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Synthesis of 2-Hydroxy-1,4-oxazin-3-ones through Ring Transformation of 3-Hydroxy-4-(1,2-dihydroxyethyl)-β-lactams and a Study of Their Reactivity

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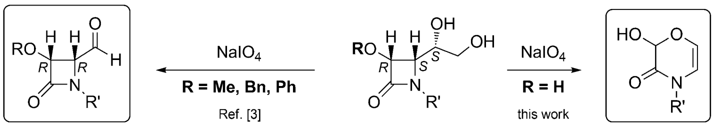
Abstract: The reactivity of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams with regard to the oxidant sodium periodate was evaluated, unexpectedly resulting in the exclusive formation of new 2-hydroxy-1,4-oxazin-3-ones through a C3–C4 bond cleavage of the intermediate 4-formyl-3-hydroxy-β-lactams followed by a ring expansion. This peculiar transformation stands in sharp contrast with the known $NaIO_4$-mediated oxidation of 3-alkoxy- and 3-phenoxy-4-(1,2-dihydroxyethyl)-β-lactams, which exclusively leads to the corresponding 4-formyl-β-lactams without a subsequent ring enlargement. In addition, this new class of functionalized oxazin-3-ones was further evaluated for its potential use as building blocks in the synthesis of a variety of differently substituted oxazin-3-ones, morpholin-3-ones and pyrazinones. Furthermore, additional insights into the mechanism and the factors governing this new ring-expansion reaction were provided by means of density functional theory calculations.

Keywords: β-lactams • bond cleavage • density functional calculations • oxazin-3-ones • reaction mechanisms • ring expansion

Introduction

Besides their biological relevance as potential antibiotics,[1] β-lactams have also acquired a prominent position in organic chemistry as synthons for further elaboration by exploiting the strain energy associated with the four-membered ring system. Indeed, selective bond cleavage of the 2-azetidinone ring followed by interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks. In this way, β-lactams act as important intermediates toward a wide variety of nitrogen-containing acyclic and heterocyclic target compounds.[2]

Although this unique nature of the β-lactam skeleton has been thoroughly exploited, the tandem heterolytic β-lactam C3–C4 bond cleavage–ring expansion protocol has received much less attention compared with the more celebrated amide bond cleavage. In the present paper, a convenient and straightforward approach toward new 2-hydroxy-1,4-oxazin-3-ones **2** is disclosed through an unexpected ring rearrangement of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **1** (R=H) upon treatment with sodium periodate ($NaIO_4$) (Scheme 1), most probably through C3–C4 bond cleavage of the intermediate 4-formyl-3-hydroxy-β-lactams followed by ring enlargement. This transformation is indeed peculiar, because 3-alkoxy- and 3-phenoxy-4-(1,2-dihydroxyethyl)-β-lactams **1** (R=Me, Bn, Ph) are known to be oxidized to the corresponding 4-formyl-β-lactam derivatives **3** under the same reaction conditions, without subsequent rearrangement into six-membered heterocycles (Scheme 1).[3]



3 **1** **2**

Scheme 1. $NaIO_4$-mediated oxidation of 4-(1,2-dihydroxyethyl)-β-lactams **1**.

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Albeit starting from different substrates and triggered by different reaction conditions, two other approaches involving ring enlargement of appropriate β-lactam derivatives toward morpholinone scaffolds have been reported in the literature. The first method involves a $SnCl_2{\cdot}2H_2O$-promoted carbenium ion rearrangement of 4-acyl-β-lactams bearing an acetal functionality at the C3 carbon, yielding the corresponding 1,4-oxazin-2,3-diones in good yields (75–95 %).[4] The second approach comprises a single-step molecular iodine-catalyzed rearrangement of 3-alkoxy-4-formyl-β-lactams into monocyclic γ-lactams upon treatment with allylic and propargylic trimethylsilanes, which inevitably leads to 2-alkoxy-1,4-oxazin-3-ones as minor constituents (4–9 %), except for the reaction of 4-formyl-3-methoxy-1-(4-methoxybenzyl)azetidin-2-one with allyltrimethylsilane, which gives rise to the corresponding morpholinone in 66 % yield.[5] Whereas in these two routes 4-acyl- and 4-formyl-β-lactams have been prepared as the substrates to perform the ring enlargement, in the present paper a different type of starting compounds, that is, 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **1**, served as substrates for the ring rearrangement. In addition to the experimental results, the mechanism and the factors governing this unexpected transformation were further investigated by means of density functional theory (DFT) calculations, which fully supported the proposed route.

Results and Discussion

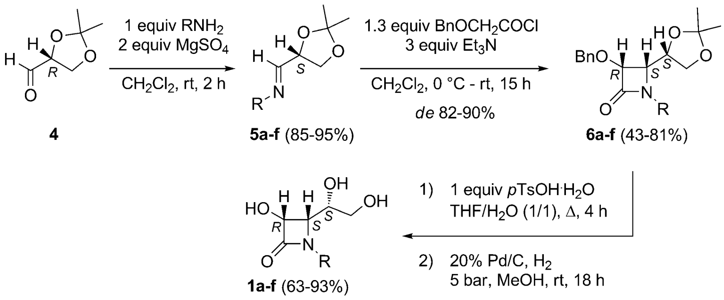
The synthesis of the starting β-lactams **1** was performed by means of a two-step literature procedure.[3] Thus, (*R*)-glyceraldehyde acetonide **4** was condensed with different primary amines in dichloromethane in the presence of $MgSO_4$ as drying agent, and the resulting chiral imines **5** were used as substrates in the Staudinger synthesis of β-lactams **6**. Therefore, imines **5** were treated with benzyloxyacetyl chloride in dichloromethane in the presence of triethylamine to afford the corresponding optically active β-lactams **6** in 43–81 % yield and with high diastereomeric excess (Scheme 2, Table 1). The *cis*-diastereoselectivity could be deduced from the ^1H NMR spectra of β-lactams **6**, because the coupling constants between the 3H and 4H protons on the β-lactam ring varied between 4.8 and 5.0 Hz ($CDCl_3$), which correspond well with those reported in the literature for *cis*-β-lactams.[6] Subsequently, the latter azetidin-2-ones **6** could be easily converted into the premised chiral 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **1** by consecutive hydrolysis in THF/H_2O (1:1) by using one equivalent of *p*-toluenesulfonic acid under reflux for four hours and hydrogenolysis of the benzyl ether moiety by using 20 % (w/w) palladium on activated carbon in methanol at room temperature for 18 hours, yielding β-lactams **1** in 63–93 % yield after column chromatography (SiO_2) or recrystallization from EtOAc/hexane (30:1).

Table 1. Synthesis of imines **5**, 3-benzyloxy-β-lactams **6** and 3-hydroxy-β-lactams **1**.

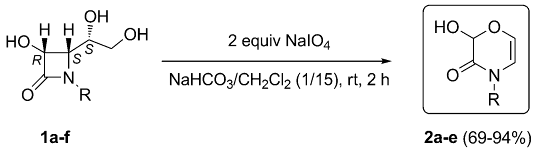
Entry	R	Compound **5** (yield [%])	Compound **6** (yield [%])[a]	d.r. (**6**)[b]	Compound **1** (yield [%])[a]
1	*i*Pr	**5a** (93)	**6a** (81)	91:9	**1a** (83)
2	*i*Bu	**5b** (94)	**6b** (50)	92.5:7.5	**1b** (74)
3	*n*Bu	**5c** (95)	**6c** (43)	92.5:7.5	**1c** (63)
4	*c*Hex	**5d** (90)	**6d** (65)	93.5:6.5	**1d** (88)
5	*n*Pr	**5e** (92)	**6e** (70)	95:5	**1e** (68)
6	*i*Pent	**5f** (85)	**6f** (50)	94:6	**1f** (93)

[a] After purification by column chromatography (SiO_2) or recrystallization. [b] Determined by ^1H NMR spectroscopy and GC.

In the next stage, the reactivity of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **1** with regard to the oxidant sodium periodate ($NaIO_4$) was investigated as a potential entry into the synthetically useful class of 4-formyl-β-lactams,[3] which are known to be attractive synthons for further elaboration. Indeed, significant interest has been focused on the synthesis and reactivity of 4-formyl-β-lactams as viable intermediates in (medicinal) organic synthesis, as illustrated by their use in the asymmetric synthesis of bi- and polycyclic β-lactams, different kinds of heterocycles, alkaloids, non proteinogenic α- and β- amino acids, amino sugars, taxoids, and complex natural products such as biotin, cisapride, and sphingosines.[7] In analogy, 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **1** were treated with two equivalents of $NaIO_4$ in a two-phase system of saturated aqueous sodium bicarbonate and dichloromethane (1:15) at room temperature for two hours, but the expected 4-formyl-β-lactams were not detected. Nonetheless, a full and selective substrate conversion occurred, and detailed spectroscopic analysis finally revealed the molecular structure of the obtained reaction products to be exclusively 2-hydroxy-1,4-oxazin-3-ones **2**, which were isolated in good yields (69–94 %). Only in the case of an *n*-propyl unit as the *N*-substituent, was a complex reaction mixture obtained (Scheme 3, Table 2). This remarkable reactivity stands in sharp contrast with the known



Scheme 2. Synthesis of 3-hydroxy-β-lactams **1**.



Scheme 3. Synthesis of 2-hydroxy-1,4-oxazin-3-ones **2**.

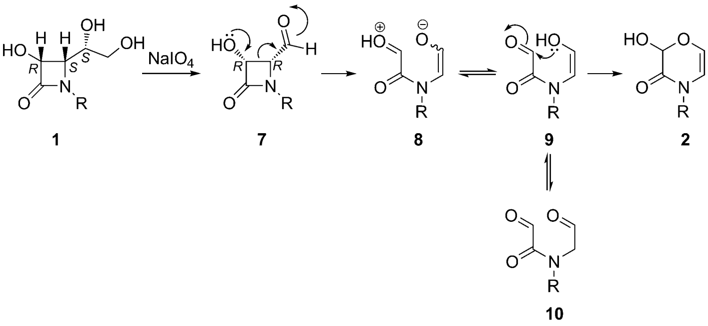
Table 2. Synthesis of 2-hydroxy-1,4-oxazin-3-ones **2**.

Entry	R	Compound **2** (yield [%])[a]
1	*i*Pr	**2a** (69)
2	*i*Bu	**2b** (73)
3	*n*Bu	**2c** (75)
4	*c*Hex	**2d** (94)
5	*n*Pr	complex reaction mixture
6	*i*Pent	**2e** (70)

[a] After purification by column chromatography (SiO_2).

$NaIO_4$-mediated oxidation of 3-alkoxy- and 3-phenoxy-4-(1,2-dihydroxyethyl)-β-lactams, which exclusively leads to the corresponding 4-formyl-β-lactam derivatives **3** under the same reaction conditions.[3]

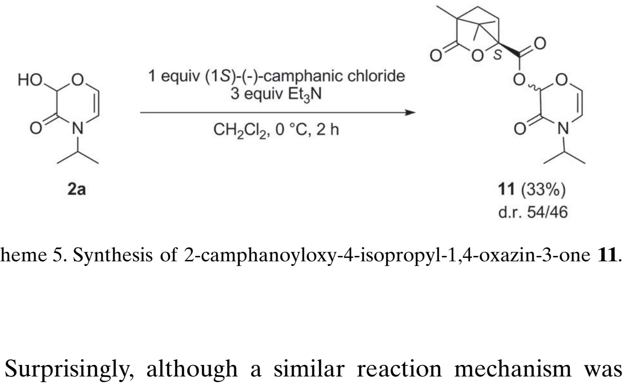
From a mechanistic point of view, the formation of the latter 2-hydroxy-1,4-oxazin-3-ones **2** can be rationalized considering the initial oxidation of the starting 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **1** toward the corresponding 4-formyl-β-lactams **7**, which proved to be unstable under the given reaction conditions. Considering the presence of the electron-donating hydroxyl functionality at C3, a subsequent C3−C4 bond cleavage in β-lactams **7** toward intermediates **8**/**9** is facilitated, whether or not periodate-promoted through activation of the aldehyde. Finally, ring closure of the latter intermediates **9** results in the selective formation of 2-hydroxy-1,4-oxazin-3-ones **2** (Scheme 4). In an attempt to further assess the intrinsic reactivity of 4-formyl-β-lactams **7**, 3-benzyloxy-4-formyl-1-isopropyl-β-lactam **3**[3] (R = Bn, R′ = *i*Pr) was subjected to hydrogenolysis (1 bar H_2) as a possible entry into the corresponding 4-formyl-3-hydroxy-β-lactam **7a**. However, as could be anticipated, the substrate was over-reduced to provide the 3-hydroxy-4-(hydroxymethyl)azetidin-2-one system instead. Subsequent Swern oxidation of the primary alcohol by using oxalyl chloride, DMSO, and Et_3N gave rise to the exclusive formation of 2-hydroxy-1,4-oxazin-3-one **2a**; no traces of the desired 4-formyl-3-hydroxy-β-lactam **7a** could be found in the reaction mixture, pointing to the high intrinsic reactivity of 4-formyl-3-hydroxy-β-lactams **7** as probably the main driving force governing this new ring-expansion reaction. The presence of periodate is apparently not essential to effect this rearrangement, although it might have a propitious influence by coordinating to the carbonyl moiety in intermediates **7**.



Scheme 4. Proposed reaction mechanism for the formation of 2-hydroxy-1,4-oxazin-3-ones **2**.

As mentioned before, it should be stressed that this ring-expansion reaction is not compatible with β-lactam substrates bearing an alkoxy or phenoxy group at the C3 position.

