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# Tandem Ugi MCR/Mitsunobu Cyclization as a Short, Protecting-Group-Free Route to Benzoxazinones with Four Diversity Points

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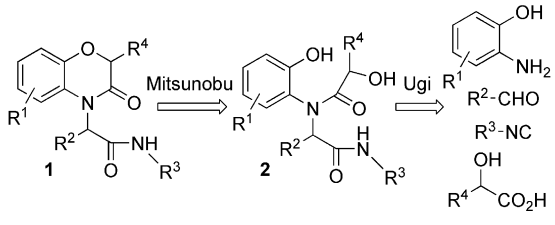
A tandem Ugi/Mitsunobu protocol, starting from *o*-aminophenols, α-hydroxy acids, amines and aldehydes gives benzo[*b*][1,4]oxazin-3-ones of general formula **1** in two high-yielding steps, with the introduction of up to four diversity inputs. The mildness of the methodology allows the stereospecific synthesis of enantiomerically pure products as well as the introduction of additional functional groups. The overall procedure can also be carried out in a one-pot manner.

## Introduction

The Ugi multicomponent reaction (U-MCR)[1–3] is particularly well suited for diversity-oriented syntheses, because it uses just one step to introduce four diversity inputs – represented by carbonyl compounds, amines, carboxylic acids and isocyanides – that are easily available in a wide variety. Furthermore, the Ugi MCR produces a dramatic increase in structural complexity in just one step and is also "atom-economical", the only side-product being water (1 equiv.). However, an important drawback is represented by the acyclic nature of the obtained products when the classical version of this venerable reaction is exploited. Many efforts have therefore been devoted to expand its scope, also enabling exploration of scaffold diversity, and achieving access to drug-like heterocycles.[4–6] The most fruitful strategy directed towards this goal is probably represented by the combination of the Ugi reaction with post-condensation transformations.[7–10] Our group has been quite active in recent years in implementing this general strategy by coupling the Ugi reaction with metathesis processes,[11–13] other organometal-catalysed reactions,[14,15] acyl nucleophilic substitutions[16] and, last but not least, intramolecular or intermolecular aliphatic nucleophilic substitutions.[15,16]

In particular, the introduction of an alcohol moiety and a suitable nucleophile (phenol, sulfonamide) into two of the four components of the U-MCR allows a post-condensation Mitsunobu[17] or Mitsunobu-like[18] cyclization, which can lead to a variety of oxaza or diaza heterocycles. The scaffold nature can be varied in several ways: (1) by changing the type of nucleophile, (2) by suitable positioning of the nucleophile and the leaving group in any two of the components (in the case of the Ugi reaction, this leads to 12 different theoretical possibilities), or (3) by changing the lengths and the natures of the spacers that connect the additional functionalities. We have already reported the application of this approach to short syntheses of 3,4-dihydrobenzo[*f*][1,4]oxazepin-5-ones,[19–21] 1-sulfonyl-3,4-dihydrobenzo[*e*][1,4]diazepin-5-ones,[20,22] 1-sulfonyl-1,4-diazepan-5-ones,[22] benzo[*e*][1,3]oxazin-4-ones[23] and 3-aminoisochromenes.[24] In these syntheses the additional alcohol moiety was always implanted into the amine or the carbonyl component. In continuation of these studies we decided this time to introduce the alcohol group into the carboxylic component, through the use of α-hydroxy acids as starting materials. On the other hand, the nucleophile (a phenol) was located in the starting amine, in particular through the use of *ortho*-aminophenols. The heterocyclic systems resulting from this two-step protocol (Ugi + Mitsunobu) is a benzo[*b*][1,4]oxazin-3-one of general formula **1** (Scheme 1).




Scheme 1.

Benzo[*b*][1,4]oxazin-3-ones represent a typical drug-like structure, incorporated in many pharmacologically active compounds. Particularly interesting, because of their similarity with compounds **1**, are the derivatives substituted at

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N-4 with carboxymethyl or (aminocarbonyl)methyl groups, which have been shown to be active as selective modulators of ATP-dependent calcium channels,[25–27] as inhibitors of aldose reductase,[28] as antagonists of hU-II receptors[29] or as integrin antagonists.[30] The synthetic routes employed in these medicinal chemistry works were definitely longer and less convergent than the two-step protocol described here. Moreover, they were also not suited for the introduction of the $R^2$ substituents.

Although α-halo acids had been used previously in a similar approach,[31] we reasoned that the use of α-hydroxy acids could grant a more general scope, because of their easier synthesis, especially when needed in enantiomerically pure form, their greater configurational stability, their higher compatibility with polyfunctionalised inputs, and also the milder, neutral conditions of the Mitsunobu step. Here we report the results of our study, which has demonstrated the potential for the preparation of compounds **1** in high yields, with the introduction of up to four diversity inputs, and with a broad scope.

## Results and Discussion

The protocol was first studied with the model compound **1a**, with use, as starting material, either of unprotected glycolic acid or of a derivative of it protected at the hydroxy group. The use of glycolic acid as such under typical Ugi conditions (MeOH, room temp., 48 h) gave the adduct **2a** in only 32% yield. With (*p*-methoxybenzyloxy)acetic acid[32] the yield of the Ugi step was slightly better (43%) but hydrogenolysis of the protecting group to give **2a** (85% yield) was found to be rather sluggish. Because the use of a protecting group did not bring any clear advantage, while adding an additional step, we concentrated on the optimization of the reaction with glycolic acid itself. After various experiments with different alcohols (methanol, ethanol, trifluoroethanol, 2-propanol, *tert*-butyl alcohol) as solvents, we found that the best one was 2-propanol. In this solvent the yield was raised to 63%. This is probably due to suppression of the competitive transformation of glycolic acid into esters, detected with lower alcohols; 2-propanol represents the best compromise, because with bulkier *tert*-butyl alcohol the reaction became very slow, and the yields dropped.

On the other hand, the Mitsunobu cyclization of **2a** was not problematic at all, giving **1a** in high yields with the use of the DEAD/$PPh_3$ system at 0 °C in $CH_2Cl_2$. THF as solvent gave very similar results but, we chose to use $CH_2Cl_2$ because of fewer solubility problems in general and an easier workup.

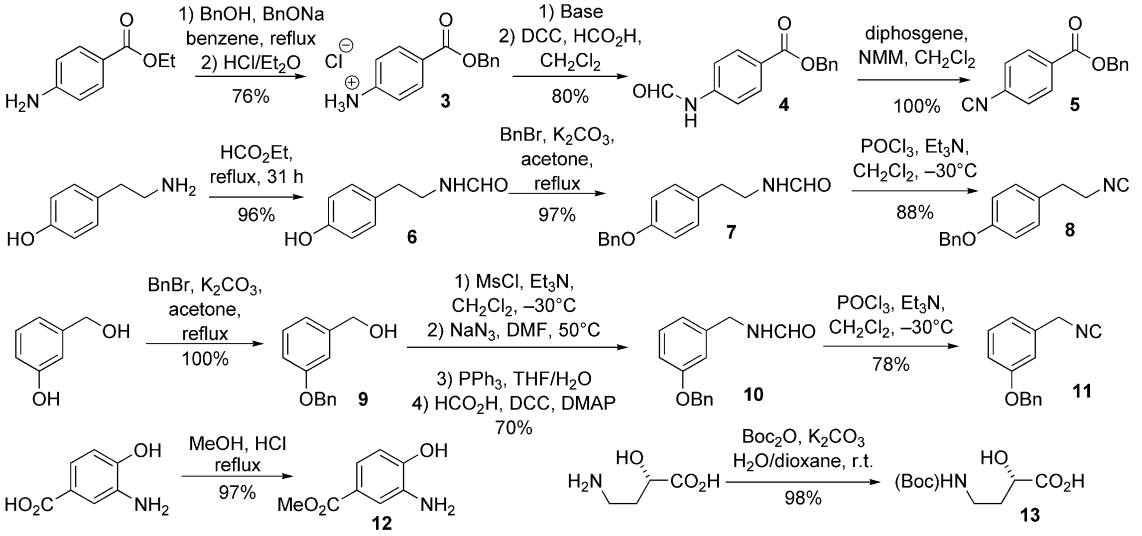
We then extended the protocol to other substrates (Table 1) and obtained 14 benzoxazinones differentiated by four diverse appendages. In order to better establish the scope and limitations, we preferred during this study to determine the specific yields of both steps, so the Ugi adducts were isolated by evaporation of the solvent and chromatography before being subjected to the Mitsunobu cyclization conditions. However, this intermediate purification is not really necessary, and the benzoxazinones **1** can be obtained with the same overall yields by a "one-pot" sequence (see the Experimental Section). This was demonstrated for compound **1f**, for which the yield obtained on carrying out the

Table 1. Two-step synthesis of the benzoxazinones **1**.

| Product | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Ugi cond.[a] | Yield of **2** [%] | Yield of **1** [%][b] | *dr* of **2** | *dr* of **1** |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | H | *i*Pr | *c*Hex | H | A | 63 | 90 | – | – |
| **1b** | H | *cy*Hex | *t*Bu | H | A | 67 | 94 | – | – |
| **1c** | H | *i*Pr | 4-(BnO$_2$C)C$_6$H$_4$ | H | A[c] | 62 | 86 | – | – |
| **1d** | H | *i*Bu | *t*Bu | H | A | – | – | – | – |
| **1e** | H | Ph | *n*Pent | H | A | 81 | 87 | – | – |
| **1f** | H | Ph | 4-(BnO)C$_6$H$_4$(CH$_2$)$_2$ | H | A[c] | 62 | 90 | – | – |
| | | | | | D[c] | | 56 | – | – |
| **1g** | H | 3-furyl | 4-(BnO)C$_6$H$_4$(CH$_2$)$_2$ | H | A[c] | 57 | 80 | – | – |
| **1h** | 4-Me | 3-thienyl | *t*Bu | H | A | 67 | 95 | – | – |
| **1i** | 4-Me | 4-MeOC$_6$H$_4$ | 3-(BnO)C$_6$H$_4$CH$_2$ | H | A[c] | 62 | 94 | – | – |
| **1j** | 4-Cl | 3-BrC$_6$H$_4$ | *n*Bu | H | B | 49 | 95 | – | – |
| **1k** | 4-CO$_2$Me | 4-MeC$_6$H$_4$ | *c*Hex | H | C | 30 | 80 | – | – |
| **1l** | 4-CO$_2$Me | Ph | *c*Hex | H | B | 56 | 84 | – | – |
| **1m** | 4-Cl | 4-pyridyl | *n*Bu | H | A | – | – | – | – |
| **1n** | H | Ph | *c*Hex | CH$_3$ (*S*)[d] | A | 75 | 48[e] | 50:50[f] | 72:28[f] |
| **1o** | 4-Cl | *i*Pr | *n*Bu | CH$_3$ (*S*) | A | 45 | 60[e] | 49:51[f] | 64:36[f] |
| **1p** | H | 3-BrC$_6$H$_4$ | *n*Bu | (Boc)NH(CH$_2$)$_2$ (*S*) | A[g] | 68 | 41[e] | 50:50[f] | 84:16[f] |

[a] The Ugi reaction was typically carried out with the aminophenol (0.5 M, 1 equiv.) and 1.2 equiv. each of isocyanide, aldehyde and carboxylic acid in the presence of molecular sieves (3 Å) for 48 h. Conditions A: *i*PrOH as solvent at room temp. Conditions B: MeOH, room temp. Conditions C: MeOH, 50 °C. Conditions D: "one-pot" procedure (see Experimental Section). The reported yield is after chromatography. [b] All Mitsunobu reactions were carried out with DEAD/$PPh_3$ (1.5 equiv. each) in $CH_2Cl_2$ (0.03 M) at 0 °C for 1 h. [c] In these cases the isocyanide was used as the limiting agent (1.2 equiv. of all the other three reagents). [d] This synthesis was also carried out by starting from racemic lactic acid. [e] Cyclization was carried out on the inseparable diastereoisomeric mixture of **2**. The reported yield is the overall yield for both diastereoisomers of **1**. [f] Determined by HPLC. [g] In this case the carboxylic acid was used as the limiting agent (1.2 equiv. of all the other three reagents).



