-(4-methoxybenzyl)azetidin-2-one 4e**

Yellow oil. R_f = 0.13 (hexane/EtOAc 2/1). Yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (3H, s), 2.84 (1H, d × d, J = 8.0,

1.9 Hz), 3.46 (1H, d × d, J = 8.0, 4.8 Hz), 3.64 (1H, d, J = 1.9 Hz), 3.82 (3H, s), 4.34 (1H, d, J = 14.7 Hz), 4.65 (1H, d, J = 14.7 Hz), 5.66 (1H, d, J = 4.8 Hz), 6.90–6.93 (2H, m), 7.29–7.33 (2H, m), 7.37–7.39 (1H, m), 7.44–7.49 (2H, m), 7.56–7.58 (1H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.83 (s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.0, 45.1, 54.9, 55.3, 59.7, 60.7, 75.9, 114.3, 122.1 (q, J = 3.7 Hz), 123.8 (q, J = 273.7 Hz), 125.3 (q, J = 3.9 Hz), 126.7, 128.6, 129.2, 130.2, 131.2 (q, J = 32.5 Hz), 137.0, 159.6, 163.3, 169.9. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1768, 1750; ν_{max} = 1513, 1328, 1245, 1221, 1165, 1122, 1089, 1070, 1030, 806. MS (70 eV): m/z (%) 436 (M^+ + 1, 76). HRMS (ESI) Calcd for $C_{22}H_{21}F_3NO_5^+$ 436.1366 $[M + H]^+$, found 436.1376.

Synthesis of (1*S**,3*S**,4*R**,5*R**)-3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones 11 and (1*S**,3*R**,4*S**,5*R**)-3-aryl-4-hydroxy-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 12

As a representative example, the synthesis of (1*S**,3*S**,4*R**,5*R**)-4-hydroxy-6-(4-methoxybenzyl)-3-[3-(trifluoromethyl)phenyl]-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11e** is described. To a solution of (3*S**,4*R**,2′*R**,3′*R**)-3-acetoxy-4-{3-[3-(trifluoromethyl)phenyl]oxiran-2-yl}-1-(4-methoxybenzyl)azetidin-2-one **4e** (0.44 g, 1 mmol, 1 equiv.) in MeOH/H_2O (1/1, 20 mL), potassium carbonate (0.28 g, 2 mmol, 2 equiv.) was added. After stirring for 24 hours at room temperature, the solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (20 mL). The resulting mixture was washed with H_2O (3 × 10 mL), after which the combined aqueous phases were extracted again with CH_2Cl_2 (3 × 10 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude (1*S**,3*S**,4*R**,5*R**)-4-hydroxy-6-(4-methoxybenzyl)-3-[3-(trifluoromethyl)phenyl]-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11e**, which was purified in 69% (0.27 g) yield by column chromatography on silica gel (hexane/EtOAc 1/1).

(1*S**,3*S**,4*R**,5*R**)-4-Hydroxy-6-isopropyl-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 11a

Colorless oil. R_f = 0.07 (hexane/EtOAc 1/1). Yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (3H, d, J = 6.7 Hz, $(C\underline{H}_3)_2CH$), 0.98 (3H, d, J = 6.7 Hz, $(C\underline{H}_3)_2CH$), 3.02 (1H, s(broad)), 3.45 (1H, septet, J = 6.7 Hz), 4.14 (1H, d, J = 3.6 Hz), 4.66 (1H, s(broad)), 5.29 (1H, d, J = 3.6 Hz), 5.56 (1H, s(broad)), 7.21–7.25 (1H, m), 7.31–7.35 (2H, m), 7.42–7.44 (2H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 19.8, 20.7, 44.2, 63.7, 77.7, 86.7, 92.2, 124.4, 127.4, 128.4, 138.8, 165.8. IR (ATR, cm^{-1}): ν_{OH} = 3377; $\nu_{C=O}$ = 1724; ν_{max} = 1390, 1235, 1102, 1071, 1018, 785, 736, 699. MS (70 eV): m/z (%) 248 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{14}H_{18}NO_3^+$ 248.1281 $[M + H]^+$, found 248.1282.

(1*S**,3*S**,4*R**,5*R**)-4-Hydroxy-6-(4-methoxyphenyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 11b

Colorless oil. R_f = 0.17 (hexane/EtOAc 1/1). Yield 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (1H, s(broad)), 3.74 (3H, s), 4.56 (1H, d, J = 3.7 Hz), 4.76 (1H, s(broad)), 5.42 (1H, d, J = 3.7 Hz), 5.49 (1H, s(broad)), 6.73–6.77 (2H, m), 6.97–7.01 (2H, m), 7.17–7.26 (3H, m), 7.31–7.32 (2H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 55.5, 64.7, 75.4, 86.5, 91.7, 114.4, 118.4, 124.8, 127.7, 128.4, 129.8, 137.5, 156.6, 162.7. IR (ATR, cm^{-1}): ν_{OH} = 3415; $\nu_{C=O}$ = 1722; ν_{max} = 1507, 1244, 1065, 1029, 827, 733, 697. MS (70 eV): m/z (%) 312 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{18}H_{18}NO_4^+$ 312.1230 $[M + H]^+$, found 312.1233.