According to this reaction mechanism, the observed ring expansion of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **1** toward 2-hydroxy-1,4-oxazin-3-ones **2** should proceed with loss of chirality, which was supported experimentally by measurement of the optical rotation of 4-cyclohexyl-2-hydroxy-1,4-oxazin-3-one **2d** ($[\alpha]_D = 0.0°$, $c = 1.22$, CH_2Cl_2). In addition, esterification of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **2a** with one equivalent of (1*S*)-(−)-camphanic chloride in CH_2Cl_2 at 0 °C for two hours in the presence of three equivalents of triethylamine afforded the corresponding 2-camphanoyloxy-4-isopropyl-1,4-oxazin-3-one **11** as a mixture of two diastereoisomers in a ratio of 54:46 (based on ^{1}H NMR spectroscopic analysis and GC), pointing to the racemic character of 2-hydroxy-1,4-oxazin-3-ones **2** (Scheme 5).

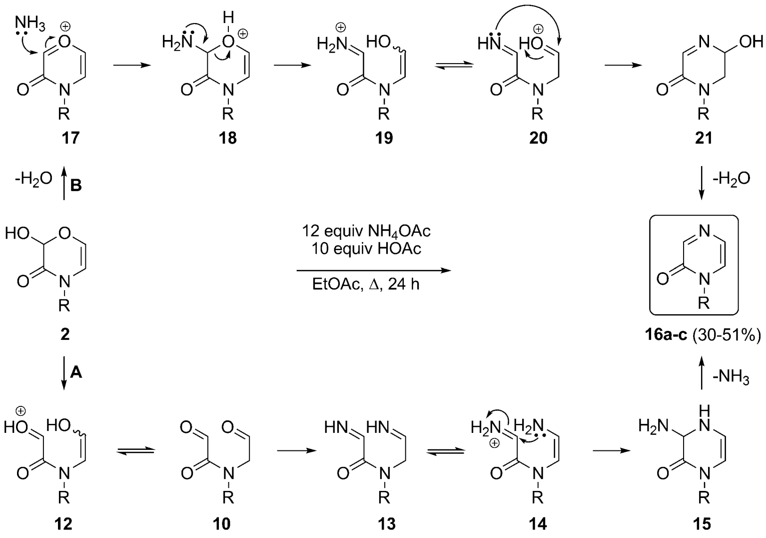


Scheme 5. Synthesis of 2-camphanoyloxy-4-isopropyl-1,4-oxazin-3-one **11**.

Surprisingly, although a similar reaction mechanism was proposed, the achiral outcome observed in the above-described ring-expansion reactions contradicts the reported formation of optically pure 2-alkoxy-1,4-oxazin-3-ones in the molecular iodine-catalyzed rearrangement of chiral 3-alkoxy-4-formyl-β-lactams.[5] In the latter case, although not discussed in the original paper, the chiral outcome could be explained by the partial carbenium ion character of the zwitterionic intermediates, which could control the subsequent intramolecular nucleophilic attack and enable it to occur from the same side from which the initial β-lactam C3−C4 bond was cleaved. A similar stereochemical control (“memory effect”) has been described in the literature for reactions of carbenium ions in which the latter “remember” how they were formed before taking part in the second step.[8] In our case, however, the hydroxyl group in intermediates **8**, formed after C3−C4 bond cleavage of the intermediate 4-formyl-β-lactams **7**, can induce prototropy toward intermediates **9**. Since these intermediates **9** possess a planar configuration due to the presence of a polycentric molecular orbital (PCMO) spread over the entire molecule, there is no stereocontrol during the subsequent intramolecular nucleophilic attack, resulting in the formation of racemic 2-hydroxy-1,4-oxazin-3-ones **2** (Scheme 4).

Although a less expensive, achiral approach toward 2-hydroxy-1,4-oxazin-3-ones **2** starting from the oxidation of the commercially available racemic solketal[9] can be developed applying the same reaction sequence as mentioned above, the use of optically pure (*R*)-glyceraldehyde acetonide **4** provided some additional mechanistic insights into this unexpected transformation.

Subsequently, with the intention to support the proposed mechanistic rationale, the synthesis of the aza-analogues of the former 2-hydroxy-1,4-oxazin-3-ones **2** was envisaged. Thus, treatment of the latter compounds **2** with 12 equivalents of NH_4OAc and 10 equivalents of HOAc in ethyl acetate furnished the corresponding 1*H*-pyrazin-2-ones **16** in 30–51 % yield after heating at reflux for 24 hours (Scheme 6, Table 3).[10] This transformation suggests a reaction mechanism in which acetic acid-mediated hydrolysis of the hemi-acetal in 2-hydroxy-1,4-oxazin-3-ones **2** gives rise to the selective formation of dialdehydes **10**, which are subsequently transformed into the corresponding diimines **13** and enamino imines **14** through the action of ammonium acetate. Finally, ring closure followed by the elimination of ammonia results in the selective formation of 1*H*-pyrazin-2-ones **16** (Scheme 6, Route A). However, alternative reaction pathways should not be excluded. For example, initial elimination of water followed by the addition of ammonia can account for the formation of 2-amino-1,4-oxazin-3-ones **18**, which subsequently undergo an acetic acid-mediated ring opening toward the corresponding intermediates **19**/**20**. Finally, ring closure and elimination of water give rise to the formation of 1*H*-pyrazin-2-ones **16** (Scheme 6, Route B).



Scheme 6. Synthesis of 1*H*-pyrazin-2-ones **16**.

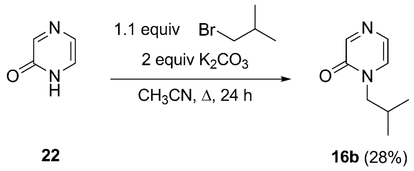
Table 3. Synthesis of 1*H*-pyrazin-2-ones **16**.

Entry	R	Compound **16** (yield [%])[a]
1	*i*Pr	**16a** (45)
2	*i*Bu	**16b** (51)
3	*n*Bu	**16c** (30)

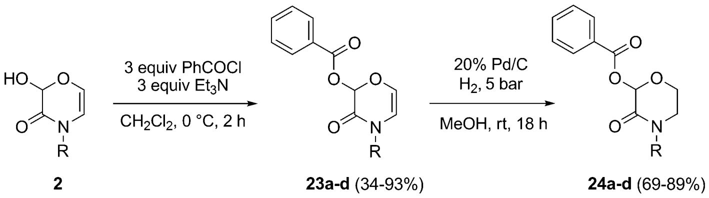
[a] After purification by column chromatography (SiO_2) or recrystallization from EtOAc/hexane (30:1).

To confirm the formation of 1*H*-pyrazin-2-ones **16**, an independent synthesis was performed. Alkylation of 1*H*-pyrazin-2-one **22** by means of 1.1 equivalents of isobutyl bromide and two equivalents of potassium carbonate in acetonitrile heated at reflux afforded the expected 1-isobutyl-1*H*-pyrazin-2-one **16b** in 28 % yield (Scheme 7),[11] which was identical to the compound obtained from 1-isobutyl-2-hydroxy-1,4-oxazin-3-one **2b** (Scheme 6).

To show the capacity of the above-described method to prepare a broad array of oxazin-3-ones and morpholin-3-ones bearing chemical diversity, several functionalities in 2-hydroxy-1,4-oxazin-3-ones **2** were selectively manipulated. In a first approach, the hydroxyl group in the latter heterocycles **2** was protected upon treatment with three equivalents of benzoylchloride in dichloromethane in the presence of triethylamine, furnishing the corresponding 2-benzoyloxy-1,4-oxazin-3-ones **23** after two hours at 0 °C (Scheme 8, Table 4). As morpholine chemistry is of significant importance because of the occurrence of these scaffolds in a large number of biologically active compounds that are useful in different therapeutical areas,[12] the search for new, functional-



Scheme 7. Synthesis of 1-isobutyl-1*H*-pyrazin-2-one **16b** through alkylation of 1*H*-pyrazin-2-one **22**.



Scheme 8. Synthesis of 2-benzoyloxy-1,4-oxazin-3-ones **23** and 2-benzoyloxymorpholin-3-ones **24**.

Table 4. Synthesis of 2-benzoyloxy-1,4-oxazin-3-ones **23** and 2-benzoyloxymorpholin-3-ones **24**.

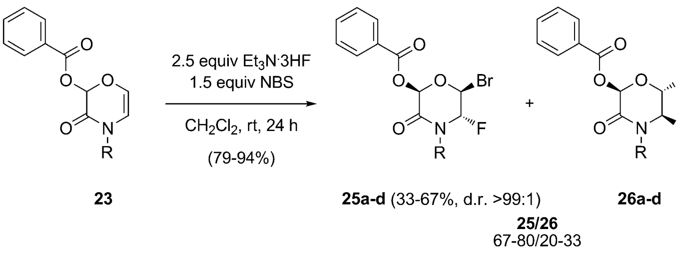
Entry	R	Compound **23** (yield [%])[a]	Compound **24** (yield [%])[a]
1	*i*Pr	**23a** (45)	**24a** (69)
2	*i*Bu	**23b** (64)	**24b** (79)
3	*n*Bu	**23c** (93)	**24c** (82)
4	*c*Hex	**23d** (34)	**24d** (89)

[a] After purification by column chromatography (SiO_2) or recrystallization from EtOAc/hexane (30:1).

ized morpholine derivatives remains a relevant issue in medicinal chemistry. In particular, morpholin-3-one derivatives have attracted considerable interest owing to their biological and pharmacological activity, because they comprise key features in HIV-protease inhibitors,[13] non-peptide ligands with high affinity and selectivity for tachykinin receptors,[14] cornea permeable calpain inhibitors exhibiting anti-cataract properties,[15] A549 lung cancer cell inhibitors,[16] and potassium channel openers useful in the treatment of urinary incontinence.[17] In that respect, the attention was turned to the catalytic hydrogenation of the double bond in 2-benzoyloxy-1,4-oxazin-3-ones **23** to provide an entry to the morpholin-3-one framework. Thus, the latter compounds **23** were converted into the corresponding 2-benzoyloxymorpholin-3-ones **24** in high yields (69–89 %) and purity upon treatment with 20 % (w/w) palladium on activated carbon in methanol at room temperature for 18 hours with 5 bar of hydrogen gas (Scheme 8, Table 4).

The growing interest in organofluorine chemistry and its numerous applications in agrochemistry and pharmaceutical chemistry are a result of the unique physical, chemical, and biological properties of fluorine as a substituent in organic compounds.[18] In that respect, various fluorinated compounds have been successfully used as building blocks in drug design to modulate the bioactivity, pharmacokinetic properties, and therapeutic efficacy, resulting in top-selling fluorinated pharmaceuticals.[19] However, (mono)fluorinated morpholin-3-ones have received only very limited attention in the literature. Nonetheless, incorporation of fluorine can be used to tune the physicochemical properties, and thus we became intrigued as to whether the use of appropriate fluorinating agents could introduce fluorine in a site-selective manner in the above-synthesized heterocyclic compounds. In a first attempt, 2-benzoyloxy-1,4-oxazin-3-ones **23** were smoothly bromofluorinated with 2.5 equivalents of triethylamine trishydrofluoride ($Et_3N{\cdot}3HF$) and 1.5 equivalents of *N*-bromosuccinimide (NBS) in dichloromethane at room temperature for 24 hours, resulting in the regiospecific formation of a diastereomeric mixture of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **25** and **26** through *anti*-addition across the C−C double bond (**25**:**26** = 67–80/20–33, Scheme 9, Table 5).

A detailed spectroscopic analysis of the obtained reaction mixtures revealed that the Br^+-initiated electrophilic-addition across the double bond of 2-benzoyloxy-1,4-oxazin-3-ones **23** proceeded with complete regioselectivity, which was determined based on the experimental coupling pattern in the ^{13}C NMR spectra (Scheme 10), because one carbonyl carbon appeared as a singlet whereas the other clearly coupled with fluorine and appeared as a doublet with a coupling constant between $J = 3.4$ and 3.5 Hz (^{13}C NMR, $CDCl_3$). Since these values are in good agreement with $^3J_{F-C=O}$ coupling constants of 0–3.4 Hz (^{13}C NMR, $CDCl_3$) reported in the literature for C(=O)NCHF-systems,[20] and no $^4J_{F-C=O}$, $^5J_{F-C=O}$, and $^6J_{F-C=O}$ coupling pattern is described for compounds bearing analogous structural subunits,[20a-c,21] the regiospecificity was unambiguously assigned (Scheme 10), pointing to the *N*-acyliminium ion character of the intermediates during the bromofluorination.

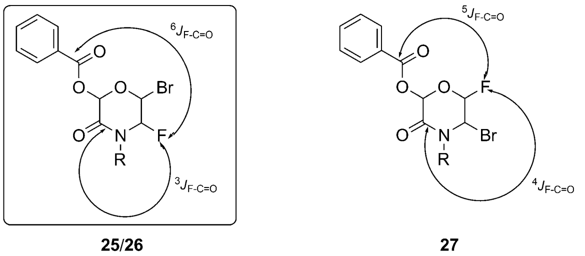


Scheme 9. Synthesis of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **25** and **26**.

Table 5. Synthesis of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **25** and **26**.

Entry	R	Ratio **25**/**26**[a]	Compound **25** (yield [%])[b]
1	*i*Pr	75:25	**25a** (63)
2	*i*Bu	80:20	**25b** (33)
3	*n*Bu	80:20	**25c** (42)
4	*c*Hex	67:33	**25d** (67)

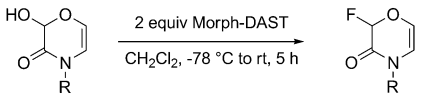
[a] Based on ^{1}H NMR spectroscopic analysis and/or GC of the crude reaction mixture. [b] After purification by column chromatography (SiO_2) or recrystallization from EtOAc/hexane (30:1).