Scheme 2. Preparation of custom inputs for the synthesis of benzoxazinones.

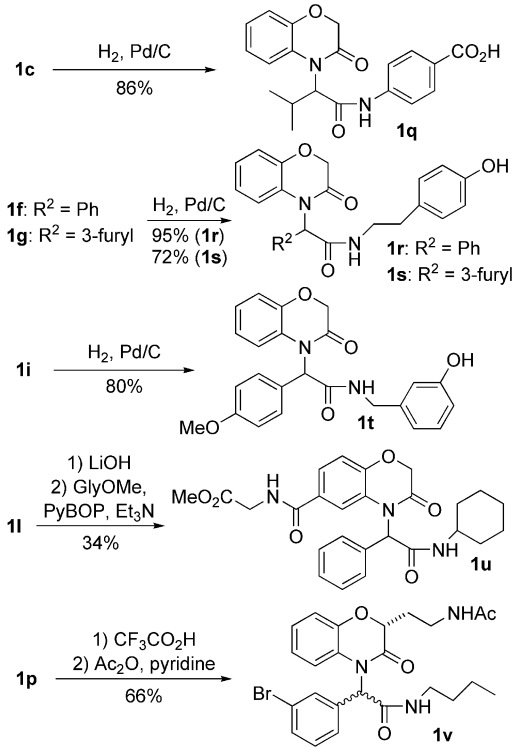
Mitsunobu reaction directly on the Ugi crude product was identical with the overall yield of the two separate steps (56%).

The yields of the Ugi step were in general good when starting from aromatic aldehydes, but somewhat lower for aliphatic aldehydes. As far as these are concerned, only α-branched compounds can be used, as shown by the failed preparation of **2d** when starting from isovaleraldehyde. With *o*-aminophenols containing electron-withdrawing groups the yields were less satisfactory, probably because of the lower nucleophilicities of the amines. In this case an improvement was achieved by reverting to methanol as solvent and increasing the reaction temperature (see the syntheses of **2j**–**2l**). Strange behaviour, however, was observed with *p*-tolualdehyde (compare **2k** with **2l**), which was remarkably less efficient than benzaldehyde despite their similar steric and electronic requirements. Moreover, pyridine-4-carbaldehyde failed to give the expected Ugi adduct **2m**.

The use of substituted α-hydroxy acids gave comparable yields in the Ugi step. As expected, diastereoselectivity was almost absent, with nearly 1:1 inseparable diastereomeric mixtures being obtained. Indeed, there are no examples in the literature of a decent reagent-controlled asymmetric induction in Ugi reactions of chiral carboxylic acids.

As far as the Mitsunobu step is concerned, when $R^4$ = H the yields were very high (>80%) in all cases, whereas decreases were observed with secondary alcohols ($R^4 \neq H$; see the preparation of **1n**–**p**). However, comparison of the diastereoisomeric ratios of these adducts **1n**–**p** with those measured at the level of **2n**–**p** showed the cyclization efficiencies to be highly dependent on the relative configurations of **2n**–**p**. The observed lower yields are therefore mainly attributable to just one of the two stereoisomeric intermediates. In the case of **1p**, for example, the yields for the two diastereoisomers were calculated to be 69% and 13%. Not having established the relative configurations of **1n**–**p** we were unable to attempt to interpret this outcome.

Obviously, the different ratio might also arise from a nonstereospecific Mitsunobu reaction. This would bring about partial racemization. This hypothesis was ruled out by HPLC analysis of products **1n**, derived either from racemic or from (*S*)-lactic acid, on a chiral column. The adducts derived from (*S*)-lactic acid turned out to be enantiomerically pure within the detection limits, indicating that the Mitsunobu reaction is completely stereospecific (most probably proceeding with inversion of configuration). This result also confirms that no racemization takes place during the



Scheme 3.

Ugi step, and so it is possible to obtain enantiomerically pure benzoxazinones when starting from easily available enantiomerically pure α-hydroxy acids.

The mildness of the protocol also allowed the use of polyfunctionalised, custom-made inputs. Scheme 2 shows the synthesis of the new isonitriles **5**, **8** and **11** (completely odourless), of the known aminophenol **12**[33] and of the known α-hydroxy acid **13**,[34] each containing an additional, protected, functional group. The resulting adducts could be further manipulated as demonstrated by the transformation of **1c**, **1f**, **1g**, **1i**, **1l** and **1p** into the six additional benzoxazinones **1q**–**1v** (Scheme 3). In the cases of **1u** and **1v** a fifth diversity input was introduced.

## Conclusions

Although some limitations are evident (in particular it is not possible to employ aliphatic aldehydes unbranched at their α-positions), we have demonstrated the broad generality of this two-step synthesis of the benzo[*b*][1,4]oxazin-3-ones **1**, preparing 20 members of this family. In comparison with the previous work with α-halo acids,[31] we were successfully able to use aliphatic aldehydes, aromatic isocyanides and *p*-aminophenols containing strongly electron-withdrawing groups. Most importantly, enantiomerically pure α-hydroxy acids have also been used, as well as inputs containing additional functional groups. The procedure was demonstrated to be stereospecific, and it can also be carried out in a one-pot fashion. It therefore appears the method of choice for the combinatorial synthesis of complex conformationally biased peptidomimetics containing this "privileged" structure.

## Experimental Section

**General:** NMR spectra were taken at room temp. in $CDCl_3$ or in [$D_6$]DMSO at 300 MHz ($^1$H), and 75 MHz ($^{13}$C), variously with TMS ($^1$H NMR in $CDCl_3$: $\delta$ = 0.000 ppm), the central peak of DMSO ($^1$H NMR in [$D_6$]DMSO: $\delta$ = 2.506 ppm), the central peak of $CDCl_3$ ($^{13}$C in $CDCl_3$: $\delta$ = 77.02 ppm) or the central peak of DMSO ($^{13}$C in [$D_6$]DMSO: $\delta$ = 39.43 ppm) as internal standard. Chemical shifts are reported in ppm ($\delta$ scale). Peak assignments were made with the aid of gCOSY and gHSQC experiments. In ABX systems, the proton A is considered upfield and B downfield. GC–MS was carried out with an HP 1 column (12 m long, 0.2 mm wide), electron impact at 70 eV and a mass temperature of about 170 °C. Only *m*/*z* values > 33 were detected. All analyses were performed (unless otherwise stated) with a constant He flow of 0.9 mL min$^{-1}$ with initial temp. of 100 °C, initial time 2 min, rate 20 °C min$^{-1}$, final temp. 280 °C, injector temp. 250 °C, detector temp. 280 °C. HPLC analyses were carried out with an HP 1090 instrument and a DAD detector. TLC analyses were carried out on silica gel plates and viewed under UV (254 nm). $R_f$ values were measured after elution of 7–9 cm. Column chromatography was carried out by the "flash" methodology with 220–400 mesh silica. IR spectra were recorded as $CHCl_3$ solutions. Petroleum ether (boiling range 40–60 °C) is abbreviated as PE. In extractive workup, aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were always dried with $Na_2SO_4$ and filtered before evaporation of the solvent under reduced pressure. All reactions in dry solvents were carried out under nitrogen.

**General Procedure for the Ugi Reactions to Give Compounds 2**

**Conditions A:** The aminophenol of choice (1 mmol) was dissolved in dry *i*PrOH (2 mL) and treated with the carboxylic acid (1.2 mmol), freshly activated powdered molecular sieves (3 Å, 300 mg), the aldehyde (1.2 mmol) and the isocyanide (1.2 mmol). The mixture was stirred at room temp. for 48 h and was then diluted with $CH_2Cl_2$, filtered, concentrated and chromatographed with PE/AcOEt. In the cases of **2c**, **2g**, **2f** and **2i**, 1 mmol of isocyanide and 1.2 mmol of the other three components were used. In the case of **2p**, 1 mmol of α-hydroxy acid and 1.2 mmol of the other three components were used.

**Conditions B:** As Conditions A, but in MeOH as the solvent.

**Conditions C:** As Conditions A, but in MeOH as the solvent and at 50 °C.

The resulting products **2**, pure by TLC, were not characterized, but were directly subjected to the next step. The NMR spectra of these compounds turned out to be quite complex at room temp., owing to the presence of amide rotamers and of small amounts of other isomers, probably derived from cyclization of the phenol hydroxy group onto the tertiary amide carbonyl group.

**HPLC Analysis of 2n, 2o and 2p and of 1o and 1p for the Determination of Diastereoisomeric Ratios:** Column Hypercarb 100 × 2, 1 mm; flow = 0.2 mL min$^{-1}$; sample concentration = 300 μg mL$^{-1}$ in MeCN; injected: 5 μL; $T$ = 55 °C; isocratic elution with MeCN + 10%THF/water (85:15); $\lambda$ = 220 nm.

**HPLC Analysis of 1n:** Column Daicel Chiralpak, 1 mm; flow = 1 mL min$^{-1}$; sample concentration = 300 μg mL$^{-1}$ in *i*PrOH; injected: 20 μL; $T$ = 35 °C; isocratic elution with *n*-hexane/*i*PrOH (80:20); on racemic sample: $t_R$ = 5.49 [minor (*R*)], 6.74 [major (*S*)], 9.11 [minor (*S*)], 14.57 [major (*R*)] min; on sample derived from (*S*)-lactic acid only the peaks at $t_R$ = 5.49 (28%) and 14.57 (72%) min were present.

**General Procedure for the Mitsunobu Cyclizations To Give Compounds 1:** A solution of a compound **2** (0.3 mmol) in dry $CH_2Cl_2$ (10 mL) was cooled to 0 °C and treated with $PPh_3$ (0.45 mmol) and DEAD (40% in toluene, 0.45 mmol). After stirring for 1 h, the mixture was concentrated and chromatographed with PE/AcOEt mixtures. Separation of compounds **1** from triphenylphosphane oxide and diethyl hydrazodicarboxylate was in all cases untroublesome, because both side products are considerably more polar.

**One-Pot Synthesis of Compound 1f (Conditions D):** 2-Aminophenol (212.2 mg, 1.94 mmol) was dissolved in dry *i*PrOH (4 mL) and treated with glycolic acid (147.5 mg, 1.94 mmol), benzaldehyde (197 μL, 1.94 mmol) and the isocyanide **8** (383.6 mg, 1.62 mmol). The mixture was stirred at room temp. for 48 h and was then concentrated to dryness, taken up with dry $CH_2Cl_2$ (54 mL) and cooled to 0 °C. The solution was treated with $PPh_3$ (637 mg, 2.43 mmol) and DEAD in toluene (40%, 1.11 mL, 2.43 mmol) and stirred at 0 °C for 1 h. Concentration and chromatography (PE/AcOEt, 80:20 to 70:30) gave pure **1f** as a solid (449.7 mg, 56%).