(1*S**,3*S**,4*R**,5*R**)-4-Hydroxy-6-(4-methoxybenzyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 11c

White crystals. R_f = 0.12 (hexane/EtOAc 1/1). Recrystallization from hexane/EtOAc (1/30). Mp 158 °C. Yield 39%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (1H, d, J = 6.0 Hz), 3.79 (3H, s), 3.82 (1H, d, J = 14.9 Hz), 3.985 (1H, d, J = 14.9 Hz), 3.988 (1H, d, J = 3.6 Hz), 4.31 (1H, d, J = 6.0 Hz), 5.37 (1H, d, J = 3.6 Hz), 5.46 (1H, s(broad)), 6.74–6.76 (2H, m), 6.80–6.84 (2H, m), 7.28–7.30 (1H, m), 7.32–7.38 (4H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 44.5, 55.3, 65.2, 76.2, 87.9, 92.2, 114.3, 124.4, 126.4, 127.5, 128.5, 129.8, 138.3, 159.2, 165.9. IR (ATR, cm^{-1}): ν_{OH} = 3332; $\nu_{C=O}$ = 1720; ν_{max} = 1512, 1246, 1176, 1121, 1097, 1070, 1036, 809, 736. MS (70 eV): m/z (%) 326 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{19}H_{20}NO_4^+$ 326.1387 $[M + H]^+$, found 326.1388.

(1*S**,3*S**,4*R**,5*R**)-4-Hydroxy-6-isopropyl-3-[3-(trifluoromethyl)phenyl]-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 11d

Colorless oil. R_f = 0.15 (hexane/EtOAc 1/1). Yield 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69 (3H, d, J = 6.7 Hz), 0.97 (3H, d, J = 6.7 Hz), 3.44 (1H, septet, J = 6.7 Hz), 3.77 (1H, s(broad)), 4.18 (1H, d, J = 3.6 Hz), 4.67 (1H, s(broad)), 5.31 (1H, d, J = 3.6 Hz), 5.59 (1H, s(broad)), 7.45–7.52 (2H, m), 7.68–7.70 (2H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.71 (s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 19.6, 20.6, 44.3, 63.7, 77.6, 86.7, 91.5, 121.4 (q, J = 3.6 Hz), 124.0 (q, J = 276.9 Hz), 124.2 (q, J = 3.8 Hz), 127.9, 129.0, 130.7 (q, J = 32.4 Hz), 140.2, 165.9. IR (ATR, cm^{-1}): ν_{OH} = 3324; $\nu_{C=O}$ = 1748; ν_{max} = 2975, 1389, 1331, 1233, 1196, 1163, 1122, 1075, 1025, 1008, 940, 805, 788, 704, 670. MS (70 eV): m/z (%) 316 (M^+ + 1, 100).

(1*S**,3*S**,4*R**,5*R**)-4-Hydroxy-6-(4-methoxybenzyl)-3-[3-(trifluoromethyl)phenyl]-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 11e

White crystals. R_f = 0.15 (hexane/EtOAc 1/1). Mp 132 °C. Yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (1H, s(broad)), 3.79 (3H, s), 3.91 (1H, d, J = 14.7 Hz), 3.96 (1H, d, J = 14.7 Hz), 4.01 (1H, d, J = 3.6 Hz), 4.23 (1H, s(broad)), 5.40 (1H, d, J = 3.6 Hz), 5.46 (1H, s(broad)), 6.73–6.75 (2H, m), 6.79–6.81 (2H, m), 7.48–7.51 (2H, m), 7.55–7.56 (1H, m), 7.61–7.63 (1H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.51 (s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 44.7, 55.2, 65.4, 76.4, 88.0, 91.7, 114.3, 121.4 (q, J = 3.9 Hz), 124.1 (q, J = 272.4 Hz), 124.3 (q, J = 3.6 Hz), 126.1, 127.9, 129.1, 129.7, 130.7 (q, J = 32.3 Hz); 139.7, 159.3, 165.8. IR (ATR, cm^{-1}): ν_{OH} = 3359; $\nu_{C=O}$ = 1724; ν_{max} = 1513, 1329, 1310, 1251, 1157, 1119, 1095, 1067, 1036, 702. MS (70 eV): m/z (%) 394 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{20}H_{18}F_3NO_4Cl^-$ 428.0882 $[M + Cl^-]$, found 428.0885.