Scheme 10. Possible regioisomers for the bromofluorination of 2-benzoyloxy-1,4-oxazin-3-ones **23**.

The full configuration of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **25** was established by X-ray analysis of 2-benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one **25a** (see the Supporting Information), providing irrefutable proof for the formation of 2,6-*cis*-2-benzoyloxy-6-bromomorpholin-3-ones **25** as the major diastereoisomers.

In another strategy to introduce fluorine, selective deoxyfluorination of 2-hydroxy-1,4-oxazin-3-ones **2** was effected in the presence of two equivalents of Morph-DAST in dichloromethane, resulting in a complete conversion toward 2-fluoro-1,4-oxazin-3-ones **28** in 78–94 % yield (Scheme 11, Table 6). The presence of a monofluorinated carbon center was unambiguously assigned based on the coupling constants between the proton and the fluoro atom at C2, because the observed *J* values of 52.7–53.7 Hz (^{1}H NMR, ^{19}F NMR, $CDCl_3$) correspond well with those reported in the literature (J = 50–57 Hz, ^{1}H NMR, $CDCl_3$).[22] Also, the ^{13}C NMR spectra revealed a coupling between the carbon and the fluorine at the C2 position, characterized by *J* values of between 233.1 and 234.2 Hz (^{13}C NMR, $CDCl_3$). These results are in good accordance with ^{13}C NMR data ($CDCl_3$) reported in the literature for compounds bearing similar structural subunits.[22b,23]



2 **28a-d** (78-94%)

Scheme 11. Synthesis of 2-fluoro-1,4-oxazin-3-ones **28**.

Table 6. Synthesis of 2-fluoro-1,4-oxazin-3-ones **28**.

Entry	R	Compound **28** (yield [%])[a]
1	*i*Pr	**28a** (87)
2	*i*Bu	**28b** (78)
3	*n*Bu	**28c** (94)
4	*c*Hex	**28d** (90)

[a] After purification by column chromatography (SiO_2).

Theoretical rationalization: The proposed reaction mechanism for the ring transformation of 4-formyl-3-hydroxy-β-lactams **7** into 2-hydroxy-1,4-oxazin-3-ones **2** (Scheme 4) was further investigated by means of DFT calculations. Moreover, the difference in reactivity between β-lactams **7** and 4-formyl-3-methoxy-β-lactams **3** (Scheme 1, R = Me), which do not rearrange into six-membered heterocycles under the same reaction conditions, was investigated.

The B3LYP/6-31+G(d,p) level of theory was used for geometry optimizations.[24] Stationary points were characterized as minima (ground states) or first-order saddle points (transition states) by normal modes analysis. IRC (intrinsic reaction coordinate) calculations[25] followed by full geometry optimizations were used to verify the corresponding reactants (or reactant complexes) and products (or product complexes). The B3LYP functional has been proven to produce good geometries but is less accurate for energy calculations.[26] Therefore energies were refined with the recently developed M06-2X[27] functional, which is able to account for dispersion effects, and a 6-31+G(d,p) basis set. The effect of the solvent environment was taken into account by means of a continuum model,[28] however, due to the low dielectric constant of the solvent (dichloromethane $\varepsilon = 8.93$) the effect is expected to be small. Thermal free-energy corrections were taken from B3LYP/6-31+G(d,p) optimizations at 1 atm and 298 K. All computations were carried out with the Gaussian 09 program package.[29]

Ring transformation without assistance of a second β-lactam: The first step in the proposed transformation of β-lactams **7** to oxazin-3-ones **2** is the ring opening of the β-lactam nucleus (Scheme 4, R = Me). This ring opening could give rise to an unstable zwitterionic species **8**, which is easily converted to intermediate **9** by a proton transfer. However, a concerted reaction mechanism in which β-lactam **7** is directly converted to intermediate **9** was found more plausible. Indeed, the Gibbs free energy of activation ($\Delta G^{\neq}$) for the β-lactam ring opening involving a simultaneous proton transfer is 35.6 kJ mol^{-1} lower in energy than that for the formation of the zwitterionic intermediate **8** (Figure 1, **TS(7–9)** and **TS(7–8)**, respectively). The subsequent ring closure of intermediate **9** toward oxazin-3-one **2**, which also involves a simultaneous proton transfer, has a relatively high Gibbs free energy of activation ($\Delta G^{\neq} = 145.6$ kJ mol^{-1}), indicating this model might be inappropriate to represent the system. Finally, a concerted reaction mechanism in which β-lactam **7** is directly converted to oxazin-3-one **2** by simultaneous ring opening and ring closure was considered. The Gibbs free energy of activation for this conversion was found to be higher than that for the conversion of β-lactam **7** to intermediate **9** or zwitterionic intermediate **8** and therefore seems very unlikely.

As mentioned earlier, this ring transformation is not observed for β-lactam substrates bearing an alkoxy or phenoxy group instead of a hydroxyl group at the C3 position. For comparative purposes, the hypothetical ring transformation of 4-formyl-3-methoxy-β-lactam **3** (R = Me, R′ = Me) to 2-methoxy-1,4-oxazin-3-one **30** was investigated as well (see Figure S1 in the Supporting Information). The reaction mechanism with the ring opening of the β-lactam **3** to an unstable zwitterionic species **29** has a free energy of activation of 138.4 kJ mol^{-1}, which is higher than the earlier proposed mechanism for compound **7**. Moreover, if this relatively high Gibbs free energy of activation would be overcome, the formed (yet very unstable species) **29** will readily go back to β-lactam **3** instead of reacting further to the oxazin-3-one **30** ($\Delta G^{\neq} = 0.9$ kJ mol^{-1} and 105.4 kJ mol^{-1}, respectively). Furthermore, the concerted reaction mechanism in which β-lactam **3** is directly converted to oxazin-3-one **30** has a high Gibbs free energy of activation ($\Delta G^{\neq} = 167.0$ kJ mol^{-1}).

Ring transformation with assistance of a second β-lactam: To make the model more realistic, a second β-lactam was added to the system. All barriers were brought down by β-lactam assistance (Figure 2). In case of proton transfer, the

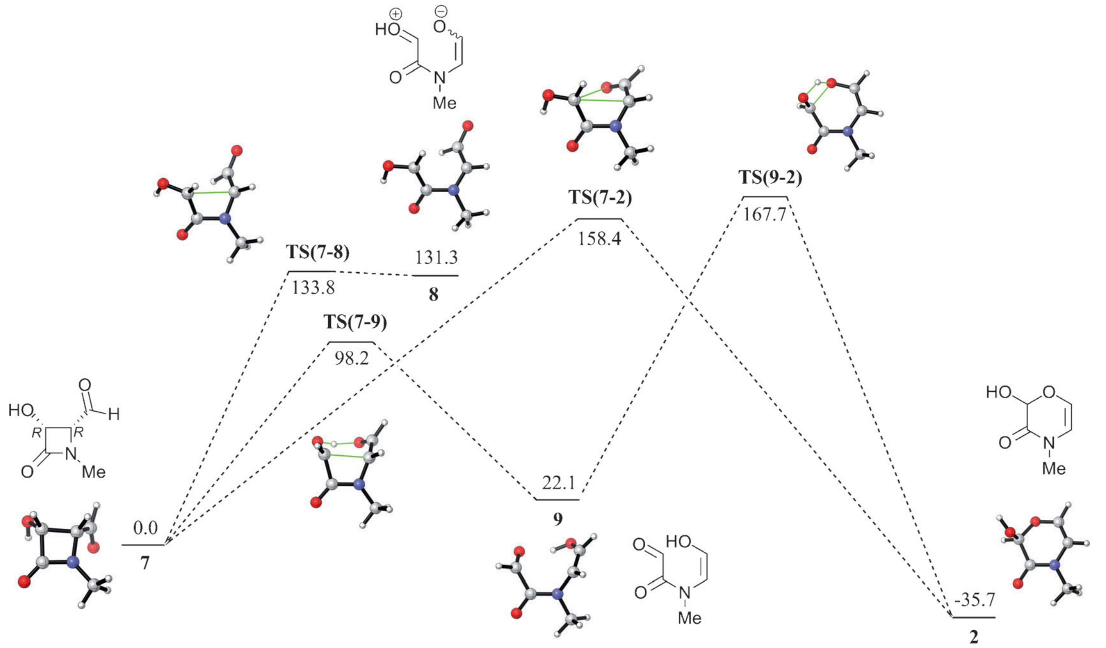


Figure 1. Gibbs free energy profile for the ring transformation of 4-formyl-3-hydroxy-β-lactams **7** to 2-hydroxy-1,4-oxazin-3-ones **2**, without assistance of a second β-lactam.

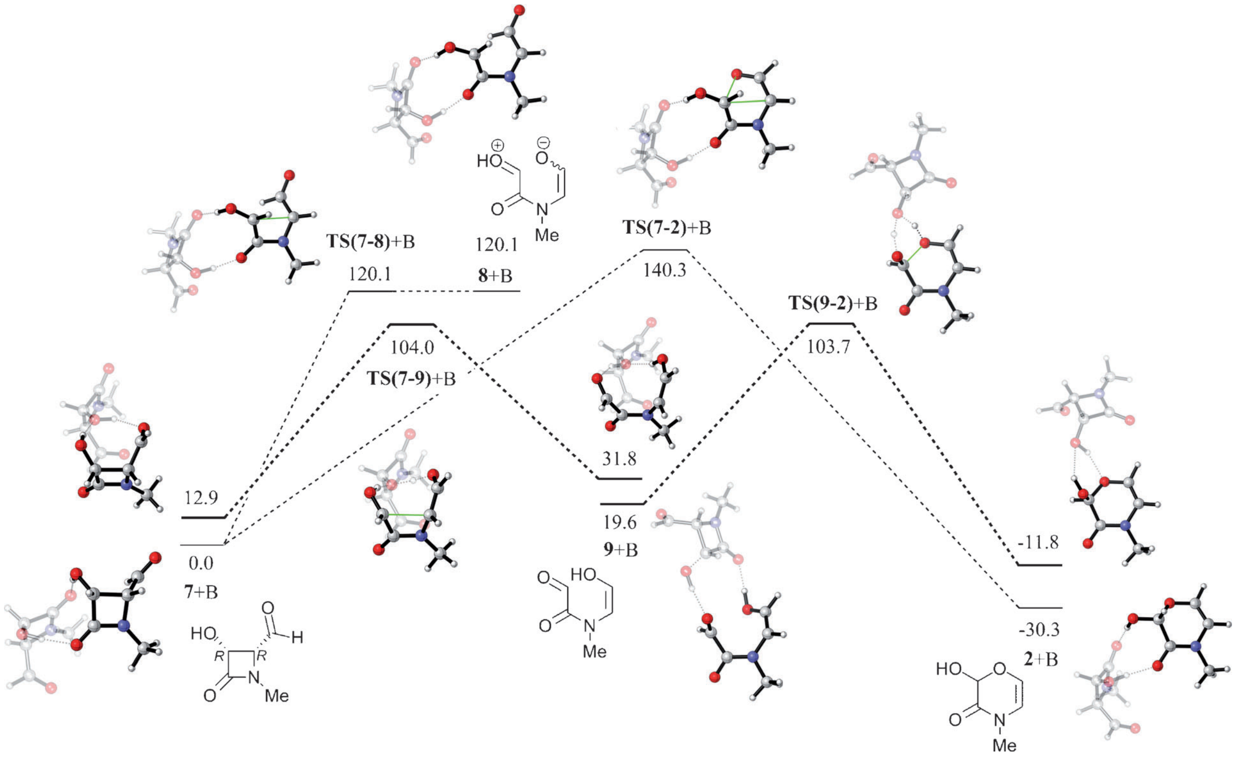


Figure 2. Gibbs free energy profile for the ring transformation of 4-formyl-3-hydroxy-β-lactams **7** to 2-hydroxy-1,4-oxazin-3-ones **2**, with assistance of a second β-lactam.

hydroxyl group of the second β-lactam acts as a proton conduit, accepting the proton from the first β-lactam and donating its own. If no proton transfer takes place, the second β-lactam stabilizes transition states and reactants due to intermolecular H-bonds. The reaction mechanism proposed for compound **7**, ring opening to intermediate **9** and subsequent ring closure of intermediate **9** toward oxazin-3-one **2** with simultaneous proton transfer in both steps, was found to be most plausible. Indeed, the Gibbs free energy of activation for the β-lactam ring opening with a simultaneous proton transfer is lower in energy than that for the ring opening with formation of the zwitterionic intermediate **8** and for the simultaneous ring opening and ring closure ($\Delta G^{\neq}=91.1$, 120.1 and 140.3 kJ mol^{-1} for **TS(7–9)** + B, **TS(7–8)** + B and **TS(7–2)** + B, respectively). Moreover, the Gibbs free energy of activation for the subsequent ring closure of intermediate **9** with a simultaneous proton transfer was brought down significantly ($\Delta G^{\neq}=145.6$ kJ mol^{-1} for **TS(9–2)** and 84.1 kJ mol^{-1} for **TS(9–2)** + B, Figures 1 and 2, respectively), demonstrating the need for the assistance of a second β-lactam for the reaction to proceed.

Thus, the transformation of 4-formyl-3-hydroxy-β-lactams **7** into 2-hydroxy-1,4-oxazin-3-ones **2** is facilitated by the proton transfer of the hydroxyl group and assistance of the hydroxyl group of a second β-lactam. Both mechanisms are not feasible for the β-lactam substrates bearing an alkoxy or phenoxy group.