**Synthesis of Compounds 1q–1t:** A solution of **1c**, **1f**, **1g** or **1i** (0.25 mmol) in EtOH (96%, 5 mL) was hydrogenated in the presence of Pd/C (10%) for the required time (**1c**: 42 h; **1f**: 22 h; **1g**: 72 h; **1i**: 23 h) at room temp. and standard pressure. In the case of **1f**, for solubility reasons, hydrogenation was carried out in a mixture of EtOH (96%, 5 mL) and $CH_2Cl_2$ (2 mL). When the reaction

was complete, filtration of the catalyst and concentration gave pure **1q**, **1r** and **1t**. Only in the case of **1g** was the product slightly impure and therefore chromatographed (PE/AcOEt, 55:45).

**Synthesis of Compound 1u:** A solution of **1l** (118.0 mg, 0.28 mmol) in THF (3 mL) was treated with aqueous LiOH (2 M, 490 μL, 0.98 mmol) and stirred at room temp. for 23 h. After addition of aqueous HCl (0.5 M, 10 mL), the mixture was extracted three times with $Et_2O$ and once with AcOEt. The combined organic phases were washed with brine, and the mixture was concentrated to dryness. The residue was taken up in dry $CH_2Cl_2$ (2 mL) and treated with glycine methyl ester hydrochloride (58.1 mg, 0.46 mmol), triethylamine (155 μL, 1.12 mmol) and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP, 222.3 mg, 0.43 mmol). After the mixture had been stirred at room temp. for 22 h and concentrated to dryness, chromatography ($CH_2Cl_2$/acetone, 90:10 to 85:15) afforded pure **1u** as a foam (45.0 mg, 34%).

**Synthesis of Compounds 1v:** A solution of **1p** (diastereomeric mixture in a 84:16 ratio, 89.6 mg, 0.16 mmol) in dry $CH_2Cl_2$ (0.5 mg) was treated with trifluoroacetic acid (250 μL, 3.37 mmol) and stirred at room temp. for 30 min. The solvent was evaporated, and the residue was taken up with *n*-heptane and concentrated again (in order to remove trifluoroacetic acid azeotropically; this procedure was repeated twice). The residue was taken up in dry pyridine (0.5 mL) and treated with acetic anhydride (45 μL, 0.48 mmol). After stirring at room temp. for 3 h, the reaction mixture was poured into HCl (0.5 M, 25 mL) and extracted three times with AcOEt. The organic phases were washed with brine, concentrated and chromatographed with $CH_2Cl_2$/acetone (80:20). The two diastereomers could be separated to afford the pure, faster running, major diastereoisomer (45.6 mg) and a mixture enriched (80:20) in the minor, slower running, diastereoisomer (7.2 mg). Overall yield: 66%.

**Spectral and Analytical Data for the Benzoxazinones 1**

**Note:** In the cases of compounds **1** derived from aliphatic aldehydes (**1a**, **1b**, **1c**, **1o**, **1q**), as a result of restricted rotation around the exocyclic N–C bond, even at 50 °C the signals of C*H*-$R^2$, *C*H-$R^2$ and of C-4a tend to be very broad in the $^1$H and $^{13}$C NMR spectra.

***N*-Cyclohexyl-3-methyl-2-{3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}butanamide (1a):** $R_f$ = 0.83 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 50 °C): $\delta$ = 0.71 (d, *J* = 6.9 Hz, 3 H, $CH_3$), 1.08 (d, *J* = 6.9 Hz, 3 H, $CH_3$), 1.02–1.44 (m, 5 H, cyclohexyl), 1.50–1.93 (m, 5 H, cyclohexyl), 2.83 [sept, *J* = 6.2 Hz, 1 H, C*H*($CH_3$)$_2$], 3.77 [ddq, *J* = 3.9 (q), 9.9, 13.8 Hz (d), 1 H, C*H*NH], 4.52 and 4.63 (AB system, *J* = 15.0 Hz, 2 H, $CH_2O$), 4.61 (br. d, 1 H, C*H*–*i*Pr), 6.56 (br. s, 1 H, N*H*), 6.97–7.06 (m, 3 H), 7.61–7.68 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 18.4, 20.3 ($CH_3$), 24.5, 24.6, 25.5, 32.6, 32.7 (cyclohexyl $CH_2$), 25.8 [*C*H($CH_3$)$_2$], 48.1 (CHNH), 63.3 (very br., *C*H–*i*Pr), 68.6 ($CH_2O$), 117.1, 118.2, 123.2, 124.9 (aromatic CH), 128.7 (very br., C–N), 146.3 (C–O), 168.3, 168.6 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3674, 3004, 2928, 2852, 1669, 1601, 1496, 1386, 1358, 1184, 1038, 921 cm$^{-1}$. GC–MS: $t_R$ = 9.49 min. MS: *m*/*z* (%) = 330 (23.9) $[M]^+$, 288 (3.4), 204 (100.0), 189 (3.9), 182 (11.1), 176 (10.8), 162 (13.2), 160 (6.5), 149 (55.4), 134 (9.2), 120 (35.7), 93 (6.9), 83 (8.4), 77 (7.4), 65 (7.0), 55 (26.7), 43 (7.3), 41 (23.5), 39 (7.3). HRMS ($ESI^-$): calcd. for $C_{19}H_{25}N_2O_3$ 329.1865 $[M - H]^+$; found 329.1850.

***N*-*tert*-Butyl-2-cyclohexyl-2-{3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}acetamide (1b):** $R_f$ = 0.83 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 50 °C): $\delta$ = 0.79 [dq, *J* = 3.3 (d), 7.9 Hz (q), 1 H, cyclohexyl], 0.93–1.22 (m, 3 H, cyclohexyl), 1.31 [s, 9 H, $(CH_3)_3C$], 1.26–1.40 (m, 2 H, cyclohexyl), 1.53–1.68 (m, 2 H, cyclohexyl), 1.68–1.80 (m, 1 H, cyclohexyl), 1.96–2.06 (m, 1 H, cyclohexyl), 2.50 [tq, *J* = 3.3 (t), 11.1 Hz (q), 1 H, cyclohexyl], 4.54 and 4.62 (AB system, *J* = 15.0 Hz, 2 H, $CH_2O$), 4.58–4.68 (br. signal, 1 H, C*H*–*c*Hex), 6.49 (br. s, 1 H, N*H*), 6.97–7.06 (m, 3 H), 7.60–7.68 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 45 °C): $\delta$ = 25.5, 25.6, 26.3, 28.4, 31.0 (cyclohexyl $CH_2$), 28.7 [($CH_3$)$_3$C], 34.7 (cyclohexyl CH), 51.3 [*C*($CH_3$)$_3$], 64.5 (very br., *C*H–*c*Hex), 68.6 ($CH_2O$), 117.1, 118.2, 123.3, 124.8 (aromatic CH), 129.0 (very br., C–N), 146.3 (C–O), 168.0, 168.7 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3677, 3408, 2925, 2852, 1673, 1605, 1498, 1393, 1359, 1190, 1124, 1029, 920 cm$^{-1}$. GC–MS: $t_R$ 9.15 min. MS: *m*/*z* (%) = 344 (9.6) $[M]^+$, 262 (25.4), 245 (23.0), 244 (50.4), 196 (8.5), 189 (27.5), 162 (26.9), 150 (51.2), 149 (92.7), 140 (6.3), 134 (20.5), 120 (23.1), 95 (100.0), 93 (13.2), 91 (5.7), 79 (8.1), 77 (14.2), 67 (19.7), 65 (10.4), 57 (28.0), 55 (23.6), 53 (7.3), 41 (37.1), 39 (9.9). HRMS ($ESI^+$): calcd. for $C_{20}H_{28}N_2O_3Na$ 367.1998 $[M + Na]^+$; found 367.1982.

***N*-[(4-Benzyloxycarbonyl)phenyl]-3-methyl-2-{3-oxo-2*H*-benzo[*b*]-(1,4)oxazin-4(3*H*)-yl}butanamide (1c):** $R_f$ = 0.75 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 50 °C): $\delta$ = 0.78 (d, *J* = 6.6 Hz, 3 H, $CH_3$), 1.13 (d, *J* = 6.6 Hz, 3 H, $CH_3$), 2.99 [m$_c$, 1 H, C*H*-($CH_3$)$_2$], 4.59 and 4.66 (AB system, *J* = 15.3 Hz, 2 H, $CH_2O$), 4.55–4.65 (br. signal, 1 H, C*H*–*i*Pr), 5.34 (s, 2 H, $CH_2Ph$), 6.97–7.08 (m, 3 H), 7.28–7.40 (m, 5 H), 7.50–7.58 (m, 1 H), 7.60 (d, *J* = 8.7 Hz, 2 H), 8.02 (d, *J* = 8.7 Hz, 2 H), 9.11 (br. s, NH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 50 °C): $\delta$ = 18.5, 20.2 ($CH_3$), 25.8 [*C*H($CH_3$)$_2$], 66.6 ($CH_2O$), 117.4, 117.8, 119.2 (×2), 123.4, 125.3, 128.1 (×2), 128.2, 128.6 (×2), 131.0 (×2, aromatic CH), 126.0, 136.3, 142.1, 146.5 (aromatic quat.), 165.8, 168.1, 169.4 (C=O) ppm. *Note*: As a result of restricted rotation, the signals of *C*H–*i*Pr and of C-4a are very broad and cannot be detected by $^{13}$C NMR spectroscopy. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3670, 3599, 3524, 3304, 3012, 1701, 1663, 1596, 1498, 1467, 1360, 1310, 1264, 1171, 1106, 1041, 919, 849 cm$^{-1}$. HRMS ($ESI^+$): calcd. for $C_{27}H_{27}N_2O_5$ 459.1920 $[M + H]^+$; found 459.1922.

**2-{3-Oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}-*N*-pentyl-2-phenylacetamide (1e):** $R_f$ = 0.69 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.86 (t, *J* = 7.0 Hz, 3 H, $CH_3$), 1.15–1.35 (m, 4 H, $CH_2$), 1.45 (quint, *J* = 7.3 Hz, 2 H, $HNCH_2CH_2$), 3.15–3.40 (m, 2 H, $NHCH_2$), 4.65 and 4.73 (AB system, *J* = 15.3 Hz, 2 H, $CH_2O$), 6.10 (s, 1 H, CH-Ph), 6.11 (br. signal, 1 H NH), 6.87 (ddd, *J* = 2.0, 6.7, 8.1 Hz, 1 H), 6.94–7.07 (m, 3 H), 7.28–7.41 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 14.1 ($CH_3$), 22.2, 28.88, 28.92 ($CH_2$), 39.9 ($CH_2NH$), 61.6 (CHPh), 68.2 ($CH_2O$), 117.1, 117.4, 122.8, 124.6, 127.8 (×2), 128.3, 128.9 (×2, aromatic CH), 128.7, 133.9, 145.9 (aromatic quat.), 166.5, 167.6 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3426, 3032, 2928, 1678, 1603, 1495, 1467, 1394, 1342, 1271, 1201, 1127, 1039, 922 cm$^{-1}$. GC–MS: $t_R$ 10.7 min. MS: *m*/*z* (%) = 352 (6.6) $[M]^+$, 239 (82.3), 238 (30.7), 210 (38.1), 152 (5.6), 118 (5.9), 106 (5.3), 92 (10.0), 91 (100.0), 90 (11.0), 79 (5.9), 77 (14.9), 65 (7.4), 43 (21.6), 39 (5.7). HRMS ($ESI^+$): calcd. for $C_{21}H_{24}N_2O_3Na$ 375.1685 $[M + Na]^+$; found 375.1692.