(1*S,3*R**,4*S**,5*R**)-4-Hydroxy-6-isopropyl-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 12a**

White crystals. R_f = 0.29 (hexane/EtOAc 1/1). Mp 150 °C. Yield 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, d, J = 6.7 Hz), 1.38 (3H, d, J = 6.7 Hz), 2.20 (1H, s(broad)), 3.88 (1H, d × d, J = 8.6, 5.0 Hz), 3.90 (1H, septet, J = 6.7 Hz), 4.19–4.21 (1H, m), 4.70 (1H, d, J = 8.6 Hz), 5.07 (1H, d, J = 3.6 Hz), 7.33–7.40 (5H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 19.8, 21.6, 45.8, 58.1, 78.3, 81.5, 83.6, 126.5, 128.6, 128.7, 137.4, 165.6. IR (ATR, cm^{-1}): ν_{OH} = 3384; $\nu_{C=O}$ = 1719; ν_{max} = 1348, 1306, 1100, 1085, 1007, 968, 780, 759, 705. MS (70 eV): m/z (%) 248 (M^+ + 1, 100). HRMS (ESI) Calcd for $C_{14}H_{18}NO_3^+$ 248.1281 $[M + H]^+$, found 248.1279.

Synthesis of (1*S,3*S**,4*R**,5*R**)-3-aryl-4-hydroxy-6-(4-methoxybenzoyl)-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones 13**

As a representative example, the synthesis of (1*S**,3*S**,4*R**,5*R**)-4-hydroxy-6-(4-methoxybenzoyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **13a** is described. To a solution of (1*S**,3*S**,4*R**,5*R**)-4-hydroxy-6-(4-methoxybenzyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **11c** (0.33 g, 1 mmol, 1 equiv.) in CH_3CN/H_2O (2/1, 10 mL), potassium persulfate (0.92 g, 3.4 mmol, 3.4 equiv.) and potassium dihydrogen phosphate (0.93 g, 6.8 mmol, 6.8 equiv.) were added. After stirring for 4 hours at reflux, the solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The resulting mixture was washed with H_2O (2 × 5 mL), a saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL), after which the combined aqueous phases were extracted again with CH_2Cl_2 (3 × 10 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude (1*S**,3*S**,4*R**,5*R**)-4-hydroxy-6-(4-methoxybenzoyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **13a**, which was purified in 46% (0.16 g) yield by preparative HPLC.

(1*S,3*S**,4*R**,5*R**)-4-Hydroxy-6-(4-methoxybenzoyl)-3-phenyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 13a**

Colorless oil. R_f = 0.59 (hexane/EtOAc 1/1). Yield 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (1H, s(broad)), 3.80 (3H, s), 4.79 (1H, s(broad)), 5.01 (1H, s(broad)), 5.36 (1H, s(broad)), 5.61 (1H, s(broad)), 6.71 (2H, d, J = 8.4 Hz), 7.13 (2H, d, J = 8.4 Hz), 7.25–7.28 (1H, m), 7.32–7.35 (2H, m), 7.44–7.46 (2H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 55.4, 63.2, 76.7, 84.9, 90.6, 113.3, 123.2, 124.8, 127.7, 128.7, 131.9, 138.2, 162.3, 163.9, 165.7. IR (ATR, cm^{-1}): ν_{OH} = 3423; $\nu_{C=O}$ = 1797, 1664; ν_{max} = 1602, 1306, 1258, 1171, 1096, 1026, 908, 748, 727, 698. MS (70 eV): m/z (%) 362 (M^+ + Na, 71), 340 (M^+ + 1, 8), 312 (M^+ − CO, 100). HRMS (ESI) Calcd for $C_{18}H_{18}NO_4^+$ 312.1230 $[M - CO + H]^+$, found 312.1230.

(1*S,3*S**,4*R**,5*R**)-4-Hydroxy-6-(4-methoxybenzoyl)-3-[3-(trifluoromethyl)phenyl]-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 13b**

Colorless oil. R_f = 0.30 (hexane/EtOAc 19/1). Yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.17 (1H, s(broad)), 3.81 (3H, s), 4.79 (1H, d, J = 4.4 Hz), 4.96 (1H, s(broad)), 5.41 (1H, d, J = 4.4 Hz), 5.60 (1H, s(broad)), 6.75 (2H, d, J = 8.9 Hz), 7.29 (2H, d, J = 8.9 Hz), 7.42–7.46 (1H, m), 7.52–7.54 (1H, m), 7.60–7.62 (1H, m), 7.78 (1H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.77 (s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 55.5, 63.3, 77.3, 84.9, 90.1, 113.4, 121.7 (q, J = 3.8 Hz), 123.9 (q, J = 272.6 Hz), 122.7, 124.7 (q, J = 3.7 Hz), 128.3, 129.3, 131.1 (q, J = 32.5 Hz), 131.9, 139.4, 161.8, 164.1, 165.7. MS (70 eV): m/z (%) 430 (M^+ + Na, 70), 408 (M^+ + 1, 12), 380 (M^+ − CO, 100). HRMS (ESI) Calcd for $C_{20}H_{17}F_3NO_5^+$ 408.1053 $[M + H]^+$, found 408.1049.

β-Lactamase inhibition assay

Each compound (500 μM) was incubated with β-lactamase from *Enterobacter cloacae* (0.25 mg L^{-1}) at 35 °C for 10 minutes, after which the residual enzymatic activity was measured by following the rate of nitrocefin (150 μM) hydrolysis at 480 nm in 100 mM phosphate buffer, pH 7.0, and 10% (v/v) DMSO. Each reaction was performed in triplicate.

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