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FULL PAPER

Total Synthesis of the Natural Herbicide MBH-001 and Analogues

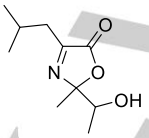
Birgit Kuhn,*[a] David M. Barber,[a] Hansjörg Dietrich,[a] Uwe Döller,[a] Michael G. Hoffmann,[a] Dirk Schmutzler,[a] Stefan Schnatterer,[a] Martin E. Maier,*[b] Tamer Kocakaya,[b] Marius Morkunas[b]

Dedication ((optional))

Abstract: The first total synthesis of the natural herbicide MBH-001 (**1**) is reported. Structurally it is a 2-methyloxazol-5(2*H*)-one with a (1-hydroxyethyl) substituent at the 2-position. By relying on cyclic nitrones, a flexible route to MBH-001 and relevant analogs was developed. Key steps include the reaction of a 2-hydroxyimino ester with an aldehyde to form a 5-oxo-2,5-dihydrooxazole 3-oxide. In an aldol-type reaction, the anion of these cyclic nitrones reacted with an aldehyde at the 2-position. A final reduction of the nitrone to the corresponding imine using zinc led to the target compounds. The cyclic nitrones are also accessible by reacting an α-keto acid with an oxime. These two versatile synthetic routes enabled us to prepare the first MBH-001 analogues for structure activity relationship analysis of the herbicidal efficacy. Thus, furthering our aim of developing new herbicides to tackle the ever-growing problem of weed resistance.

Introduction

Whilst the search for novel biologically active natural products is time consuming, it can be worth the effort. This process may result in lead structures and the discovery of new targets for pharmaceutical or agrochemical research. Nevertheless, a lack of chemical methods to synthesize the desired natural product can pose a significant problem and prevent the new lead from being further developed. This way scientists at Bayer Crop Science came across the natural product MBH-001, 2-(1-hydroxy-ethyl)-4-isobutyl-2-methyloxazol-5(*2H*)-one (**1**) in a Japanese patent application[1] (Figure 1). It was reported that this heterocycle is produced by an insect symbiotic microorganism N1-Ishi-YC50807. Compound **1** is an unique natural product with reported strong herbicidal activity (200 g/ha) against monocots and dicots. Regarding the mode of action of MBH-001 (**1**) nothing was mentioned. Typical modes of action of herbicides are inhibition of photosynthesis, fatty acid biosynthesis, amino acid biosynthesis, cell division or pigment biosynthesis.[2] In order to confirm the structure and to allow for the elucidation of the mode of action a total synthesis of **1** was required. Ideally, the synthesis route should be flexible enough to allow access to analogs for structure activity studies. Quite recently, heterocyclic compounds called conflamides, which also feature an N,O-acetal were isolated from the mushroom *Albatrellus confluens*.[3]



MBH-001 (**1**)

Figure 1. Structure of the herbicide MBH-001 (**1**).

A retrosynthesis (Scheme 1) for oxazolone **1** seems fairly simple. Thus, reaction of α-imino ester **2** with 3-hydroxybutanone (acetoin, **3**) might lead to **1**. In addition, oxazolones like **4a** or **5** appear as promising precursors. Thus, an aldol type reaction of **4a** with acetaldehyde might produce **1**. Alternatively, alkylation of oxazolone **5** under basic conditions might give rise to **1**. The problem is that such oxazolones can be present as tautomers (Scheme 1), possibly resulting in the formation of regioisomers in reactions.[4] Indeed, the regiochemistry of 5-oxazolones in the reaction with electrophiles depends on the substituents on the oxazolones, the type of electrophile and the reaction conditions. For example, 2-aryl substituted azlactones **6a** react with nitrostyrenes **7** at the 2-position to form the oxazol-5(2*H*)-one **8**. In contrast, a sterically demanding *tert*-butyl substituent in **6b** directs the electrophile to the 4-position resulting in oxazol-5(4*H*)-ones **9**.[5]