***N*-{[2-(4-Benzyloxy)phenyl]ethyl}-2-{3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}-2-phenylacetamide (1f):** $R_f$ = 0.60 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 2.65–2.81 (m, 2 H, $NHCH_2CH_2$), 3.53 (q, *J* = 6.5 Hz, 2 H, $NHCH_2$), 4.57 and 4.68 (AB system, *J* = 15.3 Hz, 2 H, $CH_2O$), 5.02 (s, 2 H, $CH_2Ph$), 6.00 (s, 1 H, CHPh), 6.05 (t, *J* = 5.4 Hz, 1 H, NH), 6.79–6.90 (m, 3 H), 6.94–7.03 (m, 5 H), 7.29 (s, 5 H), 7.32–7.46 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 34.4 ($CH_2CH_2NH$), 41.1 ($CH_2NH$), 61.6 (CHPh), 68.1 ($CH_2O$), 70.0 ($CH_2Ph$), 114.9 (×2), 117.1, 117.2, 122.8, 124.6, 127.4 (×2), 127.9 (×2), 128.0, 128.3, 128.6 (×2), 128.9 (×2), 129.7 (×2, aromatic CH), 128.8, 130.8,

133.8, 137.1, 145.9, 157.6 (aromatic quat.), 166.6, 167.9 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3668, 3594, 3419, 2992, 1669, 1601, 1492, 1395, 1338, 1253, 1029, 910 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $C_{31}H_{28}N_2O_4Na$ 515.1947 $[M + Na]^+$; found 515.1922.

***N*-{[2-(4-Benzyloxy)phenyl]ethyl}-2-(3-furyl)-2-{3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}acetamide (1g):** $R_f$ = 0.66 (PE/AcOEt, 1:1). $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 2.62–2.80 (m, 2 H, $NHCH_2CH_2$), 3.44 [dq, $J$ = 6.6 Hz (q), 13.2 (d), 1 H, NHC*H*H], 3.44 [dq, $J$ = 6.6 Hz (q), 13.2 (d), 1 H, NHC*H*H], 3.60 [dq, $J$ = 6.6 Hz (q), 13.2 (d), 1 H, NHC*H*H], 4.47 and 4.66 (AB system, $J$ = 15.3 Hz, 2 H, $CH_2O$), 5.00 (s, 2 H, $CH_2Ph$), 6.13 (t, $J$ = 5.4 Hz, 1 H, NH), 6.23 (d, $J$ = 1.2 Hz, 4-H of furyl), 6.30 (s, 1 H, CHAr), 6.80 (d, $J$ = 8.7 Hz, 2 H, *H ortho* to OBn), 6.87–7.05 (m, 6 H), 7.29 (t, $J$ = 3.9 Hz, 1 H, H furyl), 7.30–7.45 (m, 5 H), 7.66 (d, $J$ = 0.9 Hz, 1 H, H furyl) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 34.4 ($CH_2CH_2NH$), 40.9 ($CH_2NH$), 52.2 (CHAr), 67.9 ($CH_2O$), 69.9 ($CH_2Ph$), 110.1, 142.3, 143.2 (CH furyl), 114.9 (×2), 117.2, 117.3, 122.8, 124.6, 127.4 (×2), 128.0, 128.6 (×2), 129.6 (×2, aromatic CH), 118.3 (furyl quat.), 130.6, 137.0, 145.8, 157.4 (aromatic quat., the missing signal probably falls under the signal at $\delta$ = 128.6 ppm), 166.4, 167.4 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3672, 3613, 3420, 3002, 1715, 1684, 1609, 1497, 1385, 1337, 1191, 1126, 1020, 919, 804 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $C_{29}H_{26}N_2O_5Na$ 505.1739 $[M + Na]^+$; found 505.1742.

***N*-*tert*-Butyl-2-{6-methyl-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}-2-(3-thienyl)acetamide (1h):** $R_f$ = 0.69 (PE/AcOEt, 1:1). $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.32 [s, 9 H, $C(CH_3)_3$], 2.20 (s, 3 H, Ar-$CH_3$), 4.60 and 4.66 (AB system, $J$ = 15.0 Hz, 2 H, $CH_2O$), 5.91 (br. s, 1 H, NH), 6.23 (s, 1 H, CHAr), 6.77 (ddd, $J$ = 0.6, 1.8, 8.4 Hz, 1 H, 8-H), 6.86–6.92 (m, 2 H, 5-H and 7-H), 7.06 (dd, $J$ = 1.4, 5.0 Hz, 1 H, 5-H of thienyl), 7.30 (dd, $J$ = 3.0, 5.1 Hz, 1 H, 4-H of thienyl), 7.41 (dt, $J$ = 1.4, 3.1 Hz, 1 H, 2-H of thienyl) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 21.0 (Ar-$CH_3$), 28.5 [$C(CH_3)_3$], 51.8 [$C(CH_3)_3$], 57.3 (CHAr), 68.3 ($CH_2O$), 116.7, 117.9, 124.9 (CH of benzoxazine), 124.4 (2-C of thienyl), 126.3 (4-C of thienyl), 127.5 (2-C of thienyl), 127.9, 132.4, 134.7, 143.8 (aromatic quat.), 166.3, 166.6 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3672, 3603, 3413, 2964, 1677, 1610, 1502, 1431, 1366, 1272, 1023, 918 $cm^{-1}$. GC–MS: $t_R$ = 9.71 min. MS: *m*/*z* (%) = 358 (5.1) $[M]^+$, 259 (71.5), 230 (12.1), 134 (5.5), 112 (17.8), 97 (100.0), 96 (8.3), 91 (6.6), 85 (7.0), 77 (11.8), 65 (6.2), 57 (23.9), 45 (6.2), 42 (6.1), 41 (17.6), 39 (7.9). HRMS ($ESI^+$): calcd. for $C_{19}H_{22}N_2O_3SNa$ 381.1249 $[M + Na]^+$; found 381.1251.

***N*-[(3-Benzyloxyphenyl)methyl]-2-(4-methoxyphenyl)-2-{6-methyl-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}acetamide (1i):** $R_f$ = 0.65 (PE/AcOEt, 1:1). $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 2.18 (s, 3 H, Ar-$CH_3$), 3.78 (2, 3 H, $OCH_3$), 4.47 and 4.50 [AB part of ABX system, $J$ = 15.1 (AB), 5.6 (AX), 5.6 Hz (BX), 2 H, $ArCH_2N$], 4.58 and 4.67 (AB system, $J$ = 15.3 Hz, 2 H, $CH_2O$), 5.03 (s, 2 H, $ArCH_2O$), 5.94 (s, 1 H, CHAr), 6.35 (br. t, $J$ = 5.6 Hz, 1 H, NH), 6.73–6.92 (m, 8 H), 7.20 (t, $J$ = 8.0 Hz, 1 H, *H meta* to OBn), 7.29–7.45 (m, 7 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 21.0 (Ar-$CH_3$), 43.8 ($CH_2N$), 55.3 ($OCH_3$), 61.7 (CHAr), 68.3 ($CH_2O$), 69.9 ($PhCH_2O$), 113.7, 114.1, 114.5 (×2), 116.8, 117.3, 119.9, 125.0, 127.5 (×2), 128.0, 128.6 (×2), 129.5 (×2), 129.7 (aromatic CH), 125.9, 128.8, 132.5, 136.9, 139.5, 143.8, 159.1, 159.6 (aromatic quat.), 166.4, 168.1 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3676, 3596, 3421, 2996, 2837, 1675, 1608, 1488, 1441, 1353, 1250, 1022, 917 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $C_{32}H_{30}N_2O_5Na$ 545.2052 $[M + Na]^+$; found 545.2053.

***N*-Butyl-2-(3-bromophenyl)-2-{6-chloro-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}acetamide (1j):** $R_f$ = 0.63 (PE/AcOEt, 1:1). $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.90 (t, $J$ = 7.3 Hz, 3 H, $CH_3CH_2$), 1.23–1.35 (m, 2 H, $CH_2CH_3$), 1.43–1.54 (m, 2 H, $NCH_2CH_2$), 3.24–3.40 (m, 2 H, $NCH_2$), 4.64 and 4.72 (AB system, $J$ = 15.3 Hz, 2 H, $CH_2O$), 6.03 (s, 1 H, CHAr), 6.07 (br. t, $J$ = 5.2 Hz, 1 H, NH), 6.92–6.98 (m, 2 H, 7-H and 8-H), 7.06 (t, $J$ = 1.2 Hz, 1 H, 5-H), 7.26 (t, $J$ = 7.8 Hz, 1 H, 5′-H), 7.30 [dt, $J$ = 1.6 (t), 7.8 Hz (d), 1 H, 6′-H], 7.49 [dt, $J$ = 1.6 (t), 7.2 Hz (d), 1 H, 4′-H], 7.53 (s, 1 H, 2′-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.7 ($CH_3$), 20.0 ($CH_2CH_3$), 31.3 ($NCH_2CH_2$), 39.9 ($CH_2N$), 60.9 (CHAr), 68.2 ($CH_2O$), 117.5 (C-5), 118.2 (C-7 or C-8), 123.2 (aromatic quat.), 124.6 (C-7 or C-8), 126.5 (C-6′), 127.9, 129.4 (aromatic quat.), 130.5 (C-5′), 130.9 (C-2′), 131.9 (C-4′), 135.8 (aromatic quat.), 144.6 (C-8a), 166.1, 166.6 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3432, 2997, 2955, 2873, 1694, 1600, 1494, 1418, 1355, 1190, 1046 $cm^{-1}$. GC–MS: $t_R$ = 11.83 min. MS: *m*/*z* (%) = 454 (1.6), 452 (6.1), 450 (4.7) $[M]^+$, 355 (22.2), 353 (88.5), 351 (73.2), 326 (6.2), 324 (26.9), 322 (22.2), 243 (7.8), 242 (9.2), 240 (5.5), 198 (7.4), 196 (7.7), 184 (8.4), 183 (6.8), 182 (5.0), 171 (92.2), 169 (100.0), 154 (12.4), 126 (6.6), 111 (7.5), 104 (5.7), 102 (6.1), 99 (9.6), 90 (20.0), 89 (47.8), 78 (6.7), 77 (14.6), 76 (10.4), 75 (14.8), 63 (20.0), 57 (57.0), 51 (7.8), 42 (7.5), 41 (47.7), 39 (13.1). HRMS ($ESI^+$): calcd. for $C_{20}H_{21}BrClN_2O_3$ 451.0424 $[M + H]^+$; found 451.0433.