Conclusion

For the first time, 2-hydroxy-1,4-oxazin-3-ones were prepared through ring transformation of the corresponding 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams involving an unexpected C3–C4 bond cleavage of the β-lactam nucleus in the intermediate 4-formyl-3-hydroxy-β-lactams, followed by a ring expansion. Furthermore, the synthetic applicability of these new oxazin-3-one derivatives was demonstrated by means of their transformation into the biologically relevant classes of substituted oxazin-3-ones, morpholin-3-ones, and pyrazinones. This comprises the first report on the full and selective conversion of β-lactam scaffolds into 1,4-oxazin-3-ones in high yields and purity. In addition to the experimental results, the rationale of this new ring-expansion reaction was further validated by means of DFT calculations.

Experimental Section

General: ^{1}H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+). ^{19}F NMR spectra were recorded at 282 MHz (JEOL ECLIPSE+). Mass spectra were obtained with a mass spectrometer (70 eV) by using a GC-MS coupling (20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or were recorded using a direct inlet system (electron spray, 4000 V). High resolution electron spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight. IR spectra were recorded on a Perkin-Elemer Spectrum BX FT-IR spectrometer. All compounds were analyzed in neat form with an ATR (Attenuated Total Reflectance) accessory. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Elemental analyses were obtained by means of a Perkin-Elmer 2400 Series II apparatus. Dichloromethane was distilled over calcium hydride, while diethyl ether and THF were distilled from sodium and sodium benzophenone ketyl before use. Other solvents were used as received from the supplier.

General procedure for the synthesis of (*E*)-*N*-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amines 5: $MgSO_4$ (20 mmol) and the appropriate amine (10 mmol) were added to a solution of (*R*)-glyceraldehyde acetonide **4** (10 mmol) in anhydrous CH_2Cl_2 (40 mL). After stirring for 2 h at room temperature, $MgSO_4$ was removed by filtration. Evaporation of the solvent in vacuo afforded imine **5** in high purity (>95 % based on ^{1}H NMR spectroscopy), which was used as such in the next reaction step due to its hydrolytic instability (no HRMS data could be obtained).

(*E*)-*N*-Isobutyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine (5b): $[\alpha]_{D}^{20}=+60.9$ ($c=1.5$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.90$ and 0.91 (2×d, $J=6.8$ Hz, 2×3H), 1.41 and 1.46 (2×s, 2×3H), 1.91 (nonet, $J=6.8$ Hz, 1H), 3.19–3.30 (m, 2H), 3.92 and 4.21 (2×(d×d), $J=8.4$ Hz, 6.3 Hz, 6.1 Hz, 2×1H), 4.58 (d×d×d, $J=6.3$ Hz, 6.1 Hz, 5.4 Hz, 1H), 7.61 ppm (d, $J=5.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=20.3$ (2×CH_3), 25.3 (CH_3), 26.4 (CH_3), 29.0 (CH), 67.2 (CH_2), 68.9 (CH_2), 76.8 (CH), 109.8 (C), 162.9 ppm (CH); IR (ATR): $\tilde{\nu}=1674$ cm $^{-1}$ (C=N); MS (70 eV): *m/z* (%): 186 (100) [M^{+}+H].

(*E*)-*N*-Butyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine (5c): $[\alpha]_{D}^{20}=+61.3$ ($c=2.0$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.92$ (t, $J=7.2$ Hz, 3H), 1.32 (sextet, $J=7.2$ Hz, 2H), 1.40 and 1.46 (2×s, 2×3H), 1.59 (pentet, $J=7.2$ Hz, 2H), 3.42 (t, $J=7.2$ Hz, 2H), 3.91 and 4.20 (2×(d×d), $J=8.5$ Hz, 6.5 Hz, 6.2 Hz, 2×1H), 4.57 (d×d×d, $J=6.5$, 6.2, 5.5 Hz, 1H), 7.63 ppm (d×t, $J=5.5$, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=13.6$ (CH_3), 20.1 (CH_2), 25.2 (CH_3), 26.3 (CH_3), 32.4 (CH_2), 60.5 (CH_2), 67.1 (CH_2), 76.8 (CH), 109.7 (C), 162.5 ppm (CH); IR (ATR): $\tilde{\nu}=1673$ cm^{-1} (C=N); MS (70 eV): *m/z* (%): 186 (100) [M^{+}+H].

(*E*)-*N*-Cyclohexyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine (5d): $[\alpha]_{D}^{20}=+55.4$ ($c=1.6$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.13$–1.51 (m, 5H), 1.40 and 1.46 (2×s, 2×3H), 1.59–1.80 (m, 5H), 2.97–3.07 (m, 1H), 3.88 and 4.20 (2×(d×d), $J=8.3$, 6.3, 6.3 Hz, 2×1H), 4.55 (d×d×d, $J=6.3$, 6.3, 5.7 Hz, 1H), 7.65 ppm (d, $J=5.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=24.3$ (2×CH_3), 25.2 (CH_2), 25.3 (CH_2), 26.2 (CH_2), 33.7 (CH_2), 33.9 (CH_2), 67.1 (CH_2), 68.8 (CH), 76.8 (CH), 109.6 (C), 160.4 (CH) ppm; IR (ATR): $\tilde{\nu}=1672$ cm^{-1} (C=N); MS (70 eV): *m/z* (%): 212 (100) [M^{+}+H].

(*E*)-*N*-[((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methylidene]propylamine (5e): $[\alpha]_{D}^{20}=+70.7$ ($c=1.6$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.90$ (t, $J=7.2$ Hz, 3H), 1.41 and 1.46 (2×s, 2×3H), 1.63 (sextet, $J=7.2$ Hz, 2H), 3.39 (t, $J=7.2$ Hz, 2H), 3.92 and 4.20 (2×(d×d), $J=8.2$ Hz, 6.5 Hz, 6.4 Hz, 2×1H), 4.57 (d×d×d, $J=6.5$, 6.4, 5.5 Hz, 1H), 7.63 ppm (d×t, $J=5.5$, 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=11.5$ (CH_3), 23.4 (CH_2), 25.3 (CH_3), 26.3 (CH_3), 62.6 (CH_2), 67.2 (CH_2), 76.8 (CH), 109.8 (C), 162.7 ppm (CH); IR (ATR): ν<Ü=>= 1673 cm^{-1} (C=N); MS (70 eV): *m/z* (%): 172 (100) [M^{+}+H].

(*E*)-*N*-Isopentyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine (5f): $[\alpha]_{D}^{20}=+69.7$ ($c=1.6$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.91$ (d, $J=7.7$ Hz, 6H), 1.40 and 1.46 (2×s, 2×3H), 1.48 (q, $J=7.7$ Hz, 2H), 1.61 (nonet, $J=7.7$ Hz, 1H), 3.43 (t, $J=7.7$ Hz, 2H), 3.91 and 4.20 (2×(d×d), $J=8.0$, 6.9, 6.4 Hz, 2×1H), 4.56 (d×d×d, $J=$ 6.9, 6.4, 5.2 Hz, 1H), 7.64 ppm (d, $J=5.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=22.3$ (2×CH_3), 25.3 (CH_3), 25.6 (CH), 26.3 (CH_3), 39.4 (CH_2), 59.0 (CH_2), 67.2 (CH_2), 76.8 (CH), 109.8 (C), 162.5 ppm (CH); IR (ATR): $\tilde{\nu}=1673$ cm^{-1} (C=N); MS (70 eV): *m/z* (%): 200 (100) [M^{+}+H].

General procedure for the synthesis of (3*R*,4*S*)-3-benzyloxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones 6: A solution of benzyloxyacetyl chloride (13 mmol) in CH_2Cl_2 (25 mL) was added dropwise to an ice-cooled solution of imine **5** (10 mmol) and triethylamine (30 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at room temperature for 15 h and was then washed with water (50 mL). Subsequently, the aqueous phase was extracted with CH_2Cl_2 (3×30 mL), after which the combined organic fractions were dried over $MgSO_4$, followed by removal of the drying agent by filtration. After evaporation of the solvent in vacuo, the crude reaction mixture was purified by means of column chromatography on silica gel or recrystallization, affording pure (3*R*,4*S*)-3-benzyloxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one **6**.

(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (6a): TLC $R_f=0.12$ (EtOAc/hexane 1:6); $[\alpha]_{D}^{20}=+102.8$ ($c=1.0$ in CH_2Cl_2), *de*: 82 %; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.29$ (d, $J=6.7$ Hz, 6H), 1.34 and 1.44 (2×s, 2×3H), 3.62 (d×d, $J=8.2$, 6.1 Hz, 1H), 3.69 (d×d, $J=8.8$, 5.0 Hz, 1H), 3.92 (septet, $J=6.7$ Hz, 1H), 4.16–4.30 (m, 2H), 4.54 (d, $J=5.0$ Hz, 1H), 4.64 and 4.92 (2×d, $J=$

11.9 Hz, 2×1H), 7.28–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=19.5 (CH$_3$), 21.3 (CH$_3$), 25.2 (CH$_3$), 26.8 (CH$_3$), 44.4 (CH), 59.8 (CH), 66.9 (CH$_2$), 72.8 (CH$_2$), 77.2 (CH), 79.6 (CH), 109.3 (C), 127.8 (CH), 128.0 (CH), 128.5 (CH), 137.1 (C), 166.8 ppm (C); IR (ATR): $\tilde{\nu}$= 1747 cm^{-1} (C=O); MS (70 eV): m/z (%): 320 (100) [M^++H]; HRMS (ESI) calcd for $C_{18}H_{26}NO_4$: 320.1862 [M+H]$^+$; found: 320.1867.

(3*R*,4*S*)-3-Benzyloxy-1-isobutyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (6b): M.p. 103.5 °C; TLC R_f=0.22 (EtOAc/hexane 1:6); $[\alpha]_D^{20}$= +96.9 (c=0.4 in CH$_2$Cl$_2$), *de*: 85%; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.88 and 0.93 (2×d, J=7.2 Hz, 2×3H), 1.33 and 1.42 (2×s, 2×3H), 1.92–2.09 (m, 1H), 3.07 and 3.23 (2×(d×d), J=13.6, 8.3, 6.3 Hz, 2×1H), 3.63 (d×d, J=8.8, 6.3 Hz, 1H), 3.66 (d×d, J=8.8, 5.0 Hz, 1H), 4.15 (d×d, J=8.8 Hz, 6.3 Hz, 1H), 4.32 (d×t, J=8.8 Hz, 6.3 Hz, 1H), 4.62 (d, J=5.0 Hz, 1H), 4.64 and 4.92 (2×d, J=11.8 Hz, 2×1H), 7.28–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=20.2 (CH$_3$), 20.4 (CH$_3$), 25.1 (CH$_3$), 26.8 (CH$_3$), 27.0 (CH), 48.7 (CH$_2$), 60.8 (CH), 66.7 (CH$_2$), 72.6 (CH$_2$), 77.2 (CH), 80.3 (CH), 109.3 (C), 127.7 (CH), 127.9 (CH), 128.4 (CH), 137.2 (C), 167.6 ppm (C); IR (ATR): $\tilde{\nu}$=1737 cm^{-1} (C=O); MS (70 eV): m/z (%): 334 (100) [M^++H]; elemental analysis calcd (%) for $C_{19}H_{27}NO_4$: C 68.44, H 8.16, N 4.20; found: C 68.70, H 8.10, N 4.32.

(3*R*,4*S*)-3-Benzyloxy-1-butyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (6c): M.p. 98.8 °C; recrystallization from ethanol; $[\alpha]_D^{20}$= +96.7 (c=0.5 in CH$_2$Cl$_2$), *de*: 85%; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.92 (t, J=7.3 Hz, 3H), 1.32 (sextet, J=7.3 Hz, 2H), 1.33 and 1.43 (2×s, 2×3H), 1.47–1.66 (m, 2H), 3.21 (d×t, J=13.8, 7.0 Hz, 1H), 3.44 (d×t, J= 13.8, 7.0 Hz, 1H), 3.63 (d×d, J=8.2, 6.5 Hz, 1H), 3.64 (d×d, J=8.8, 4.9 Hz, 1H), 4.15 (d×d, J=8.2, 6.5 Hz, 1H), 4.31 (d×t, J=8.8, 6.5 Hz, 1H), 4.59 (d, J=4.9 Hz, 1H), 4.63 and 4.91 (2×d, J=11.6 Hz, 2×1H), 7.29–7.37 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=13.7 (CH$_3$), 20.2 (CH$_2$), 25.2 (CH$_3$), 26.9 (CH$_3$), 29.5 (CH$_2$), 41.0 (CH$_2$), 60.4 (CH), 66.9 (CH$_2$), 72.9 (CH$_2$), 77.2 (CH), 80.3 (CH), 109.6 (C), 127.9 (CH), 128.1 (CH), 128.6 (CH), 137.1 (C), 167.7 ppm (C); IR (ATR): $\tilde{\nu}$= 1729 cm^{-1} (C=O); MS (70 eV): m/z (%): 334 (100) [M^++H]; elemental analysis calcd (%) for $C_{19}H_{27}NO_4$: C 68.44, H 8.16, N 4.20; found: C 68.60, H 7.94, N 4.25.