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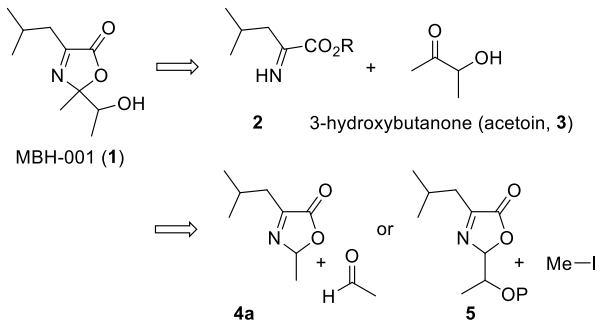
retrosynthetic considerations:



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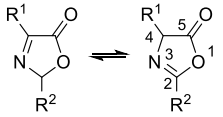
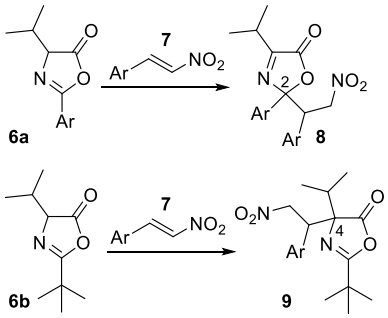


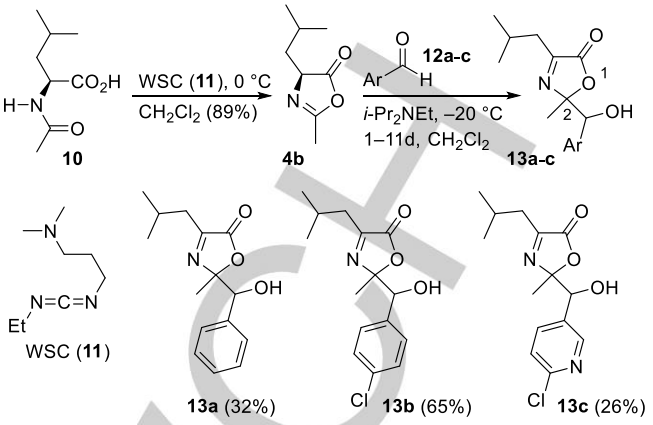
regiochemistry in the reaction with electrophiles:



Scheme 1. Retrosynthetic considerations for MBH-001 (**1**) and the issue of regioselectivity in reactions of oxazolones with electrophiles.

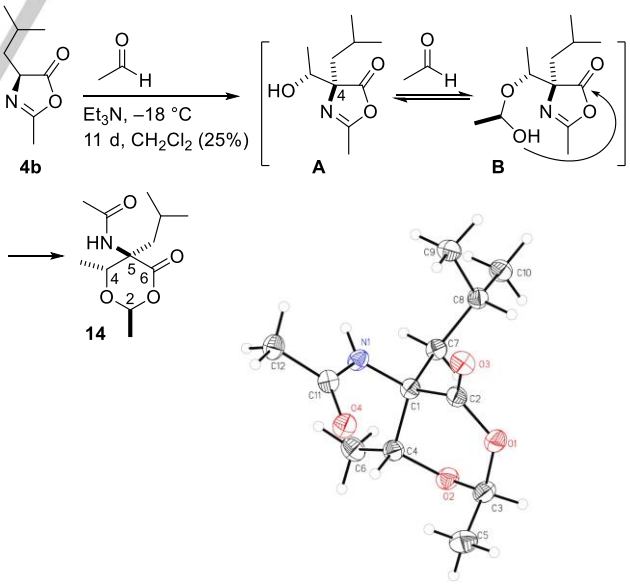
Results and Discussion

Initial studies were performed on oxazolone **4b**, obtained by the Steglich method from acylated amino acid[6] **10** using water soluble carbodiimide[7] **11** (Scheme 2). Reaction of aromatic aldehydes **12a-c** with oxazolone **4b** (isomer of **4a**) in the presence of triethylamine or diisopropylethylamine (Hünig's base) provided the desired addition products with the carbinol connected to C-2 (Scheme 2). However, preliminary tests showed that these aryl analogs **13a**-**13c** of MBH-001 have no significant herbicidal activity.



Scheme 2. Synthesis of oxazol-5(2*H*)-ones **13a** – **13c** by aldol type reactions of oxazol-5(4*H*)-one **4b** with aromatic aldehydes **12a** – **12c**.