***N*-Cyclohexyl-2-{6-(methoxycarbonyl)-3-oxo-2*H*-benzo[*b*][1,4]-oxazin-4(3*H*)-yl}-2-(4-methylphenyl)acetamide (1k):** $R_f$ = 0.57 (PE/AcOEt, 1:1). $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.00–1.45 (m, 5 H), 1.50–2.02 (m, 5 H), 2.34 (s, 3 H, $ArCH_3$), 3.83 (s, 3 H, $OCH_3$), 3.80–3.90 (m, 1 H, C*H*NH), 4.68 and 4.78 (AB system, $J$ = 15.3 Hz, 2 H, $CH_2O$), 5.77 (br. d, $J$ = 8.1 Hz, 1 H, NH), 6.03 (s, 1 H, CHAr), 7.00 (d, $J$ = 8.4 Hz, 1 H, 8-H), 7.19 (d, $J$ = 8.1 Hz, 2 H, 2′-H or 3′-H), 7.33 (d, $J$ = 8.1 Hz, 2 H, 2′-H or 3′-H), 7.67 (dd, $J$ = 1.8, 8.4 Hz, 1 H, 7-H), 7.76 (d, $J$ = 1.5 Hz, 1 H, 5-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 21.1 ($ArCH_3$), 24.6, 24.7, 25.4, 32.61, 32.64 (cyclohexyl $CH_2$), 48.8 (CHN), 52.1 ($CH_3O$), 61.7 (CHAr), 67.9 ($CH_2O$), 116.0 (C-8), 118.5 (C-5), 124.5 (C-4a or C-6a), 128.3 (C-2′ or C-3′), 128.6 (C-4a or C-6a), 129.6 (C-2′ or C-3′), 130.9, 138.8 (C-1′ and C-4′), 149.5 (C-8a), 165.1, 166.1, 166.3 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3677, 3610, 3411, 3002, 2926, 2851, 1686, 1603, 1499, 1437, 1375, 1299, 1236, 1108, 1042, 921, 880 $cm^{-1}$. GC–MS: $t_R$ = 13.98 min. MS: *m*/*z* (%) = 436 (1.2) $[M]^+$, 405 (1.7), 337 (2.9), 311 (64.7), 282 (17.6), 176 (2.6), 132 (3.5), 120 (6.9), 105 (100.0), 104 (7.6), 98 (5.9), 77 (5.3), 55 (11.9), 41 (7.9). HRMS ($ESI^+$): calcd. for $C_{25}H_{28}N_2O_5Na$ 459.1896 $[M + Na]^+$; found 459.1911.

***N*-Cyclohexyl-2-{6-(methoxycarbonyl)-3-oxo-2*H*-benzo[*b*][1,4]-oxazin-4(3*H*)-yl}-2-phenylacetamide (1l):** $R_f$ = 0.56 (PE/AcOEt, 1:1). $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.00–1.45 (m, 5 H), 1.50–1.71 (m, 3 H), 1.80–2.05 (m, 3 H), 3.83 (s, 3 H, $OCH_3$), 3.82–3.92 (m, 1 H, C*H*NH), 4.69 and 4.79 (AB system, $J$ = 15.2 Hz, 2 H, $CH_2O$), 5.79 (br. d, $J$ = 8.1 Hz, 1 H, NH), 6.10 (s, 1 H, CHAr), 7.01 (d, $J$ = 8.4 Hz, 1 H, 8-H), 7.30–7.47 (m, 5 H, phenyl CH), 7.67 (dd, $J$ = 1.8, 8.4 Hz, 1 H, 7-H), 7.76 (d, $J$ = 1.8 Hz, 1 H, 5-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 24.6 (×2), 25.4, 32.61, 32.65 (cyclohexyl $CH_2$), 48.8 (CHN), 52.1 ($CH_3O$), 61.9 (CHAr), 68.0 ($CH_2O$), 117.0 (C-8), 118.7 (C-5), 124.6 (C-4a or C-6a), 126.3 (C-7), 128.3 (C-2′ or C-3′), 128.5 (C-4a or C-6a), 128.8 (C-4′), 129.2 (C-2′ or C-3′), 134.0 (C-1′), 149.6 (C-8a), 165.2, 166.0, 166.1 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3411, 2928, 2851, 1670, 1602, 1496, 1436, 1371, 1247, 1107, 1020, 878, 823 $cm^{-1}$. GC–MS: $t_R$ = 13.17 min. MS: *m*/*z* (%) = 422 (1.4) $[M]^+$, 391 (2.0), 297 (100.0), 296 (10.7), 268 (20.3), 118 (5.1), 106 (5.9), 91 (85.2), 90 (6.2), 55 (12.7), 41 (8.0). HRMS ($ESI^+$): calcd. for $C_{24}H_{26}N_2O_5Na$ 445.1739 $[M + Na]^+$; found 445.1734.

**(2*R*,*S*)-*N*-Cyclohexyl-2-{(2*R*)-2-methyl-3-oxo-2*H*-benzo[*b*][1,4]-oxazin-4(3*H*)-yl}-2-phenylacetamides (1n):** The two diastereoisomers (A/B, 72:28) could not be separated. $R_f$ = 0.38 (PE/AcOEt, 75:25). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.80–1.45 (m, 5 H), 1.57 (diast. A, d, $J$ = 6.9 Hz, 2.16 H, $CH_3$), 1.64 (diast. B, d, $J$ = 6.9 Hz, 0.84 H, $CH_3$), 1.50–2.00 (m, 5 H), 3.75–3.94 (m, 1 H, C*H*NH), 4.66 (diast. B, q, $J$ = 6.8 Hz, 0.28 H, C*H*$CH_3$), 4.76 (diast. A, q, $J$ = 6.8 Hz, 0.72 H, C*H*$CH_3$), 5.90 (diast. B, br. d, $J$ = 8.1 Hz, 0.28 H, NH), 5.95 (diast. A, br. d, $J$ = 8.4 Hz, 0.72 H, NH), 6.11 (diast. A, s, 0.72 H, CHAr), 6.15 (diast. B, s, 0.28 H, CHAr), 6.80–7.06 (m, 4 H, CH benzoxazinone), 7.28–7.38 (m, 5 H, CH phenyl) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 16.06 (A), 16.1 (B, $CH_3$), 24.6 (×2), 25.4, 32.5 (A), 32.6 (B), 32.7 (cyclohexyl $CH_2$), 48.5 (A), 48.6 (B, CHN), 61.3 (B), 61.6 (A, CHAr), 74.0 (A), 74.1 (B, *C*HCH$_3$), 117.0 (A), 117.3 (B), 117.49 (B), 117.54 (A), 122.5 (B), 122.7 (A), 124.4 (B), 124.5 (A, C-5, C-6, C-7, C-8), 127.6 (A+B, C-3′), 127.9 (A+B, C-4′), 128.19 (B), 128.21 (A, C-5a), 128.8 (B), 128.9 (A, C-2′), 134.1 (A+B, C-1′), 144.8 (A), 145.3 (B, C-8a), 166.75 (B), 166.80 (A), 168.5 (A), 168.6 (B, C=O) ppm. (C-5), 124.6 (C-4a or C-6a), 126.3 (C-7), 128.3 (C-2′ or C-3′), 128.5 (C-4a or C-6a), 128.8 (C-4′), 129.2 (C-2′ or C-3′), 129.6 (C-2′ or C-3′), 134.0 (C-1′), 149.6 (C-8a), 165.2, 166.0, 166.1 (C=O). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3670, 3418, 3006, 2854, 1675, 1601, 1493, 1448, 1378, 1210, 1110, 1028, 918, 821 cm$^{-1}$. GC–MS: $t_R$ = 11.29 min. MS: *m*/*z* (%) = 378 (4.1) [M]$^+$, 253 (100.0), 224 (5.8), 152 (5.2), 120 (63.1), 118 (5.0), 106 (6.6), 91 (75.0), 90 (9.8), 83 (5.4), 77 (8.5), 65 (7.9), 55 (19.5), 41 (13.5), 39 (5.2). HRMS (ESI$^+$): calcd. for $C_{23}H_{26}N_2O_3Na$ 401.1841 [M + Na]$^+$; found 401.1822.

**(2*R*,*S*)-*N*-Butyl-2-{(2*R*)-6-chloro-2-methyl-3-oxo-2*H*-benzo[*b*][1,4]-oxazin-4(3*H*)-yl}-3-methylbutanamides (1o):** The two diastereoisomers (A/B, 64:36) could not be separated. $R_f$ = 0.80 (PE/AcOEt, 50:50). $^1$H NMR (300 MHz, [D$_6$]DMSO, 40 °C): $\delta$ = 0.58 (diast. B, d, $J$ = 6.6 Hz, 1.08 H, C*H*$_3$CHCH$_3$), 0.68 (diast. A, d, $J$ = 6.6 Hz, 1.92 H, C*H*$_3$CHCH$_3$), 0.74 (diast. A, t, $J$ = 7.2 Hz, 1.92 H, C*H*$_3$CH$_2$), 0.80 (diast. B, t, $J$ = 7.2 Hz, 1.08 H, C*H*$_3$CH$_2$), 1.046 (diast. A, d, $J$ = 6.3 Hz, 1.92 H, C*H*$_3$CHCH$_3$), 1.051 (diast. B, d, $J$ = 6.3 Hz, 1.08 H, C*H*$_3$CHCH$_3$), 1.10–1.37 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 1.44 (diast. A, d, $J$ = 6.9 Hz, 1.92 H, C*H*$_3$CH), 1.47 (diast. B, d, $J$ = 6.9 Hz, 1.08 H, C*H*$_3$CH), 2.42–2.56 [diast. B, m, 0.36 H, C*H*(CH$_3$)$_2$], 2.63 [diast. A, dsept, $J$ = 6.6 (sept), 10.6 Hz (d), 0.64 H, C*H*(CH$_3$)$_2$], 2.83–2.95 (diast. A, m, 0.64 H, C*H*HNH), 2.93–3.05 (diast. B, m, 0.36 H, C*H*HNH), 3.08–3.24 (diast. A + B, m, 1 H, C*H*HNH), 4.74 (diast. B, q, $J$ = 6.6 Hz, 0.36 H, C*H*CH$_3$), 4.79 (diast. A, q, $J$ = 6.6 Hz, 0.64 H, C*H*CH$_3$), 4.88 (diast. A, d, $J$ = 10.6 Hz, 0.64 H, C*H*–*i*Pr), 4.96 (diast. B, d, $J$ = 10.6 Hz, 0.36 H, C*H*–*i*Pr), 7.01–7.12 (m, 2 H, 7-H and 8-H), 7.50 (diast. A, d, $J$ = 1.8 Hz, 0.64 H, 5-H), 7.61 (diast. B, d, $J$ = 1.8 Hz, 0.36 H, 5-H), 7.94 (diast. A, br. d, $J$ = 5.7 Hz, 0.64 H, NH), 8.03 (diast. B, br. d, $J$ = 5.4 Hz, 0.36 H, NH) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO, 40 °C): $\delta$ = 13.3 (A + B, CH$_2$*C*H$_3$), 15.5 (A), 15.9 (B, *C*H$_3$CH), 17.8 (A + B, *C*H$_2$CH$_3$), 19.0 (A), 19.2 (B), 20.6 (B), 20.9 (A) [(*C*H$_3$)$_2$-CH], 25.4 (B), 26.2 (A) [*C*H(CH$_3$)$_2$], 30.6 (A + B, NCH$_2$*C*H$_2$), 38.1 (A), 38.3 (B, *C*H$_2$NH), 60.3 (B), 61.0 (A, *C*H–*i*Pr), 72.8 (A), 73.1 (B, *C*HCH$_3$), 116.5 (A), 117.0 (B, C-5), 118.1 (B), 118.2 (A), 123.3 (A), 123.5 (B, C-7 and C-8), 125.7 (B), 125.8 (A), 128.8 (A), 129.3 (B, C-4a and C-6), 143.3 (A), 143.9 (B, C-8a), 167.06 (A), 167.14 (B), 167.6 (A), 168.1 (B, C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3673, 3599, 3403, 2997, 2872, 1670, 1602, 1489, 1435, 1370, 1231, 1111, 1029, 924 cm$^{-1}$. HRMS (ESI$^+$): calcd. for $C_{18}H_{25}ClN_2O_3Na$ 375.1541 [M + Na]$^+$; found 375.1457.