(3*R*,4*S*)-3-Benzyloxy-1-cyclohexyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (6d): M.p. 99.8 °C; recrystallization from ethanol; $[\alpha]_D^{20}$= +109.9 (c=1.0, CH$_2$Cl$_2$), *de*: 87%; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=1.08–1.51 (m, 3H), 1.34 and 1.44 (2×s, 2×3H), 1.60–1.88 (m, 7H), 3.44–3.56 (m, 1H), 3.62 (d×d, J=8.4, 6.0 Hz, 1H), 3.69 (d×d, J= 8.5, 4.8 Hz, 1H), 4.18 (d×d, J=8.4, 6.3 Hz, 1H), 4.20–4.29 (m, 1H), 4.53 (d, J=4.8 Hz, 1H), 4.63 and 4.92 (2×d, J=11.9 Hz, 2×1H), 7.28–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=25.16 (CH$_3$), 25.21 (CH$_2$), 25.4 (CH$_2$), 26.8 (CH$_3$), 29.8 (CH$_2$), 31.1 (CH$_2$), 52.4 (CH), 60.0 (CH), 67.0 (CH$_2$), 72.8 (CH$_2$), 77.2 (CH), 79.6 (CH), 109.4 (C), 127.8 (CH), 128.0 (CH), 128.5 (CH), 137.1 (C), 167.0 ppm (C); IR (ATR): $\tilde{\nu}$= 1724 cm^{-1} (C=O); MS (70 eV): m/z (%): 360 (100) [M^++H]; elemental analysis calcd (%) for $C_{21}H_{29}NO_4$: C 70.17, H 8.13, N 3.90; found: C 70.07, H 7.85, N 3.86.

(3*R*,4*S*)-3-Benzyloxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-propylazetidin-2-one (6e): TLC R_f=0.12 (EtOAc/hexane 1:6); $[\alpha]_D^{20}$= +95.1 (c= 1.0 in CH$_2$Cl$_2$), *de*: 90%; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.91 (t, J=7.4 Hz, 3H), 1.34 and 1.43 (2×s, 2×3H), 1.50–1.75 (m, 2H), 3.15–3.24 and 3.34–3.43 (2×m, 2×1H), 3.63 (d×d, J=8.8, 6.1 Hz, 1H), 3.65 (d×d, J=8.8, 5.0 Hz, 1H), 4.15 (d×d, J=8.8, 6.1 Hz, 1H), 4.31 (d×t, J=8.8, 6.1 Hz, 1H), 4.60 (d, J=5.0 Hz, 1H), 4.64 and 4.92 (2×d, J=12.1 Hz, 2×1H), 7.27–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=11.5 (CH$_3$), 20.8 (CH$_2$), 25.1 (CH$_3$), 26.8 (CH$_3$), 42.8 (CH$_2$), 60.4 (CH), 66.8 (CH$_2$), 72.7 (CH$_2$), 77.2 (CH), 80.4 (CH), 109.3 (C), 127.7 (CH), 127.9 (CH), 128.5 (CH), 137.2 (C), 167.4 ppm (C); IR (ATR): $\tilde{\nu}$=1751 cm^{-1} (C=O); MS (70 eV): m/z (%): 320 (100) [M^++H]; HRMS (ESI) calcd for $C_{18}H_{26}NO_4$: 320.1862 [M+H]$^+$; found: 320.1869.

(3*R*,4*S*)-3-Benzyloxy-1-isopentyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (6 f): M.p. 93.9 °C; recrystallization from ethanol; $[\alpha]_D^{20}$= + 106.6 (c=0.9 in CH$_2$Cl$_2$), *de*: 88%; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.91 (d, J=6.1 Hz, 6H), 1.34 and 1.43 (2×s, 2×3H), 1.39–1.58 (m, 3H), 3.21 (d×d×d, J=14.3, 6.7, 6.7 Hz, 1H), 3.48 (d×d×d, J=14.3, 7.0, 7.0 Hz, 1H), 3.62–3.66 (m, 2H), 4.15 (d×d, J=7.7, 7.7 Hz, 1H), 4.31 (d×d×d, J=7.7, 7.6, 7.6 Hz, 1H), 4.58 (d, J=5.0 Hz, 1H), 4.63 and 4.91 (2×d, J=11.6 Hz, 2×1H), 7.30–7.36 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=22.3 (CH$_3$), 22.5 (CH$_3$), 25.2 (CH$_3$), 25.9 (CH), 26.9 (CH$_3$), 36.1 (CH$_2$), 39.6 (CH$_2$), 60.2 (CH), 66.9 (CH$_2$), 72.9 (CH$_2$), 77.2 (CH), 80.2 (CH), 109.6 (C), 127.9 (CH), 128.1 (CH), 128.6 (CH), 137.1 (C), 167.6 ppm (C); IR (ATR): $\tilde{\nu}$=1727 cm^{-1} (C=O); MS (70 eV): m/z (%): 348 (100) [M^++H]; elemental analysis calcd (%) for $C_{20}H_{29}NO_4$: C 69.14, H 8.41, N 4.03; found: C 69.16, H 8.44, N 4.01.

General procedure for the synthesis of (3*R*,4*S*)-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-ones 1: *p*TsOH·H$_2$O (10 mmol) was added in a single portion to a solution of (3*R*,4*S*)-3-benzyloxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one **6** (10 mmol) in THF/H$_2$O (1:1, 100 mL). After heating at reflux for 4 h, the resulting reaction mixture was allowed to cool to room temperature and was then neutralized with solid NaHCO$_3$. The mixture was extracted with EtOAc (3×40 mL), the organic layer was dried (MgSO$_4$), and the solvent was removed under reduced pressure. In the next step, palladium on activated carbon (20% w/w) was added to a solution of the latter diol (10 mmol) in methanol (60 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 for 18 h at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite and evaporation of the solvent in vacuo afforded crude (3*R*,4*S*)-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-one **1**, which was purified by means of column chromatography on silica gel or recrystallization.

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropylazetidin-2-one (1a): M.p. 85.0 °C; recrystallization from EtOAc/hexane (30:1); $[\alpha]_D^{20}$= + 171.5 (c=0. 8 in MeOH); ^{1}H NMR (300 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ= 1.16 and 1.23 (2×d, J=6.7 Hz, 2×3H), 3.29–3.36 (m, 1H), 3.46–3.60 (m, 3H), 3.66 (septet, J=6.7 Hz, 1H), 4.53 (d×d, J=7.7, 4.4 Hz, 1H), 4.57 (t, J=5.5 Hz, 1H), 4.77 (d, J=5.5 Hz, 1H), 5.91 ppm (d, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ=20.5 (CH$_3$), 21.8 (CH$_3$), 45.2 (CH), 59.6 (CH), 63.7 (CH$_2$), 72.5 (CH), 74.5 (CH), 169.0 ppm (C); IR (ATR): $\tilde{\nu}$=3237 (OH), 1706 cm^{-1} (C=O); MS (70 eV): m/z (%): 190 (100) [M^++H]; elemental analysis calcd (%) for $C_8H_{15}NO_4$: C 50.78, H 7.99, N 7.40; found: C 51.00, H 7.91, N 7.53.

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isobutylazetidin-2-one (1b): M.p. 98.3 °C; recrystallization from EtOAc/hexane (30:1); $[\alpha]_D^{20}$= + 152.8 (c=0.9 in MeOH); ^{1}H NMR (300 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ= 0.76 and 0.82 (2×d, J=7.1 Hz, 2×3H), 1.94 (nonet, J=7.1 Hz, 1H), 2.98 and 3.01 (2×(d×d), J=13.6, 7.1 Hz, 2×1H), 3.28–3.36 (m, 1H), 3.46 (d×d×d, J=11.0, 5.7, 3.9 Hz, 1H), 3.51 (d×d, J=8.3, 5.0 Hz, 1H), 3.60–3.68 (m, 1H), 4.56 (t, J=5.7 Hz, 1H), 4.65 (d×d, J=7.7, 5.0 Hz, 1H), 4.75 (d, J=5.5 Hz, 1H), 5.92 ppm (d, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$]-(CH$_3$)$_2$SO, 25 °C): δ=20.5 (CH$_3$), 20.9 (CH$_3$), 26.8 (CH), 49.0 (CH$_2$), 59.8 (CH), 63.7 (CH$_2$), 72.7 (CH), 75.0 (CH), 169.8 ppm (C); IR (ATR): $\tilde{\nu}$= 3284 (OH), 1712 cm^{-1} (C=O); MS (70 eV): m/z (%): 204 (100) [M^++H]; elemental analysis calcd (%) for $C_9H_{17}NO_4$: C 53.19, H 8.43, N 6.89; found: C 53.37, H 8.13, N 6.49.

(3*R*,4*S*)-1-Butyl-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-one (1c): TLC R_f=0.06 (EtOAc); $[\alpha]_D^{20}$= +185.6 (c=0.7, MeOH); ^{1}H NMR (300 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ=0.84 (t, J=7.4 Hz, 3H), 1.12–1.29 (m, 2H), 1.47 (pentet, J=7.3 Hz, 2H), 3.05–3.16 (m, 1H), 3.22–3.37 (m, 2H), 3.46 (d×d×d, J=11.1, 5.5, 3.4 Hz, 1H), 3.50 (d×d, J=8.6, 4.7 Hz, 1H), 3.59–3.67 (m, 1H), 4.60 (t, J=5.5 Hz, 1H), 4.61 (d×d, J=7.6, 4.7 Hz, 1H), 4.80 (d, J=5.5 Hz, 1H), 5.93 ppm (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ=14.1 (CH$_3$), 20.1 (CH$_2$), 29.5 (CH$_2$), 40.9 (CH$_2$), 59.4 (CH), 63.7 (CH$_2$), 72.7 (CH), 75.0 (CH), 169.6 ppm (C); IR (ATR): $\tilde{\nu}$=3330 (OH), 1719 cm^{-1} (C=O); MS (70 eV): m/z (%): 204 (100) [M^++H]; HRMS (ESI) calcd for $C_9H_{18}NO_4$: 204.1236 [M+H]$^+$; found: 204.1232.

(3*R*,4*S*)-1-Cyclohexyl-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-one (1d): M.p. 101.3 °C; recrystallization from EtOAc/hexane (30:1); $[\alpha]_D^{20}$= +218.3 (c=0.6 in MeOH); ^{1}H NMR (300 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ=0.97–1.22 and 1.49–1.85 (2×m, 3H and 7H), 3.19–3.28 (m, 1H), 3.32 (d×d, J=11.3, 5.8 Hz, 1H), 3.44–3.61 (m, 3H), 4.52 (d×d, J= 7.7, 5.0 Hz, 1H), 4.58 (t, J=5.8 Hz, 1H), 4.76 (d, J=4.9 Hz, 1H), 5.91 ppm (d, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ=25.3 (CH$_2$), 25.6 (CH$_2$), 25.7 (CH$_2$), 30.5 (CH$_2$), 31.2 (CH$_2$), 53.3 (CH), 59.4 (CH), 63.7 (CH$_2$), 72.6 (CH), 74.4 (CH), 169.0 ppm (C); IR (ATR): $\tilde{\nu}$=3197 (OH), 1704 cm^{-1} (C=O); MS (70 eV): *m/z* (%): 230 (100) [M^++H]; elemental analysis calcd (%) for $C_{11}H_{19}NO_4$: C 57.62, H 8.35, N 6.11; found: C 57.34, H 8.15, N 5.98.

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-propylazetidin-2-one (1e): TLC R_f=0.08 (EtOAc); $[\alpha]_D^{20}$=+229.6 (c=0.6, MeOH); ^{1}H NMR (300 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ=0.79 (t, J=7.4 Hz, 3H), 1.40–1.60 (m, 2H), 3.04–3.12 and 3.15–3.26 (2×m, 2×1H), 3.27–3.36 (m, 1H), 3.47 (d×d×d, J=11.0, 5.5, 3.3 Hz, 1H), 3.50 (d×d, J=8.3, 4.7 Hz, 1H), 3.59–3.67 (m, 1H), 4.57 (t, J=5.5 Hz, 1H), 4.62 (d×d, J=7.7, 4.7 Hz, 1H), 4.77 (d, J=5.5 Hz, 1H), 5.92 ppm (d, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$](CH$_3$)$_2$SO, 25 °C): δ=11.9 (CH$_3$), 20.8 (CH$_2$), 43.1 (CH$_2$), 59.4 (CH), 63.7 (CH$_2$), 72.6 (CH), 75.0 (CH), 169.7 ppm (C); IR (ATR): $\tilde{\nu}$=3319 (OH), 1719 cm^{-1} (C=O); MS (70 eV): *m/z* (%): 190 (100) [M^++H]; HRMS (ESI) calcd for $C_8H_{16}NO_4$: 190.1079 [M+H]$^+$; found: 190.1077.

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopentylazetidin-2-one (1f): TLC R_f=0.07 (EtOAc); $[\alpha]_D^{20}$=+163.9 (c=0.5 in MeOH); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.90 (d, J=6.1 Hz, 6H), 1.43–1.59 (m, 3H), 3.10 (d×d×d, J=14.2, 6.9, 6.9 Hz, 1H), 3.57 (d×d×d, J=14.2, 7.5, 7.4 Hz, 1H), 3.65–3.82 (m, 3H), 4.02–4.06 (m, 1H), 4.85 ppm (d, J=4.4 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=22.1 (CH$_3$), 22.5 (CH$_3$), 25.8 (CH), 35.7 (CH$_2$), 40.2 (CH$_2$), 59.4 (CH), 64.1 (CH$_2$), 71.7 (CH), 74.6 (CH), 170.6 (C) ppm; IR (ATR): $\tilde{\nu}$=3326 (OH), 1720 cm^{-1} (C=O); MS (70 eV): *m/z* (%): 218 (100) [M^++H]; HRMS (ESI) calcd for $C_{10}H_{20}NO_4$: 218.1392 [M+H]$^+$; found: 218.1390.