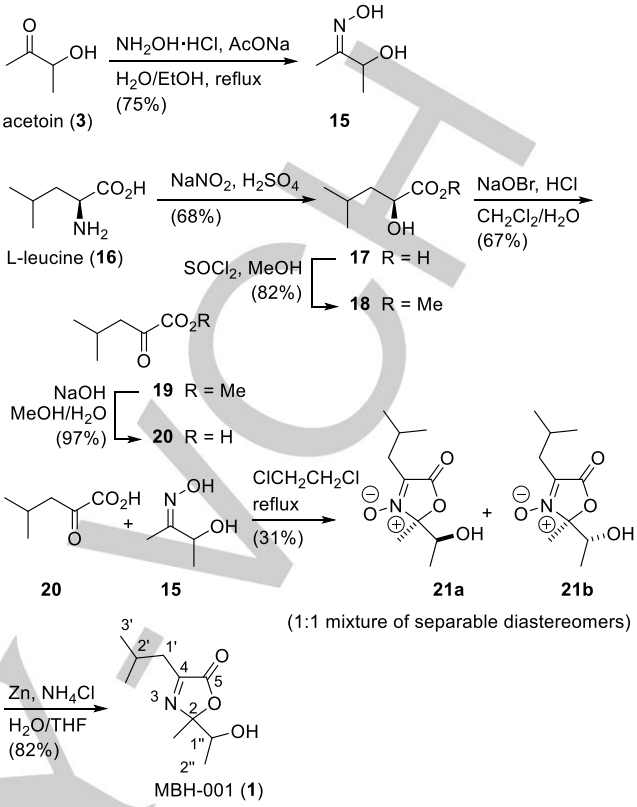
Unfortunately, the reaction of oxazolone **4b** with acetaldehyde under identical conditions took a different course (Scheme 3). Thus, it seems hydroxyalkylation takes places at C4 to form intermediate **A**. This intermediate could not be isolated since it reacted with another acetaldehyde molecule to intermediate **B** followed by opening of the oxazolone ring and formation of 1,3-dioxanone **14**, whose structure was confirmed by a single crystal X-ray diffraction. We cannot rule out that other stereoisomers are formed in this transformation. The aldol-like reaction between **4b** and acetaldehyde might be diastereoselective leading to intermediate **A**. The formation of postulated intermediate **B** certainly is an equilibrium reaction and only the indicated isomer might then cyclize to the dioxanone **14**.



Scheme 3. Reaction of oxazol-5(4*H*)-one **4b** with acetaldehyde leading to dioxanone **14** containing two molecules of acetaldehyde. Some of the atoms of the dioxanone derivative **14** are numbered.

Eventually, by taking recourse to nitrones, two solutions to the synthesis of MBH-001 and related structures could be found. In this context, a paper by Bode et al. provided a good starting point.[8] They reported the formation of 2,5-dihydrooxazole 3-oxides by reaction of α-keto acids with oximes. In their case, these heterocycles were used to protect the α-keto acid. The latter could be regenerated by reduction of the cyclic nitrone with zinc followed by treatment with acid. Accordingly, we hoped that with this strategy MBH-001 (**1**) would be accessible. First, we prepared oxime **15** by reacting acetoin (**3**) with hydroxylamine according to a known procedure (Scheme 4).[9] While several methods for the synthesis of α-keto acids are known in the literature,[10] we opted for the preparation of **20** from L-leucine (**16**) via the intermediate methyl 2-hydroxy-4-methylpentanoate (**18**). Thus, diazotation of amino acid[11] **16** led to α-hydroxy acid **17**. After its conversion to methyl ester **18** using $SOCl_2$ in methanol, the secondary alcohol of **18** was oxidized using sodium hypobromite[12] to give methyl 4-methyl-2-oxopentanoate [13] (**19**). Basic hydrolysis of ester **19** furnished keto acid[14] **20**.