**(2*R*,*S*)-2-(3-Bromophenyl)-2-{(2*R*)-2-[(2-*tert*-butoxycarbonylamino)-ethyl]-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}-*N*-butylacetamides (1p):** The two diastereoisomers (A/B, 84:16) could not be separated. $R_f$ = 0.63 (PE/AcOEt, 50:50). $^1$H NMR (300 MHz, $CDCl_3$, 50 °C, only the signals for the major diastereoisomer are reported): $\delta$ = 0.86 (t, $J$ = 7.2 Hz, C*H*$_3$CH$_2$), 1.15–1.48 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 1.41 [s, 9 H, (CH$_3$)$_3$C], 2.07–2.21 (m, 2 H, OCH–C*H*$_2$), 3.15–3.50 (m, 4 H, C*H*$_2$NH), 4.72 (dd, $J$ = 5.4, 6.9 Hz., 1 H, 2-H), 4.76 (br. s, 1 H, N*H*Boc), 6.26 (s, 1 H, CHAr), 6.37 (br. t, $J$ = 4.8 Hz, 1 H N*H*CH$_2$), 6.85–6.94 (m, 1 H), 6.95–7.05 (m, 3 H), 7.19 (t, $J$ = 7.8 Hz, 1 H, 5′-H), 7.22–7.29 (m, 1 H, 6′-H), 7.42 (d, $J$ = 7.8 Hz, 1 H, 4′-H), 7.53 (s, 1 H, 2′-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 50 °C, only the signals for the major diastereoisomer are reported): $\delta$ = 13.6 (CH$_2$*C*H$_3$), 20.0 (*C*H$_2$CH$_3$), 28.4 [C(*C*H$_3$)$_3$], 30.6 (OCH-*C*H$_2$), 31.4 (NCH$_2$*C*H$_2$), 36.8 (br., *C*H$_2$NHBoc), 39.8 (other *C*H$_2$NH), 60.2 (CHAr), 76.0 (2-C), 79.5 [very br., *C*(CH$_3$)$_3$], 117.4, 117.7, 123.0, 124.9 (C-5, C-6, C-7, C-8), 122.8 (C-Br), 126.3 (C-6′), 128.2 (C-4a), 130.1 (C-5′), 130.9 (C-2′), 131.3 (C-4′), 136.4 (C-1′), 144.8 (C-8a), 155.9, 167.1, 167.8 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3668, 3583, 3451, 2999, 2707, 1685, 1594, 1492, 1390, 1366, 1158, 1028, 922 cm$^{-1}$. HRMS (ESI$^+$): calcd. for $C_{27}H_{35}BrN_3O_5$ 560.1760 [M + H]$^+$; found 560.1756.

***N*-(4-Carboxyphenyl)-3-methyl-2-{3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}butanamide (1q):** $R_f$ = 0.40 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 55 °C): $\delta$ = 0.79 (d, $J$ = 6.6 Hz, 3 H, $CH_3$), 1.14 (d, $J$ = 6.6 Hz, 3 H, $CH_3$), 2.99 [m$_c$, 1 H, C*H*(CH$_3$)$_2$], 4.60 and 4.66 (AB system, $J$ = 15.6 Hz, 2 H, $CH_2O$), 4.50–4.75 (very br. signal, 1 H, C*H*–*i*Pr), 4.90–5.50 (very br. signal, 1 H, $CO_2$ H), 6.99–7.10 (m, 3 H), 7.52–7.61 (m, 1 H), 7.64 (d, $J$ = 8.6 Hz, 2 H, *H meta* to $CO_2$ H), 8.05 (d, $J$ = 8.6 Hz, 2 H, *H ortho* to $CO_2$ H), 9.17 (br. s, 1 H, NH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 55 °C): $\delta$ = 18.5, 20.2 ($CH_3$), 25.9 [*C*H(CH$_3$)$_2$], 68.8 ($CH_2O$), 117.4, 117.9, 119.3 (×2), 123.5, 125.4, 131.5 (×2, aromatic CH), 125.2, 128.9 (very br.), 142.7, 146.5 (aromatic quat.), 165.8, 168.1, 169.4 (C=O) ppm. *Note*: As a result of restricted rotation, the signals of *C*H–*i*Pr and of C-4a are very broad, and the first of them could not be detected by $^{13}$C NMR spectroscopy. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3674, 3510, 3261, 2961, 2661, 1676, 1593, 1496, 1387, 1357, 1309, 1265, 1170, 1114, 1040, 918, 854 cm$^{-1}$. HRMS (ESI$^-$): calcd. for $C_{20}H_{19}N_2O_5$ 367.1294 [M – H]$^+$; found 367.1302.

***N*-[2-(4-Hydroxyphenyl)ethyl]-2-{3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}-2-phenylacetamide (1r):** $R_f$ = 0.37 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 2.68 (t, $J$ = 6.9 Hz, 2 H, NHCH$_2$C*H*$_2$), 3.53 (q, $J$ = 6.5 Hz, 2 H, NHC*H*$_2$), 4.58 and 4.68 (AB system, $J$ = 15.3 Hz, 2 H, $CH_2O$), 5.97 (s, 1 H, CHPh), 6.10 (t, $J$ = 5.7 Hz, 1 H, NH), 6.24 (br. s, 1 H, OH), 6.67 (d, $J$ = 7.8 Hz, 2 H, *H ortho* to OH), 6.82–7.03 (m, 6 H), 7.24–7.35 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 34.3 (*C*H$_2$CH$_2$NH), 41.3 (CH$_2$NH), 61.9 (CHPh), 68.1 ($CH_2O$), 115.5 (×2), 117.0, 117.2, 122.8, 124.6, 127.9 (×2), 128.5, 129.0 (×2), 129.7 (×2, aromatic CH), 128.7, 129.7, 133.7, 145.8, 154.7 (aromatic quat.), 166.5, 167.9 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3661, 3588, 3418, 3308, 3030, 3004, 1672, 1604, 1490, 1400, 1338, 1202, 1052, 921 cm$^{-1}$. HRMS (ESI$^+$): calcd. for $C_{24}H_{22}N_2O_4Na$ 425.1477 [M + Na]$^+$; found 425.1466.

**2-(3-Furyl)-*N*-[2-(4-hydroxyphenyl)ethyl]-2-{3-oxo-2*H*-benzo[*b*][1,4]-oxazin-4(3*H*)-yl}acetamide (1s):** $R_f$ = 0.37 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 2.60–2.77 (m, 2 H, NHCH$_2$C*H*$_2$), 3.47 [dq, $J$ = 6.6 Hz (q), 13.2 (d), 1 H, NHC*H*H], 3.56 [dq, $J$ = 6.6 Hz (q), 13.2 (d), 1 H, NHC*H*H], 3.60 [dq, $J$ = 6.6 Hz (q), 13.2 (d), 1 H, NHC*H*H], 4.52 and 4.67 (AB system, $J$ = 15.3 Hz, 2 H, $CH_2O$), 6.04 (br. s, 1 H, OH), 6.19 (t, $J$ = 5.6 Hz, 1 H, NH), 6.24–6.27 (m, 2 H, 4-H of furyl and CHAr), 6.67 (d, $J$ = 8.4 Hz, 2 H, *H ortho* to OH), 6.88 (d, $J$ = 8.4 Hz, 2 H, H *meta* to OH), 6.85–7.04 (m, 4 H), 7.33 (t, $J$ = 1.8 Hz, 1 H, *H* furyl), 7.64

(s, 1 H, *H* furyl) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 34.3 ($CH_2CH_2NH$), 41.1 ($CH_2NH$), 52.5 (CHAr), 67.9 ($CH_2O$), 110.2, 142.3, 143.3 (CH furyl), 115.5 (×2), 117.1, 117.2, 122.8, 124.7, 129.7 (×2, aromatic CH), 118.3 (furyl quat.), 127.5, 129.9, 145.8, 154.7 (aromatic quat.), 166.4, 167.6 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3673, 3597, 3417, 2997, 1684, 1607, 1499, 1394, 1334, 1226, 1035, 921 cm$^{-1}$. GC–MS: $t_R$ = 13.15 min. MS: *m/z* (%) = 392 (5.9) [M]$^+$, 272 (36.1), 255 (43.1), 228 (100.0), 200 (23.1), 199 (7.4), 172 (25.7), 170 (6.0), 149 (17.1), 136 (25.5), 124 (18.3), 120 (63.8), 108 (31.5), 107 (26.3), 103 (9.8), 96 (7.5), 93 (9.3), 91 (12.9), 81 (96.0), 80 (15.3), 79 (10.8), 77 (34.3), 65 (12.5), 53 (12.8), 52 (7.8), 51 (11.8), 39 (8.8). HRMS (ESI$^+$): calcd. for $C_{22}H_{20}N_2O_5Na$ 415.1270 [M + Na]$^+$; found 415.129.

***N*-[(3-Hydroxyphenyl)methyl]-2-(4-methoxyphenyl)-2-{6-methyl-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}acetamide (1t):** $R_f$ = 0.45 (PE/AcOEt, 1:1). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 2.05 (br. s, OH exchanged with $H_2O$), 2.17 (s, 3 H, Ar-$CH_3$), 3.77 (2, 3 H, $OCH_3$), 4.32 and 4.49 [AB part of ABX system, *J* = 15.0 (AB), 5.4 (AX), 6.3 Hz (BX), 2 H, $ArCH_2N$], 4.53 and 4.63 (AB system, *J* = 15.2 Hz, 2 H, $CH_2O$), 5.91 (s, 1 H, CHAr), 6.44 (br. t, *J* = 5.7 Hz, 1 H, NH), 6.65–6.84 (m, 5 H), 6.83–6.93 (m, 3 H), 7.10 (t, *J* = 7.8 Hz, 1 H, *H meta* to OH), 7.34 (d, *J* = 8.7 Hz, *H meta* to $OCH_3$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 21.0 (Ar-$CH_3$), 43.7 ($CH_2N$), 55.3 ($OCH_3$), 61.9 (CHAr), 68.2 ($CH_2O$), 114.2, 114.6 (×2), 114.7, 116.8, 117.3, 119.1, 125.1, 129.68 (×2), 129.73 (aromatic CH), 125.7, 128.6, 132.5, 139.2, 143.7, 156.6, 159.7 (aromatic quat.), 166.6, 168.3 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3667, 3584, 3420, 3000, 2835, 2138, 1666, 1601, 1499, 1451, 1257, 1031, 921 cm$^{-1}$. HRMS (ESI$^-$): calcd. for $C_{25}H_{24}N_2O_5$ 431.1607 [M – H]$^+$; found 431.1608.