General procedure for the synthesis of 2-hydroxy-1,4-oxazin-3-ones 2: Saturated aqueous sodium hydrogen carbonate (1 mL) was added to a solution of (3*R*,4*S*)-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-one **1** (10 mmol) in dichloromethane (15 mL). Solid sodium periodate (20 mmol) was added over a 10 min period with vigorous stirring, and the reaction was allowed to proceed for 2 h at room temperature. The solid was removed by filtration and the filtrate was washed with water (25 mL), after which the organic fraction was dried over MgSO$_4$, followed by removal of the drying agent by filtration. After evaporation of the solvent in vacuo, the crude reaction mixture was purified by means of column chromatography on silica gel, affording pure 2-hydroxy-1,4-oxazin-3-one **2**.

2-Hydroxy-4-isopropyl-1,4-oxazin-3-one (2a): TLC R_f=0.32 (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=1.22 and 1.24 (2×d, J=6.6 Hz, 2×3H), 4.39 (d, J=4.7 Hz, 1H), 4.74 (septet, J=6.6 Hz, 1H), 5.41 (d, J=4.7 Hz, 1H), 5.78 and 6.24 ppm (2×d, J=4.1 Hz, 2×1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=19.9 (CH$_3$), 20.5 (CH$_3$), 44.5 (CH), 90.6 (CH), 104.8 (CH), 128.3 (CH), 160.6 ppm (C); IR (ATR): $\tilde{\nu}$=3288 (OH), 1671, 1642 cm^{-1} (C=O, C=C); MS (70 eV): *m/z* (%): 158 (100) [M^++H]; HRMS (ESI) calcd for $C_7H_{12}NO_3$: 158.0817 [M+H]$^+$; found: 158.0819.

2-Hydroxy-4-isobutyl-1,4-oxazin-3-one (2b): TLC R_f=0.41 (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.92 and 0.93 (2×d, J=7.2 Hz, 2×3H), 2.00 (nonet, J=7.2 Hz, 1H), 3.31 and 3.37 (2×(d×d), J=13.5, 7.2, 7.2 Hz, 2×1H), 4.72 (d, J=4.7 Hz, 1H), 5.47 (d, J=4.7 Hz, 1H), 5.69 and 6.18 ppm (2×d, J=4.1 Hz, 2×1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=19.8 (2×CH$_3$), 27.6 (CH), 53.1 (CH$_2$), 90.6 (CH), 110.6 (CH), 127.3 (CH), 161.5 ppm (C); IR (ATR): $\tilde{\nu}$=3288 (OH), 1672, 1649 cm^{-1} (C=O, C=C); MS (70 eV): *m/z* (%): 172 (100) [M^++H]; HRMS (ESI) calcd for $C_8H_{14}NO_3$: 172.0974 [M+H]$^+$; found: 172.0971.

4-Butyl-2-hydroxy-1,4-oxazin-3-one (2c): M.p. 85.5 °C; TLC R_f=0.24 (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.93 (t, J=7.2 Hz, 3H), 1.34 (sextet, J=7.2 Hz, 2H), 1.59 (pentet, J=7.2 Hz, 2H), 3.44 and 3.60 (2×(d×t), J=13.7, 7.2 Hz, 2×1H), 5.55 (s, 1H), 5.70 and 6.19 ppm (2×d, J=4.4 Hz, 2×1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=13.8 (CH$_3$), 19.8 (CH$_2$), 30.2 (CH$_2$), 45.9 (CH$_2$), 90.6 (CH), 110.2 (CH), 127.7 (CH), 161.2 ppm (C); IR (ATR): $\tilde{\nu}$=3301 (OH), 1672, 1650 cm^{-1} (C=O, C=C); MS (70 eV): *m/z* (%): 172 (100) [M^++H]; HRMS (ESI) calcd for $C_8H_{14}NO_3$: 172.0974 [M+H]$^+$; found: 172.0965.

4-Cyclohexyl-2-hydroxy-1,4-oxazin-3-one (2d): TLC R_f=0.43 (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=1.05–1.22, 1.33–1.48 and 1.68–1.88 (3×m, 1H, 4H and 5H), 4.25–4.41 (m, 2H), 5.40 (s, 1H), 5.81 and 6.21 ppm (2×d, J=4.4 Hz, 2×1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=25.3 (CH$_2$), 25.5 (CH$_2$), 30.2 (CH$_2$), 30.9 (CH$_2$), 52.2 (CH), 90.6 (CH), 105.7 (CH), 127.9 (CH), 160.7 ppm (C); IR (ATR): $\tilde{\nu}$=3297 (OH), 1671, 1646 cm^{-1} (C=O, C=C); MS (70 eV): *m/z* (%): 198 (100) [M^++H]; HRMS (ESI) calcd for $C_{10}H_{16}NO_3$: 198.1130 [M+H]$^+$; found: 198.1132.

2-Hydroxy-4-isopentyl-1,4-oxazin-3-one (2e): TLC R_f=0.35 (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.94 (d, J=6.6 Hz, 6H), 1.43-1.53 (m, 2H), 1.55-1.68 (m, 1H), 3.45-3.62 (m, 2H), 4.30 (d, J=6.1 Hz, 1H), 5.43 (d, J=6.1 Hz, 1H), 5.71 and 6.19 ppm (2×d, J=4.4 Hz, 2×1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=22.5 (2×CH$_3$), 25.7 (CH), 36.8 (CH$_2$), 44.4 (CH$_2$), 90.6 (CH), 109.9 (CH), 127.7 (CH), 161.1 ppm (C); IR (ATR): $\tilde{\nu}$=3300 (OH), 1671, 1649 cm^{-1} (C=O, C=C); MS (70 eV): *m/z* (%): 186 (100) [M^++H]; HRMS (ESI) calcd for $C_9H_{16}NO_3$: 186.1130 [M + H]$^+$; found: 186.1132.

General procedure for the synthesis of 2-camphanoyloxy-4-isopropyl-1,4-oxazin-3-one 11: Triethylamine (30 mmol) was added dropwise at 0 °C to a solution of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **2a** (10 mmol) and (1*S*)-(−)-camphanic chloride (10 mmol) in dry dichloromethane (50 mL). The mixture was stirred at the same temperature for 2 h, after which the reaction mixture was quenched with a saturated solution of NaHCO$_3$ (30 mL) and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with a solution of 10% aq HCl (2×20 mL) and water (20 mL). Drying (MgSO$_4$), removal of the drying agent by filtration and evaporation of the solvent in vacuo afforded crude 2-camphanoyloxy-4-isopropyl-1,4-oxazin-3-one **11**, which was further purified as a diastereoisomeric mixture by means of recrystallization.

2-Camphanoyloxy-4-isopropyl-1,4-oxazin-3-one (11): M.p. 141.0 °C; recrystallization from EtOAc/hexane (30:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.95, 0.97, 1.03, 1.04, and 1.11 (5×s, 4×3H and 6H), 1.23, 1.25 and 1.27 (3×d, J=6.6 Hz, 6H, 3H and 3H), 1.64–1.75, 1.88–1.98, 2.01–2.10 and 2.37–2.47 (4×m, 4×2H), 4.80 (septet, J=6.6 Hz, 2H), 5.87, 5.89, 6.20 and 6.22 (4×d, J=4.4 Hz, 4×1H), 6.59 and 6.61 ppm (2×s, 2×1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=9.7 (CH$_3$), 16.59 (CH$_3$), 16.62 (CH$_3$), 16.7 (CH$_3$), 20.0 (CH$_3$), 20.51 (CH$_3$), 20.54 (CH$_3$), 29.0 (CH$_2$), 30.5 (CH$_2$), 30.7 (CH$_2$), 44.7 (CH), 44.8 (CH), 54.7 (C), 54.8 (C), 54.9 (C), 88.9 (CH), 89.0 (CH), 90.66 (C), 90.75 (C), 105.8 (CH), 126.9 (CH), 127.0 (CH), 156.3 (C), 166.0 (C), 166.1 (C), 178.0 ppm (C); IR (ATR): $\tilde{\nu}$=1785, 1764, 1747 (OC=O), 1682, 1666 cm^{-1} (NC=O, C=C); MS (70 eV): *m/z* (%): 337 [M^+] (64); 308 (43), 140 (48), 128 (57), 125 (100), 98 (40), 97 (56), 83 (96).

General procedure for the synthesis of 1*H*-pyrazin-2-ones 16: NH$_4$OAc (1.2 mmol) and HOAc (1.0 mL) were added to a solution of 2-hydroxy-1,4-oxazin-3-one **2** (0.1 mmol) in EtOAc (1.0 mL). After heating at reflux for 24 h, the resulting reaction mixture was neutralized with solid NaHCO$_3$, after which EtOAc (10 mL) was added. Subsequently, the reaction mixture was washed with a saturated solution of NaHCO$_3$ (10 mL) and brine (5 mL). Drying (MgSO$_4$), removal of the drying agent by filtration and evaporation of the solvent in vacuo afforded crude 1*H*-pyrazin-2-one **16**, which was further purified by means of column chromatography on silica gel or recrystallization.

1-Isopropyl-1*H*-pyrazin-2-one (16a): M.p. 85.2 °C; recrystallization from EtOAc/hexane (30:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=1.38 (d, J=6.8 Hz, 6H), 5.13 (septet, J=6.8 Hz, 1H), 7.15 (d×d, J=4.4, 1.1 Hz, 1H), 7.37 (d, J=4.4 Hz, 1H), 8.14 ppm (d, J=1.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=21.4 (2×CH$_3$), 46.9 (CH), 124.0 (CH), 124.4 (CH), 149.4 (CH), 155.9 ppm (C); IR (ATR): $\tilde{\nu}$=1660, 1651, 1590 cm^{-1} (C=O, C=N, C=C); MS (70 eV): *m/z* (%): 139 (100) [M^++H]; HRMS (ESI) calcd for $C_7H_{11}N_2O$: 139.0871 [M+H]$^+$; found: 139.0870.

1-Isobutyl-1*H*-pyrazin-2-one (16b): TLC R_f=0.20 (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=0.88 (d, J=7.2 Hz, 6H), 2.10 (nonet, J=7.2 Hz, 1H), 3.64 (d, J=7.2 Hz, 2H), 7.00 (d×d, J=4.4, 1.1 Hz, 1H), 7.23 (d, J=4.4 Hz, 1H), 8.07 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=19.8 (2×CH$_3$), 27.7 (CH), 56.7 (CH$_2$), 123.5 (CH), 129.2 (CH), 149.8 (CH), 156.4 ppm (C); IR (ATR): $\tilde{\nu}$=1649, 1590 cm^{-1} (C=O, C=N, C=C); MS (70 eV): *m/z* (%): 153 (100) $[M^+ + H]$; HRMS (ESI) calcd for $C_8H_{13}N_2O$: 153.1028 $[M+H]^+$; found: 153.1027.

1-Butyl-1*H*-pyrazin-2-one (16c): TLC $R_f = 0.15$ (EtOAc/hexane 1:1); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.97$ (t, $J = 7.4$ Hz, 3H), 1.33–1.45 (m, 2H), 1.69–1.79 (m, 2H), 3.90 (t, $J = 7.4$ Hz, 2H), 7.12 (d×d, $J = 4.4$, 1.1 Hz, 1H), 7.32 (d, $J = 4.4$ Hz, 1H), 8.14 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 13.7$ (CH_3), 19.8 (CH_2), 30.7 (CH_2), 49.3 (CH_2), 123.8 (CH), 128.7 (CH), 149.7 (CH), 156.3 (C) ppm; IR (ATR): $\tilde{\nu} = 1649$, 1590 cm^{-1} (C=O, C=N, C=C); MS (70 eV): *m/z* (%): 153 (100) $[M^+ + H]$; HRMS (ESI) calcd for $C_8H_{13}N_2O$: 153.1028 $[M+H]^+$; found: 153.1027.

General procedure for the synthesis of 2-benzoyloxy-1,4-oxazin-3-ones 23: Triethylamine (30 mmol) was added dropwise at 0 °C to a solution of 2-hydroxy-1,4-oxazin-3-one **2** (10 mmol) and benzoylchloride (30 mmol) in dry dichloromethane (50 mL). The mixture was stirred at the same temperature for 2 h, after which the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (30 mL) and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with an aqueous solution of 10% HCl (2×20 mL) and water (20 mL). Drying ($MgSO_4$), removal of the drying agent by filtration, and evaporation of the solvent in vacuo afforded crude 2-benzoyloxy-1,4-oxazin-3-one **23**, which was further purified by means of column chromatography on silica gel or recrystallization.

2-Benzoyloxy-4-isopropyl-1,4-oxazin-3-one (23a): M.p. 99.3 °C; recrystallization from EtOAc/hexane (30:1); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.26$ and 1.32 (2×d, $J = 6.8$ Hz, 2×3H), 4.89 (septet, $J = 6.8$ Hz, 1H), 5.90 and 6.23 (2×d, $J = 4.7$ Hz, 2×1H), 6.72 (s, 1H), 7.42–7.47, 7.56–7.62 and 8.00–8.03 ppm (3×m, 2H, 1H and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 20.2$ (CH_3), 20.6 (CH_3), 44.6 (CH), 88.9 (CH), 105.5 (CH), 127.4 (CH), 128.6 (CH), 129.0 (C), 130.2 (CH), 133.8 (CH), 157.0 (C), 164.8 ppm (C); IR (ATR): $\tilde{\nu} = 1731$ (OC=O), 1679, 1664 cm^{-1} (NC=O, C=C); MS (70 eV): *m/z* (%): 261 $[M^+]$ (3); 156 (10), 140 (3), 105 (100), 98 (3), 77 (17); elemental analysis calcd (%) for $C_{14}H_{15}NO_4$: C 64.36, H 5.79, N 5.36; found: C 64.40, H 5.58, N 5.48.