Reaction of keto acid **20** and oxime **15** (1.5 equiv.) turned out to be quite sluggish. The reaction required 3 d in refluxing dichloroethane to get full consumption of both reaction partners. Despite this, only a moderate yield of 31% for the cyclic nitrones **21** could be obtained. The nitrones **21** were obtained as a separable mixture of diastereomers in a 1:1 ratio. Next, the isomers **21a** and **21b** were separately submitted to the reduction of the nitrone functionality to the corresponding imine. Indeed, treatment of the nitrones with activated zinc in the presence of aqueous NH_4Cl solution gave the MBH-001 diastereomers **1a** and **1b**. Characteristic ^1H NMR data for isomer **1a**, obtained from the less polar nitrone **21a** are a quartet for 1''-H (methine H) of the 1-hydroxyethyl sidechain at 3.90 ppm. The 2-CH_3 group appears at 1.58 ppm. The corresponding shift values for **1b** are 3.83 and 1.56 ppm. In the ^{13}C NMR spectrum, **1a** and **1b** also have similar chemical shifts. For example C2 and C1' of **1a** appear at 107.3 and 20.7 ppm whereas in **1b** the corresponding values are 107.6 (C2) and 20.1 (C1') ppm.



Scheme 4. First generation synthesis of MBH-001 (**1**) via nitrones **21**, obtained from keto acid **20** and oxime **15**.

The structure data of MBH-001 (**1**) could be confirmed as well as the biological efficacy cited in the old patent application[1] published by Mitsubishi Petrochemicals. A detailed evaluation of the biological data has been published.[15]

In order to analyze the SAR and different prodrug types, the hydroxyl group of the oxazolone side chain has been derivatized under standard conditions starting from the cyclic nitrones of type **21** or other MBH-001 analogs to form esters, carbonates and urethanes (vide infra). The prepared nitrone esters could be reduced to the oxazolones in medium to good yields. Some examples can later be found in Schemes 12 and 14. These derivatizations also helped us to assign the absolute stereochemistry of the active isomer of MBH-001 (**1**), which has not yet been published. Luckily, the 4-fluorobenzoyl derivative **22b** of the more polar diastereomer formed crystals suitable for X-ray analysis (Scheme 5). Moreover, the less polar MBH-001 (**1**) isomer, after being converted to the carbamate **23a** using 4-bromophenyl isocyanate could also be crystallized.

All the X-ray structures shown from this paper were deposited in the Cambridge Structural Database.[16,17] These files contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Finally, the MBH-001 diastereomers were separated by chiral HPLC [Chiralpak IC]. After conversion to the bromobenzoyl derivatives, X-ray analyses secured the absolute configurations.