***N*-Cyclohexyl-2-{6-[(methoxycarbonylmethyl)aminocarbonyl]-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl}-2-phenylacetamide (1u):** $R_f$ = 0.55 ($CH_2Cl_2$/acetone, 80:20). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.00–1.45 (m, 5 H), 1.50–1.71 (m, 3 H), 1.80–2.05 (m, 3 H), 3.77 (s, 3 H, $OCH_3$), 3.82–3.92 (m, 1 H, C*H*NH), 4.13 (d, *J* = 5.8 Hz, 2 H, $CH_2CO_2Me$), 4.66 and 4.78 (AB system, *J* = 15.3 Hz, 2 H, $CH_2O$), 5.96 (br. d, *J* = 8.1 Hz, 1 H, CHN*H*), 6.16 (s, 1 H, CHAr), 6.69 (br. t, *J* = 5.8 Hz, 1 H, $CH_2NH$), 6.99 (d, *J* = 8.4 Hz, 1 H, 8-H), 7.30–7.49 (m, 6 H, phenyl CH and 7-H), 7.63 (d, *J* = 1.8 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 24.6 (×2), 25.4, 32.55, 32.59 (cyclohexyl $CH_2$), 41.7 ($CH_2N$), 48.9 (CHN), 52.4 ($CH_3O$), 61.5 (CHAr), 68.0 ($CH_2O$), 116.8 (C-5), 117.1 (C-8), 126.3 (C-7), 128.2 (C-2′ or C-3′), 128.1, 128.3 (C-4a and C-6a), 128.7 (C-4′), 129.2 (C-2′ or C-3′), 133.7 (C-1′), 148.6 (C-8a), 165.5, 166.2, 166.6, 170.3 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3674, 3614, 3416, 3028, 2969, 2931, 1741, 1663, 1600, 1498, 1426, 1218, 1041, 926, 875 cm$^{-1}$. HRMS (ESI$^+$): calcd. for $C_{26}H_{29}N_3O_6$ 502.1954 [M + Na]$^+$; found 502.1952.

**(2*R*,*S*)-2-[(2*R*)-2-(2-Acetamidoethyl)-3-oxo-2*H*-benzo[*b*][1,4]-oxazin-4(3*H*)-yl]-2-(3-bromophenyl)-*N*-butylacetamides (1v)**

**Major Diastereoisomer:** $R_f$ = 0.40 ($CH_2Cl_2$/acetone, 80:20). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.80 (t, *J* = 7.2 Hz, C$H_3$CH$_2$), 1.00–1.21 (m, 2 H, C$H_2$CH$_3$), 1.25–1.41 (m, 2 H, H$_3$CCH$_2$C$H_2$), 1.90 ($CH_3CO$), 2.12–2.33 (m, 2 H, OCHC$H_2$), 3.13 [ddt, *J* = 5.4 (d), 7.1 (t), 13.5 Hz (d), 1 H, NC*H*HCH$_2$CH$_2$CH$_3$], 3.32 [dq, *J* = 6.7 (q), 13.3 Hz (d), 1 H, NC*H*HCH$_2$CH$_2$CH$_3$], 3.45 [dq, *J* = 14.1 (d), 5.6 Hz (q), 1 H, C*H*HNHAc], 3.45 [dq, *J* = 14.1 (d), 5.6 Hz (q), 1 H, C*H*HNHAc], 3.68 (dddd, *J* = 4.8, 7.2, 8.1, 14.1 Hz, 1 H, C*H*HNHAc), 4.75 (dd, *J* = 4.6, 5.8 Hz, 1 H, 2-H), 5.92 (t, *J* = 5.8 Hz, 1 H, NHAc), 6.34 (s, 1 H, CHAr), 6.87–6.94 (m, 2 H); 6.97–7.07 (m, 2 H), 7.16 (br. s, NHBu), 7.20 (t, *J* = 7.7 Hz, 1 H, 5′-H), 7.23–7.29 (m, 1 H, 4′-H or 5′-H), 7.41–7.46 (m, 1 H, 4′-H or 5′-H), 7.52 (br. s, 1 H, 2′-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.7 ($CH_2CH_3$), 19.9 ($CH_2CH_3$), 23.3 ($CH_3CO$), 30.2 (OCH-$CH_2$), 31.1 ($NCH_2CH_2$), 35.1 ($CH_2NHAc$), 39.7 (other $CH_2NH$), 59.2 (CHAr), 75.7 (2-C), 117.2, 117.3, 122.8, 124.7 (C-5, C-6, C-7, C-8), 122.6 (C-Br), 126.4 (C-6′), 127.8 (C-4a), 129.9 (C-5′), 130.9 (C-2′), 131.0 (C-4′), 136.2 (C-1′), 144.8 (C-8a), 166.9, 167.2, 170.8 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3673, 3447, 3327, 2994, 2960, 2864, 2827, 2698, 2655, 1791, 1733, 1667, 1595, 1497, 1387, 1204, 1106, 1032, 923 cm$^{-1}$. HRMS (ESI$^+$): calcd. for $C_{24}H_{29}BrN_3O_4$ 502.1341 [M + H]$^+$; found 502.1361.

**Minor Diastereoisomer:** $R_f$ = 0.28 ($CH_2Cl_2$/acetone, 80:20). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.89 (t, *J* = 7.2 Hz, C$H_3$CH$_2$), 1.20–1.39 (m, 2 H, C$H_2$CH$_3$), 1.40–1.52 (m, 2 H, H$_3$CCH$_2$C$H_2$), 1.97 ($CH_3CO$), 2.20–2.32 (m, 2 H, OCHC$H_2$), 3.23–3.37 (m, 2 H, NC$H_2$CH$_2$CH$_2$CH$_3$), 3.41–3.67 (m, 2 H, C$H_2$NHAc), 4.67 (t, *J* = 6.0 Hz, 1 H, 2-H), 5.90 (s, 1 H, CHAr), 5.95 (t, *J* = 5.4 Hz, 1 H, NHBu), 6.87–6.96 (m, 2 H); 6.97–7.06 (m, 2 H), 7.25 (t, *J* = 7.8 Hz, 1 H, 5′-H), 7.28–7.34 (m, 1 H, 4′-H or 5′-H), 7.46–7.52 (m, 1 H, 4′-H or 5′-H), 7.57 (br. s, 1 H, 2′-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.7 ($CH_2CH_3$), 20.0 ($CH_2CH_3$), 23.3 ($CH_3CO$), 30.0 (OCH$CH_2$), 31.3 ($NCH_2CH_2$), 35.4 ($CH_2NHAc$), 39.9 (other $CH_2NH$), 61.5 (CHAr), 76.2 (2-C), 116.6, 117.5, 123.0, 124.9 (C-5, C-6, C-7, C-8), 123.2 (CBr), 126.7 (C-6′), 128.6 (C-4a), 130.6 (C-5′), 131.1 (C-2′), 131.8 (C-4′), 136.4 (C-1′), 144.9 (C-8a), 166.9, 167.8, 170.4 (C=O) ppm.

**Benzyl 4-Aminobenzoate Hydrochloride (3):** Benzyl alcohol (12.6 mL, 121.4 mmol) was dissolved in benzene (10 mL), cooled to 0 °C and treated under nitrogen with NaH (60% in mineral oil, 243 mg, 6.07 mmol). When gas evolution had ceased, ethyl 4-aminobenzoate (5.011 g, 30.34 mmol) was added in portions. The mixture was then warmed, and the benzene/ethanol azeotropic mixture was very slowly distilled over 7 h. Two additional portions of benzene (10 mL each) were added when the mixture became too concentrated. When the product/substrate ratio was > 9:1, as indicated by GC, the mixture was cooled, poured into water and extracted three times with $Et_2O$. After concentration to dryness, the residue was taken up in dry $Et_2O$ (100 mL), cooled to 0 °C, and treated with HCl (1 M) in $Et_2O$ (36 mL). The resulting crystals were collected by suction and dried to afford pure **3** (6.12 g, 75%). M.p. 175.9–177.1 °C (without decomposition); ref.[35,36] 188–189 °C (dec.).

**Benzyl 4-(Formylamino)benzoate (4):** The hydrochloride **3** (2.950 g, 11.19 mmol) was placed in an Erlenmeyer flask and treated with NaOH (1 M, 12 mL), saturated aqueous $NaHCO_3$ (40 mL) and AcOEt (40 mL). The mixture was vigorously stirred until all the solid was dissolved. The phases were separated, and the aqueous one was re-extracted twice with AcOEt. The organic extracts were washed with brine, and the mixture was concentrated to dryness to give a solid (2.392 g, 10.5 mmol, 94%). This solid was dissolved in dry $CH_2Cl_2$ (20 mL), cooled to 0 °C and treated with 4-(dimethylamino)pyridine (129 mg, 1.05 mmol) and formic acid (0.59 mL, 15.6 mmol). Meanwhile, dicyclohexylcarbodiimide (DCC, 2.38 g, 11.5 mmol) was dissolved in $CH_2Cl_2$ (20 mL). This solution was slowly added to the cooled amine solution from a dropping funnel over 10 min. After having been stirred at 0 °C for 1 h and at room temp. for 3 h, the mixture was concentrated, taken up in AcOEt and filtered. The filtrate, upon concentration, gave a crude product (2.895 g), which was chromatographed (PE/AcOEt, 60:40 to 45:55) to give pure **4** as a white solid (2.297 g, 84%).[37] M.p. 118.6–120.3 °C. $R_f$ = 0.17 (PE/AcOEt, 60:40). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, at 25 °C, two conformations A and B were present in a 58:42 ratio): $\delta$ = 5.35 (A), 5.36 (B, s, 2 H, PhC$H_2$), 7.12 (B, d,

*J* = 8.7 Hz, 0.84 H, 3-H), 7.46–7.30 (A + B, m, 5 H, C*H* of benzyl), 7.51 (A, br. s, 0.58 H, N*H*), 7.63 (A, d, *J* = 9.0 Hz, 1.16 H, 3-H), 8.06 (A, d, *J* = 9.0 Hz, 1.16 H, 2-H), 8.08 (B, d, *J* = 8.7 Hz, 0.84 H, 2-H), 8.18 (B, br. s, 0.42 H, N*H*), 8.42 (A, d, *J* = 1.5 Hz, 0.58 H, C*H*=O), 8.84 (B, d, *J* = 11.1 Hz, 0.42 H, C*H*=O) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 66.7 (A), 66.8 (B, *C*$H_2$Ph), 117.2 (B), 119.1 (A, 3-C), 126.1 (B), 126.6 (A, 1-*C*), 128.2 (B, ×2), 128.2 (A, ×2), 128.3 (A), 128.4 (B), 128.6 (B, ×2), 128.6 (A, ×2, *C*H of benzyl), 131.1 (A), 131.7 (B, 2-C), 135.9 (B), 136.0 (A, C-1′), 140.9 (B), 141.0 (A, 4-C), 158.9 (A), 161.6 (B, NH*C*=O), 165.6 (B), 165.8 (A, *C*$O_2$Bn) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3415, 3001, 1697, 1608, 1498, 1406, 1373, 1268, 1103, 1041 cm$^{-1}$. GC–MS: $R_t$ 9.78. MS: *m*/*z* (%) = 255 (17.7) $[M]^+$, 226 (1.5), 148 (100.0), 121 (8.5), 120 (5.2), 91 (71.9), 90 (5.6), 65 (25.7), 39 (8.2). $C_{15}H_{13}NO_3$ (255.2686): calcd. C 70.58, H 5.13, N 5.49; found C 70.7, H 5.2, N 5.6.