2-Benzoyloxy-4-isobutyl-1,4-oxazin-3-one (23b): TLC $R_f = 0.11$ (EtOAc/hexane 1:19); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.96$ (d, $J = 6.6$ Hz, 6H), 1.98–2.12 (m, 1H), 3.37 and 3.48 (2×(d×d), $J = 13.4$, 7.7, 7.4 Hz, 2×1H), 5.86 and 6.18 (2×d, $J = 4.4$ Hz, 2×1H), 6.79 (s, 1H), 7.37–7.42, 7.52–7.57, and 7.98–8.08 ppm (3×m, 2H, 1H and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 19.7$ (CH_3), 19.8 (CH_3), 27.6 (CH), 53.1 (CH_2), 88.7 (CH), 111.2 (CH), 126.4 (CH), 128.6 (CH), 130.0 (CH), 133.5 (C), 133.8 (CH), 157.8 (C), 164.6 ppm (C); IR (ATR): $\tilde{\nu} = 1734$ (OC=O), 1687 cm^{-1} (NC=O, C=C); MS (70 eV): *m/z* (%): 275 $[M^+]$, (8); 246 (4), 170 (12), 154 (4), 122 (4), 106 (7), 105 (100), 77 (15).

2-Benzoyloxy-4-butyl-1,4-oxazin-3-one (23c): TLC $R_f = 0.09$ (EtOAc/hexane 1:19); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.96$ (t, $J = 7.3$ Hz, 3H), 1.39 (sextet, $J = 7.3$ Hz, 2H), 1.65 (pentet, $J = 7.3$ Hz, 2H), 3.53–3.71 (m, 2H), 5.84 and 6.19 (2×d, $J = 4.4$ Hz, 2×1H), 6.74 (s, 1H), 7.40–7.45, 7.55–7.60 and 8.00–8.03 ppm (3×m, 2H, 1H and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 13.8$ (CH_3), 19.8 (CH_2), 30.2 (CH_2), 45.9 (CH_2), 88.7 (CH), 110.7 (CH), 126.8 (CH), 128.6 (CH), 128.9 (C), 130.1 (CH), 133.9 (CH), 157.6 (C), 164.8 ppm (C); IR (ATR): $\tilde{\nu} = 1734$ (OC=O), 1686 cm^{-1} (NC=O, C=C); MS (70 eV): *m/z* (%): 275 $[M^+]$, (6); 246 (2), 170 (10), 154 (3), 122 (3), 106 (7), 105 (100), 77 (13).

2-Benzoyloxy-4-cyclohexyl-1,4-oxazin-3-one (23d): M.p. 94.6 °C; recrystallization from EtOAc/hexane (30:1); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.08$–1.25, 1.35–1.58 and 1.70–1.93 (3×m, 1H, 4H, and 5H), 4.42–4.53 (m, 1H), 5.92 and 6.20 (2×d, $J = 4.4$ Hz, 2×1H), 6.72 (s, 1H), 7.42–7.47, 7.56–7.62 and 8.00–8.03 ppm (3×m, 2H, 1H, and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 25.3$ (CH_2), 25.5 (CH_2), 30.4 (CH_2), 31.0 (CH_2), 52.3 (CH), 88.9 (CH), 106.4 (CH), 127.0 (CH), 128.6 (CH), 128.9 (C), 130.1 (CH), 133.8 (CH), 157.1 (C), 164.8 ppm (C); IR (ATR): $\tilde{\nu} = 1783$ (OC=O), 1727, 1687 cm^{-1} (NC=O, C=C); MS (70 eV): *m/z* (%): 301 $[M^+]$ (10), 272 (5), 196 (15), 105 (100), 77 (15), 55 (5); elemental analysis calcd (%) for $C_{17}H_{19}NO_4$: C 67.76, H 6.36, N 4.65; found: C 67.82, H 6.15, N 4.38.

General procedure for the synthesis of 2-benzoyloxymorpholin-3-ones 24: Palladium on activated carbon (20% w/w) was added to a solution of 2-benzoyloxy-1,4-oxazin-3-one **23** (10 mmol) in methanol (60 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 for 18 h at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite and evaporation of the solvent in vacuo afforded crude 2-benzoyloxymorpholin-3-one **24**, which was purified by means of column chromatography on silica gel or recrystallization.

2-Benzoyloxy-4-isopropylmorpholin-3-one (24a): M.p. 124.2 °C; recrystallization from EtOAc/hexane (30:1); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.20$ and 1.22 (2×d, $J = 6.7$ Hz, 2×3H), 3.23 (d×d×d, $J = 12.3$, 3.2, 1.4 Hz, 1H), 3.53 (d×d×d, $J = 12.3$, 11.9, 4.8 Hz, 1H), 3.98 (d×d×d, $J =$ 11.8, 4.8, 1.4 Hz, 1H), 4.20 (d×d×d, $J = 11.8$, 11.9, 3.2 Hz, 1H), 4.90 (septet, $J = 6.7$ Hz, 1H), 6.40 (s, 1H), 7.42–7.47, 7.56–7.61 and 8.07–8.10 ppm (3×m, 2H, 1H and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 19.0$ (CH_3), 19.4 (CH_3), 39.2 (CH_2), 44.4 (CH), 59.7 (CH_2), 89.2 (CH), 128.5 (CH), 129.5 (C), 130.2 (CH), 133.6 (CH), 162.1 (C), 165.4 ppm (C); IR (ATR): $\tilde{\nu} = 1719$ (OC=O), 1654 cm^{-1} (NC=O); MS (70 eV): *m/z* (%): 264 (100) $[M^+ + H]$; HRMS (ESI) calcd for $C_{14}H_{18}NO_4$: 264.1236 $[M+H]^+$; found: 264.1233.

2-Benzoyloxy-4-isobutylmorpholin-3-one (24b): TLC $R_f = 0.18$ (EtOAc/hexane 1:3); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.82$ and 0.84 (2×d, $J = 6.8$ Hz, 2×3H), 1.92 (nonet, $J = 6.8$ Hz, 1H), 3.12 (d×d, $J = 12.4$, 2.5 Hz, 1H), 3.18 (d, $J = 6.8$ Hz, 2H), 3.55 (d×d×d, $J = 12.4$, 12.0, 3.9 Hz, 1H), 3.80 (d×d, $J = 12.0$, 3.9 Hz, 1H), 4.14 (d×d×d, $J = 12.0$, 12.0, 2.5 Hz, 1H), 6.33 (s, 1H), 7.22–7.33, 7.37–7.47 and 7.86–7.96 ppm (3×m, 2H, 1H and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 19.9$ (CH_3), 20.1 (CH_3), 26.3 (CH), 46.4 (CH_2), 54.0 (CH_2), 59.3 (CH_2), 89.0 (CH), 128.5 (CH), 129.3 (C), 130.0 (CH), 133.6 (CH), 163.1 (C), 165.2 ppm (C); IR (ATR): $\tilde{\nu} = 1727$ (OC=O), 1669 cm^{-1} (NC=O); MS (70 eV): *m/z* (%): 278 (100) $[M^+ + H]$; HRMS (ESI) calcd for $C_{15}H_{20}NO_4$: 278.1392 $[M+H]^+$; found: 278.1391.

2-Benzoyloxy-4-butylmorpholin-3-one (24c): TLC $R_f = 0.30$ (EtOAc/hexane 1:3); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.95$ (t, $J = 7.3$ Hz, 3H), 1.36 (sextet, $J = 7.3$ Hz, 2H), 1.50–1.67 (m, 2H), 3.23 (d×d, $J = 12.4$, 2.6 Hz, 1H), 3.36–3.56 (m, 2H), 3.68 (d×d×d, $J = 12.4$, 12.0, 4.0 Hz, 1H), 3.91 (d×d, $J = 11.8$, 4.0 Hz, 1H), 4.24 (d×d×d, $J = 12.0$, 11.8, 2.6 Hz, 1H), 6.40 (s, 1H), 7.39–7.44, 7.53–7.58 and 8.05–8.08 ppm (3×m, 2H, 1H and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 13.8$ (CH_3), 20.0 (CH_2), 28.9 (CH_2), 45.8 (CH_2), 46.7 (CH_2), 59.3 (CH_2), 89.0 (CH), 128.5 (CH), 129.4 (C), 130.1 (CH), 133.6 (CH), 162.6 (C), 165.2 ppm (C); IR (ATR): $\tilde{\nu} = 1728$ (OC=O), 1667 cm^{-1} (NC=O); MS (70 eV): *m/z* (%): 278 (100) $[M^+ + H]$; HRMS (ESI) calcd for $C_{15}H_{20}NO_4$: 278.1392 $[M+H]^+$; found: 278.1392.

2-Benzoyloxy-4-cyclohexylmorpholin-3-one (24d): M.p. 96.1 °C; TLC $R_f = 0.63$ (EtOAc); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.05$–1.19, 1.34–1.54 and 1.69–1.90 (3×m, 1H, 4H and 5H), 3.26 (d×d×d, $J = 12.4$, 3.3, 1.6 Hz, 1H), 3.54 (d×d×d, $J = 12.4$, 11.9, 4.4 Hz, 1H), 3.96 (d×d×d, $J = 11.9$, 4.4, 1.6 Hz, 1H), 4.20 (d×d×d, $J = 11.9$, 11.9, 3.3 Hz, 1H), 4.41–4.52 (m, 1H), 6.39 (s, 1H), 7.42–7.47, 7.55–7.61 and 8.07–8.11 ppm (3×m, 2H, 1H and 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 25.5$ (CH_2), 25.6 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 40.4 (CH_2), 52.6 (CH), 59.8 (CH_2), 89.3 (CH), 128.5 (CH), 129.5 (C), 130.1 (CH), 133.6 (CH), 162.2 (C), 165.4 ppm (C); IR (ATR): $\tilde{\nu} = 1724$ (OC=O), 1649 cm^{-1} (NC=O); MS (70 eV): *m/z* (%): 304 (100) $[M^+ + H]$; elemental analysis calcd (%) for $C_{17}H_{21}NO_4$: C 67.31, H 6.98, N 4.62; found: C 67.56, H 6.89, N 4.78.

General procedure for the synthesis of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones 25 and 26: $Et_3N{\cdot}3HF$ (25 mmol) was added to a solution of 2-benzoyloxy-1,4-oxazin-3-one **23** (10 mmol) in dry dichloromethane (50 mL) at 0 °C. Subsequently, *N*-bromosuccinimide (15 mmol) was added at 0 °C and the resulting mixture was stirred at room temperature for 24 h. Afterwards, the mixture was poured in aq. 0.5 M NaOH (50 mL) and extraction was performed with dichloromethane (3×50 mL). The combined organic layers were washed with an aqueous solution of 1 M NaOH (2×50 mL) and brine (50 mL). After drying with $MgSO_4$ and filtration of the drying agent, the solvent was evaporated in vacuo, affording a diastereoisomeric mixture of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-one **25** and **26**, which were separated by means of column chromatography on silica gel or recrystallization.

2-Benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one (25 a): M.p. 122.8 °C; recrystallization from EtOAc/hexane (30:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.31$ (d×d, $J=6.7$, 1.4 Hz, 3H), 1.33 (d, $J=6.7$ Hz, 3H), 4.84 (septet×d, $J=6.7$, 1.2 Hz, 1H), 5.72 (d×d, $J=56.8$, 1.5 Hz, 1H), 6.38 (d×d, $J=5.1$, 1.5 Hz, 1H), 6.69 (s, 1H), 7.43–7.48, 7.57–7.63 and 8.10–8.13 ppm (3×m, 2H, 1H, and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-118.95$ ppm (d×d, $J=56.8$, 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=19.5$ (CH_3), 20.6 (CH_3), 45.9 (d, $J=2.3$ Hz, CH), 75.0 (d, $J=33.4$ Hz, CH), 85.8 (CH), 91.5 (d, $J=210.0$ Hz, CH), 128.6 (CH), 130.4 (CH), 134.0 (C), 161.2 (d, $J=3.5$ Hz, C), 164.7 ppm (C); IR (ATR): $\tilde{\nu}=1735$ (OC=O), 1690 cm^{-1} (NC=O); MS (70 eV): m/z (%): 360/2 (100) [M^{+}+H]; elemental analysis calcd (%) for $C_{14}H_{15}BrFNO_4$: C 46.69, H 4.20, N 3.89; found: C 46.89, H 4.66, N 4.45.

2-Benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one (26 a): Filtrate after recrystallization from EtOAc/hexane (30:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.28$–1.35 (m, 6H), 4.82 (septet×d, $J=6.6$, 1.5 Hz, 1H), 5.68 (d×d, $J=57.4$, 1.3 Hz, 1H), 6.44 (d, $J=1.1$ Hz, 1H), 6.46 (d×d, $J=4.5$, 1.3 Hz, 1H), 7.38–7.48, 7.57–7.63 and 8.08–8.13 ppm (3×m, 2H, 1H and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-116.94$ ppm (d×d, $J=57.4$, 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=19.3$ (CH_3), 20.5 (CH_3), 46.0 (d, $J=2.3$ Hz, CH), 78.0 (d, $J=35.7$ Hz, CH), 87.4 (CH), 91.2 (d, $J=211.1$ Hz, CH), 128.2 (C), 128.6 (CH), 130.4 (CH), 134.2 (CH), 161.8 (d, $J=3.5$ Hz, C), 164.3 ppm (C); IR (ATR): $\tilde{\nu}=1736$ (OC=O), 1691 cm^{-1} (NC=O); MS (70 eV): m/z (%): 360/2 (100) [M^{+}+H].

2-Benzoyloxy-6-bromo-5-fluoro-4-isobutylmorpholin-3-one (25 b): TLC $R_f=0.14$ (EtOAc/hexane 1:19); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.04$ (d, $J=7.2$ Hz, 6H), 2.03–2.17 (m, 1H), 3.29 and 3.64 (2×(d×d×d), $J=13.9$, 7.2, 1.2 Hz, 2×1H), 5.68 (d×d, $J=57.7$, 1.4 Hz, 1H), 6.34 (d×d, $J=5.3$, 1.4 Hz, 1H), 6.70 (s, 1H), 7.44–7.49, 7.58–7.64 and 8.10–8.13 ppm (3× m, 2H, 1H and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-122.75$ ppm (d×d, $J=57.7$, 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=20.1$ (CH_3), 20.2 (CH_3), 27.5 (CH), 53.3 (CH_2), 74.2 (d, $J=33.5$ Hz, CH), 85.9 (CH), 95.7 (d, $J=212.3$ Hz, CH), 128.6 (CH), 130.5 (CH), 134.0 (C), 161.9 (d, $J=3.5$ Hz, C), 164.6 ppm (C); IR (ATR): $\tilde{\nu}=1736$ (OC=O), 1704 cm^{-1} (NC=O); MS (70 eV): m/z (%): 374/6 (100) [M^{+}+H].

2-Benzoyloxy-6-bromo-5-fluoro-4-isobutylmorpholin-3-one (26 b): TLC $R_f=0.14$ (EtOAc/hexane 1:19); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.01$ and 1.04 (2×d, $J=7.2$ Hz, 2×3H), 2.08 (nonet, $J=7.2$ Hz, 1H), 3.29 and 3.65 (2×(d×d×d), $J=13.9$, 7.2, 1.5 Hz, 2×1H), 5.62 (d × d, $J=58.0$, 1.2 Hz, 1H), 6.43 (d×d, $J=5.4$, 1.2 Hz, 1H), 6.47 (d, $J=1.2$ Hz, 1H), 7.44-7.49, 7.59–7.64 and 8.08–8.13 ppm (3×m, 2H, 1H and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-121.17$ ppm (d × d, $J=58.0$, 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=20.07$ (CH_3), 20.13 (CH_3), 27.3 (CH), 53.1 (CH_2), 77.3 (d, $J=32.3$ Hz, CH), 87.4 (CH), 95.5 (d, $J=212.3$ Hz, CH), 128.2 (C), 128.7 (CH), 130.5 (CH), 134.2 (CH), 162.8 (d, $J=3.5$ Hz, C), 164.3 (C) ppm; IR (ATR): $\tilde{\nu}=1744$ (OC=O), 1705 cm^{-1} (NC=O); MS (70 eV): m/z (%): 374/6 (100) [M^{+}+H].

2-Benzoyloxy-6-bromo-4-butyl-5-fluoromorpholin-3-one (25 c): TLC $R_f=0.12$ (EtOAc/hexane 1:19); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.98$ (t, $J=7.5$ Hz, 3H), 1.44 (sextet, $J=7.5$ Hz, 2H), 1.61–1.81 (m, 2H), 3.44–3.54 and 3.71–3.81 (2×m, 2×1H), 5.67 (d×d, $J=57.9$, 1.1 Hz, 1H), 6.33 (d×d, $J=5.4$, 1.1 Hz, 1H), 6.68 (s, 1H), 7.44–7.49, 7.58–7.64 and 8.10–8.14 ppm (3×m, 2H, 1H, and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-122.55$ ppm (d×d, $J=57.9$, 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=13.8$ (CH_3), 20.0 (CH_2), 29.6 (CH_2), 46.3 (CH_2), 74.3 (d, $J=32.3$ Hz, CH), 85.8 (CH), 95.5 (d, $J=212.3$ Hz, CH), 128.6 (CH), 130.5 (CH), 134.0 (C), 161.5 (d, $J=3.4$ Hz, C), 164.6 (C) ppm; IR (ATR): $\tilde{\nu}=1736$ (OC=O), 1702 cm^{-1} (NC=O); MS (70 eV): m/z (%): 374/6 (100) [M^{+}+H].

2-Benzoyloxy-6-bromo-4-butyl-5-fluoromorpholin-3-one (26 c): TLC $R_f=0.12$ (EtOAc/hexane 1:19); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.97$ (t, $J=7.4$ Hz, 3H), 1.42 (sextet, $J=7.4$ Hz, 2H), 1.64–1.76 (m, 2H), 3.39–3.53 and 3.72–3.82 (2×m, 2×1H), 5.61 (d×d, $J=58.2$ Hz, 1.1 Hz, 1H), 6.42 (d×d, $J=5.7$, 1.1 Hz, 1H), 6.44 (d, $J=1.1$ Hz, 1H), 7.43–7.48, 7.58–7.64, and 8.08–8.13 ppm (3×m, 2H, 1H, and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-120.66$ ppm (d×d, $J=58.2$, 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=13.8$ (CH_3), 19.9 (CH_2), 29.5 (CH_2), 46.1 (CH_2), 77.4 (d, $J=34.6$ Hz, CH), 87.3 (CH), 95.4 (d, $J=213.5$ Hz, CH), 128.2 (C), 128.7 (CH), 130.5 (CH), 134.2 (CH), 162.4 (d, $J=3.4$ Hz, C), 164.3 ppm (C); IR (ATR): $\tilde{\nu}=1743$ (OC=O), 1702 cm^{-1} (NC=O); MS (70 eV): m/z (%): 374/6 (100) [M^{+}+H].

2-Benzoyloxy-6-bromo-4-cyclohexyl-5-fluoromorpholin-3-one (25 d): M.p. 101.5 °C; recrystallization from EtOAc/hexane (30:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.08$–1.25, 1.34–1.54, 1.69–1.75 and 1.86–1.99 (4×m, 1H, 4H, 1H and 4H), 4.41–4.50 (m, 1H), 5.73 (d×d, $J=57.3$, 1.3 Hz, 1H), 6.36 (d×d, $J=4.7$, 1.3 Hz, 1H), 6.69 (s, 1H), 7.43–7.48, 7.58–7.63, and 8.10–8.13 ppm (3×m, 2H, 1H and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-117.86$ ppm (d×d, $J=57.3$, 4.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=25.4$ (CH_2), 25.5 (CH_2), 25.8 (CH_2), 30.0 (CH_2), 31.0 (CH_2), 53.4 (CH), 75.0 (d, $J=33.4$ Hz, CH), 85.9 (CH), 91.8 (d, $J=211.2$ Hz, CH), 128.6 (CH), 130.4 (CH), 134.0 (C), 161.2 (d, $J=3.4$ Hz, C), 164.7 ppm (C); IR (ATR): $\tilde{\nu}=1736$ (OC=O), 1681 cm^{-1} (NC=O); MS (70 eV): m/z (%): 400/2 (100) [M^{+}+H]; elemental analysis calcd (%) for $C_{17}H_{19}BrFNO_4$: C 51.01, H 4.78, N 3.50; found: C 51.13, H 4.78, N 3.45.

2-Benzoyloxy-6-bromo-4-cyclohexyl-5-fluoromorpholin-3-one (26 d): Spectral data based on ^{1}H NMR and ^{13}C NMR of the crude reaction mixture. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.08$–1.23, 1.34–1.54, 1.70–1.74 and 1.86–1.99 (4×m, 1H, 4H, 1H and 4H), 4.37–4.51 (m, 1H), 5.69 (d×d, $J=56.7$, 1.1 Hz, 1H), 6.43 (d, $J=1.1$ Hz, 1H), 6.45 (d×d, $J=4.9$, 1.1 Hz, 1H), 7.43–7.49, 7.58–7.64 and 8.08–8.14 ppm (3×m, 2H, 1H and 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-115.96$ ppm (d×d, $J=56.7$, 4.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=25.4$ (CH_2), 25.5 (CH_2), 25.8 (CH_2), 29.8 (CH_2), 31.1 (CH_2), 53.5 (CH), 77.9 (d, $J=35.8$ Hz, CH), 87.5 (CH), 91.5 (d, $J=212.3$ Hz, CH), 128.3 (C), 128.6 (CH), 130.5 (CH), 134.2 (CH), 161.8 (d, $J=3.5$ Hz, C), 164.4 ppm (C); IR (ATR): $\tilde{\nu}=1736$ (OC=O), 1694 cm^{-1} (NC=O); MS (70 eV): m/z (%): 400/2 (100) [M^{+}+H].

General procedure for the synthesis of 2-fluoro-1,4-oxazin-3-ones 28: Morph-DAST (20 mmol) was added dropwise to a solution of 2-hydroxy-1,4-oxazin-3-one **2** (10 mmol) in dry dichloromethane (50 mL) at −78 °C under nitrogen atmosphere. The resulting mixture was allowed to warm to room temperature and was stirred for a further 5 h. A saturated solution of $NaHCO_3$ (50 mL) was carefully dropped to the mixture and the mixture was stirred for 15 min. The organic layer was separated and washed with water (25 mL) and brine (25 mL), after which the organic fraction was dried over $MgSO_4$, followed by removal of the drying agent by filtration. After evaporation of the solvent in vacuo, the crude reaction mixture was purified by means of column chromatography on silica gel, affording pure 2-fluoro-1,4-oxazin-3-one **28**.

2-Fluoro-4-isopropyl-1,4-oxazin-3-one (28 a): TLC $R_f=0.10$ (EtOAc/hexane 1:9); ^{1}H NMR (300 MHz, $CDCl_3$,25 °C): $\delta=1.23$ and 1.27 (2×d, $J=6.8$ Hz, 2×3H), 4.80 (septet, $J=6.8$ Hz, 1H), 5.90 (d, $J=52.7$ Hz, 1H), 5.92 and 6.27 ppm (2×d, $J=4.4$ Hz, 2×1H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-127.92$ ppm (d, $J=52.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=19.9$ (CH_3), 20.6 (CH_3), 44.7 (CH), 102.0 (d, $J=234.2$ Hz, CH), 105.8 (CH), 126.5 (CH), 156.0 ppm (d, $J=32.3$ Hz, C); IR (ATR): $\tilde{\nu}=1685$, 1664 cm^{-1} (C=O, C=C); MS (70 eV): m/z (%): 159 [M^{+}] (83); 117 (100), 88 (37), 69 (43), 43 (17), 41 (25), 40 (11).

2-Fluoro-4-isobutyl-1,4-oxazin-3-one (28 b): TLC $R_f=0.24$ (EtOAc/hexane 1:9); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.94$ (d, $J=7.0$ Hz, 6H), 2.02 (nonet, $J=7.0$ Hz, 1H), 3.38 (d×d, $J=7.0$, 1.1 Hz, 2H), 5.83 (d, $J=4.4$ Hz, 1H), 5.91 (d, $J=52.7$ Hz, 1H), 6.22 ppm (d, $J=4.4$ Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-127.69$ ppm (d, $J=52.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=19.80$ (CH_3), 19.84 (CH_3), 27.7 (CH), 53.3 (CH_2), 102.0 (d, $J=234.2$ Hz, CH), 111.4 (CH), 125.6 (CH), 156.8 ppm (C, d, $J=32.3$ Hz); IR (ATR): $\tilde{\nu}=1686$ cm^{-1} (C=O, C=C); MS (70 eV): m/z (%): 173 [M^{+}] (61); 130 (13), 117 (100), 102 (52), 69 (16), 57 (13), 41 (20).

4-Butyl-2-fluoro-1,4-oxazin-3-one (28 c): TLC $R_f=0.20$ (EtOAc/hexane 1:9); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.95$ (t, $J=7.5$ Hz, 3H), 1.35 (sextet, $J=7.5$ Hz, 2H), 1.56–1.66 (m, 2H), 3.48–3.66 (m, 2H), 5.85 (d,

$J=4.4$ Hz, 1H), 5.90 (d, $J=52.8$ Hz, 1H), 6.23 ppm (d, $J=4.4$ Hz, 1H); ^{19}F NMR (282 MHz, CDCl$_3$, 25 °C): $\delta=-127.57$ ppm (d, $J=52.8$ Hz); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=13.7$ (CH$_3$), 19.7 (CH$_2$), 30.1 (CH$_2$), 45.9 (CH$_2$), 102.0 (d, $J=234.2$ Hz, CH), 110.9 (CH), 125.8 (CH), 156.5 ppm (d, $J=32.3$ Hz, C); IR (ATR): $\tilde{\nu}=1686$ cm^{-1} (C=O, C=C); MS (70 eV): *m/z* (%): 173 [M^+] (99); 144 (52), 131 (17), 130 (27), 124 (24), 117 (100), 102 (57), 88 (17), 69 (33), 57 (19), 41 (35).

4-Cyclohexyl-2-fluoro-1,4-oxazin-3-one (28d): M.p. 91.2 °C; TLC $R_f=0.51$ (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta=1.05$–1.20, 1.34–1.51 and 1.68–1.89 (3×m, 1H, 4H and 5H), 4.34–4.45 (m, 1H), 5.90 (d, $J=53.7$ Hz, 1H), 5.93 and 6.24 ppm (2×d, $J=4.4$ Hz, 2×1H); ^{19}F NMR (282 MHz, CDCl$_3$, 25 °C): $\delta=-127.83$ ppm (d, $J=53.7$ Hz); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=25.2$ (CH$_2$), 25.4 (CH$_2$), 25.5 (CH$_2$), 30.2 (CH$_2$), 30.9 (CH$_2$), 52.3 (CH), 102.0 (d, $J=233.1$ Hz, CH), 106.6 (CH), 126.1 (CH), 156.0 ppm (d, $J=32.3$ Hz, C); IR (ATR): $\tilde{\nu}=1684$, 1662 cm^{-1} (C=O, C=C); MS (70 eV): *m/z* (%): 200 (100) [M^++H]; elemental analysis for $C_{10}H_{14}FNO_2$: C 60.29, H 7.08, N 7.03; found: C 60.50, H 6.99, N 7.08.

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