**Benzyl 4-Isocyanobenzoate (5):** A solution of the formamide **4** (870 mg, 3.408 mmol) in dry $CH_2Cl_2$ (15 mL) was cooled in ice and treated first with *N*-methylmorpholine (862 μL, 7.838 mmol) and then with diphosgene (trichloromethyl chloroformate, 247 μL, 2.045 mmol). After stirring at 0 °C for 2h, the orange suspension was treated with saturated aqueous $NaHCO_3$ (50 mL) and extracted with $Et_2O$. Chromatography (PE/$Et_2O$, 85:15) gave the pure isocyanide **5** (798 mg, 100%) as a green-brown liquid (before concentration, the fractions containing the isocyanide were colourless, but upon concentration to dryness the liquid became coloured). Because of its partial instability this product was not characterized, but was used immediately for the subsequent Ugi reactions. $R_f$ = 0.51 (PE/$Et_2O$, 80:20).

**1-(Benzyloxy)-4-(2-isocyanoethyl)benzene (8):** Tyramine (3.24 g, 23.62 mmol) was suspended in ethyl formate (30 mL) and heated at reflux for 31 h. The suspension became a solution after 12 h. After concentration, the brown solid was recrystallized from AcOEt/PE to give the formamide **6** as a slightly beige solid (3.755 g, 96%). M.p. 95.6–96.5 °C (ref.[38] 96–97 °C). This formamide (3.74 g, 22.64 mmol) was dissolved in acetone (80 mL) and treated with dry $K_2CO_3$ (7.43 g, 53.77 mmol) and benzyl bromide (2.83 mL, 23.77 mmol). The suspension was heated at reflux for 12 h. After cooling, the solid was filtered off with a sintered funnel. The mother liquors were concentrated to dryness, taken up with $CH_2Cl_2$ and washed with saturated aqueous $NH_4Cl$ and then with brine. Concentration gave a solid, which was triturated from $Et_2O$/PE to give the pure formamide **7** as a white solid (5.60 g, 97%). M.p. 108.4–109.3 °C.[39] This formamide (2.990 g, 11.71 mmol) was dissolved (by warming) in dry $CH_2Cl_2$ (45 mL). This solution was cooled to –30 °C (precipitation occurred) and treated with $Et_3N$ (5.55 mL, 39.81 mmol) and then with $POCl_3$ (1.20 mL, 12.88 mmol). The mixture darkened at once. After a few minutes, most of the solid seemed to dissolve, but the misture always remained a suspension. After stirring for 2 h and 15 min, the reaction was complete (TLC). The reaction mixture was poured into satd. aqueous $NaHCO_3$ (150 mL) and extracted with $CH_2Cl_2$. The organic extracts were washed with brine and dried, and the mixture was concentrated to dryness. The crude solid was chromatographed on 80 g of silica with PE/$CH_2Cl_2$/$Et_2O$ (10:10:1) as eluent. The pure isocyanide **10** was collected as a slightly pink solid (2.437 g, 88%). M.p. 88.7–89.2 °C. $R_f$ = 0.40 (PE/$Et_2O$, 70:30). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 2.92 (t, *J* = 7.1 Hz, 2 H, $NCH_2CH_2$), 3.56 (t, *J* = 7.2 Hz, 2 H, $NCH_2$), 5.05 (s, 2 H, $CH_2$Ph), 6.94 (d, *J* = 8.4 Hz, 2 H, C*H ortho* to OBn), 7.15 (d, *J* = 8.4 Hz, 2 H, C*H meta* to OBn), 7.46–7.29 (m, 5 H, aromatics) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 34.8 ($NCCH_2CH_2$), 43.2 (t, $NCCH_2$), 70.0 ($CH_2O$), 115.1 (×2), 127.5 (×2), 128.0, 128.6 (×2), 129.7 (×2), 128.9 (quat.), 136.9 (aromatic *C*H), 156.2 (t, N*C*), 158.0 (*C*-OBn) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2998, 2153, 1611, 1584, 1501, 1451, 1379, 1296, 1189, 1012 cm$^{-1}$. GC–MS: $t_R$ = 8.12 min. MS: *m*/*z* (%) = 237 (4.4) $[M]^+$, 120 (19.5), 91 (100.0), 89 (2.6), 65 (13.0), 63 (2.3), 51 (2.4), 39 (3.9). $C_{16}H_{15}NO$ (237.30): calcd. C 80.98, H 6.37, N 5.90; found C 80.75, H 6.45, N 5.85.

**(3-Benzyloxyphenyl)methanol (9):** A solution of (3-hydroxyphenyl)-methanol (3.75 g, 30.23 mmol) in dry acetone (100 mL) was treated with anhydrous $K_2CO_3$ (10.1 g, 73.0 mmol) and benzyl bromide (3.95 mL, 33.3 mmol). The mixture was heated at reflux with vigorous stirring for 7 h. It was then allowed to cool to room temp. and filtered, and the mixture was concentrated to dryness. Chromatography (PE/$Et_2O$, 7:3 to 1:1) gave pure **9** as a white solid (6.47 g, 100%). M.p. 46.5–48.5 °C. $R_f$ = 0.65 (PE/$Et_2O$, 20:80). The other spectroscopic data were identical to those previously reported.[40,41]

***N*-[3-(Benzyloxy)benzyl]formamide (10):** A solution of the alcohol **9** (1.03 g, 4.82 mmol) in dry $CH_2Cl_2$ (15 mL) was cooled to –30 °C and treated with triethylamine (874 μL, 6.27 mmol) and methanesulfonyl chloride (450 μL, 5.79 mmol). After stirring for 4.5 h, the mixture was quenched with saturated $NH_4Cl$ (10 mL), diluted with $H_2O$ (20 mL) and extracted with $Et_2O$. After washing with brine, concentration gave the crude mesylate. This was taken up in dry DMF (15 mL), and treated with $NaN_3$ (658 mg, 10.1 mmol). The mixture was heated at 50 °C for 17 h and then poured into $H_2O$ (30 mL). Extraction with $Et_2O$, washing with water and then with brine and concentration gave crude 1-(azidomethyl)-3-(benzyloxy)benzene as an oil (1.082 g, 4.52 mmol). $R_F$ = 0.80 (PE/$Et_2O$, 60:40). This was dissolved in tetrahydrofuran (THF, 10 mL) and treated with triphenylphosphane (1.78 g, 6.79 mmol) and distilled water (162 μL, 9.0 mmol). The mixture was heated at 65 °C for 6 h; after cooling, it was treated with HCl (1 M, 55 mL) and washed three times with AcOEt (30 mL each). The recombined organic phases were re-extracted with HCl (0.5 M, 50 mL) and discarded. The combined aqueous extracts were treated with NaOH (3 M) until pH = 13, and extracted four times with AcOEt. The organic extracts were concentrated to dryness to give crude 3-(benzyloxy)-benzylamine. This was taken up in dry $CH_2Cl_2$ (9 mL), cooled to 0 °C and treated with formic acid (257 μL, 6.78 mmol) and 4-(dimethylamino)pyridine (DMAP, 55.8 mg, 461 μmol). A solution of dicyclohexylcarbodiimide (1.035 g, 5.03 mmol) in dry $CH_2Cl_2$ (9 mL) was slowly added to this solution from a dropping funnel over 30 min. After stirring at room temp. for 3 h, the solvent was evaporated and replaced with AcOEt. The resulting suspension was filtered to remove dicyclohexylurea, concentrated and finally chromatographed ($CH_2Cl_2$/AcOEt, 90:10) to give pure **10** as a white solid (816.1 mg, 70%). $R_f$ = 0.39 ($CH_2Cl_2$/AcOEt, 90:10). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, at room temp., two conformations A and B in a 86:14 ratio were present): $\delta$ = 4.38 (B, d, *J* = 6.6 Hz, 0.28 H, $CH_2NH$), 4.46 (A, d, *J* = 6.0 Hz, 1.72 H, $CH_2NH$), 5.05 (A, s, 1.72 H, $CH_2$Ph), 5.06 (B, s, 0.28 H, $CH_2$Ph), 5.89 (br. s, 1 H, N*H*), 6.93–6.82 (m, 3 H, aromatic), 7.47–7.22 (m, 6 H, aromatic), 8.17 (B, d, *J* = 11.7 Hz, 0.14 H, C*H*=O), 8.25 (A, s, 0.86 H, C*H*=O) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, only the signals of conformer A are reported): $\delta$ = 42.1, 70.0 ($CH_2$), 114.0, 114.3, 120.2, 127.5 (×2), 128.0, 128.6 (×2), 129.9 (*C*H), 136.7, 139.1, 156.1 (quat.), 159.0 (*C*=O) ppm. $C_{15}H_{15}NO_2$ (241.2851): calcd. C 74.67, H 6.27, N 5.81; found C 74.9, H 6.2, N 5.7.

**1-(Benzyloxy)-4-(isocyanomethyl)benzene (11):** A solution of the formamide **10** (353.2 mg, 1.46 mmol) in dry $CH_2Cl_2$ (6 mL) was cooled to –30 °C and treated with triethylamine (694 μL, 4.98 mmol) and $POCl_3$ (147 μL, 1.61 mmol). The mixture was stirred at –30 °C for 4 h and then treated with saturated aqueous

$NaHCO_3$ (25 mL). The resulting mixture was extracted three times with $CH_2Cl_2$. The combined organic extracts were washed with brine, and the mixture was concentrated to dryness. Chromatography (PE/$Et_2O$, 85:15) gave pure **11** as an oil (254.7 mg, 78%). Because of partial instability, this product was not characterized but was used immediately for the subsequent Ugi reactions.

**Methyl 3-Amino-4-hydroxybenzoate (12):** A solution of commercially available 3-amino-4-hydroxybenzoic acid (1.033 g, 6.74 mmol) in absolute MeOH (15 mL) was treated with concd. aqueous HCl (1 mL) and heated at reflux for 22 h. The solution was allowed to cool to room temp. and treated with concd. ammonium hydroxide (1.3 mL) and then adjusted to pH = 9–10 with aqueous $NH_3$ (1 M). Extraction with AcOEt, concentration and chromatography (PE/AcOEt/96% EtOH, 49.6:49.6:0.8) gave pure **12** as a slightly brown solid (1.091 g, 97%). M.p. 137–139 °C. The spectroscopic and analytical data were consistent with those reported.[33]

**(*S*)-4-(*tert*-Butoxycarbonylamino)-2-hydroxybutanoic Acid (13):** Commercially available (*S*)-4-amino-2-hydroxybutanoic acid (1.790 g, 15.03 mmol) was dissolved in a solution of $K_2CO_3$ (5.193 g, 37.6 mmol) in water (50 mL) and treated with a solution of di-*tert*-butyl dicarbonate (3.815 g, 17.48 mmol) in 1,4-dioxane (20 mL). After stirring at room temp. for 24 h, the solution was extracted twice with $Et_2O$. The aqueous phase was acidified to pH = 1 with HCl (2 M), treated with solid NaCl to saturate it and extracted five times with AcOEt. The organic phases were concentrated to dryness to give **13**, pure enough for further use (3.226 g, 98%). The spectroscopic and analytical data were consistent with those reported.[34]

**Supporting Information** (see footnote on the first page of this article): HPLC chromatograms of **1n**; copies of the NMR spectra of compounds **1**.

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