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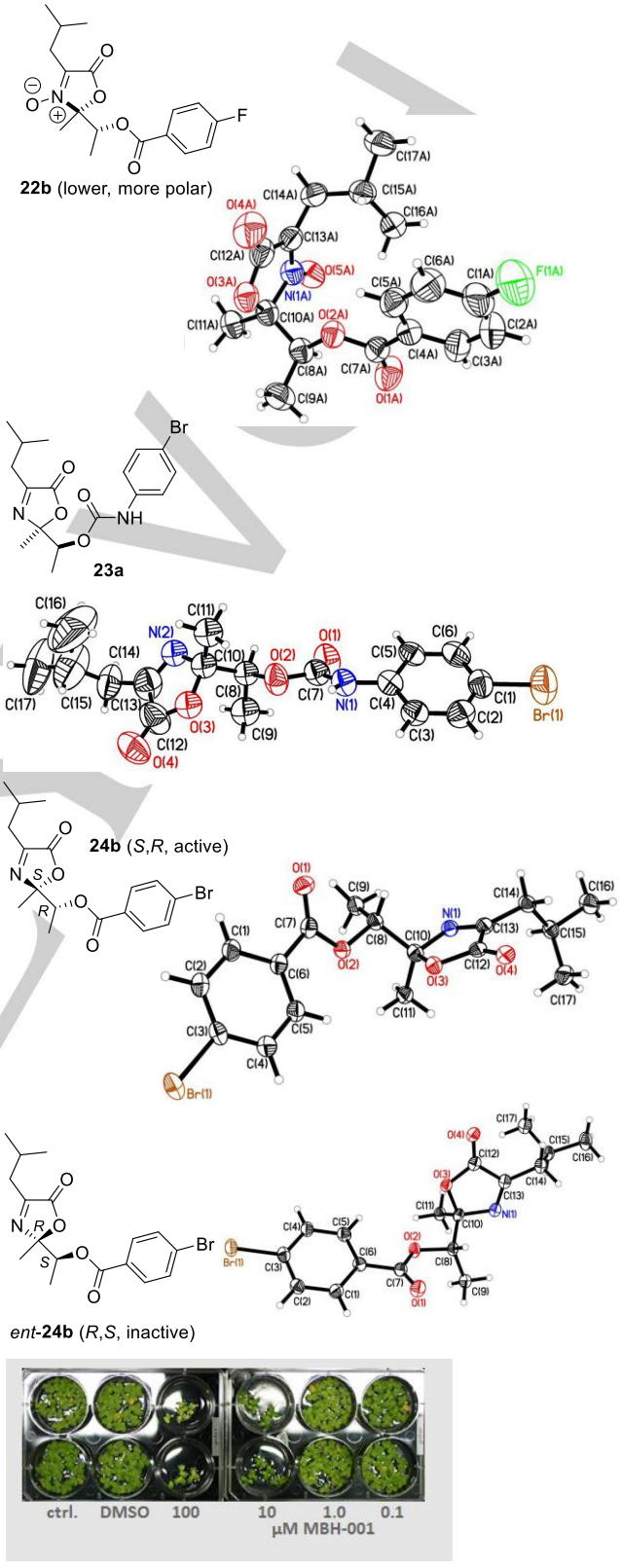
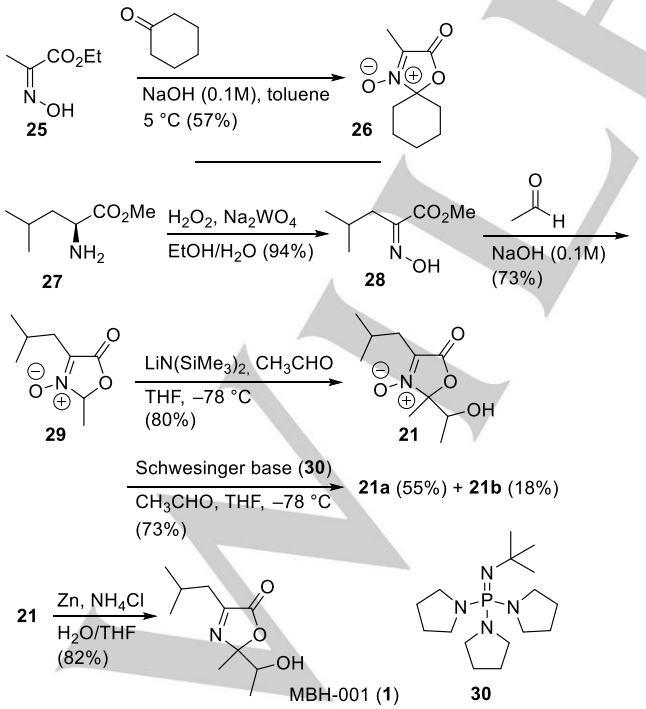
Growth inhibition studies in duckweed (*Lemna*) showed that only the more polar rel-(*S*,*R*)-diastereomer of MBH-001 (**1**) is biologically active. Other in vivo studies confirmed that the active enantiomer of **1** has the *S*,*R*-configuration.



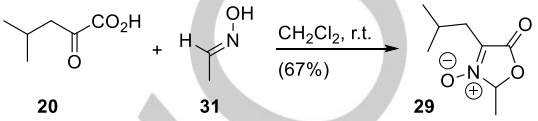
Scheme 5. Determination of the relative and absolute configuration of MBH-001 and its congeners by X-ray. Growth inhibition assay shows that only one diastereomer is active, the isomer corresponding to **24b**.

As we wanted to have access to some MBH-001 analogs for SAR studies, a more flexible route was sought. We therefore considered an alternative formation of cyclic nitrones.[18] In a model study the hydroxyimino ester[19] **25**, derived from ethyl pyruvate was reacted with cyclohexanone under various conditions (Scheme 6). Best results were obtained by stirring **25** and cyclohexanone in toluene and adding 0.65 equiv. of aqueous NaOH which gave rise to cyclic nitrone **26** in 50% yield. However, other ketones like acetoin (**3**), TBS-protected acetoin,[20] and 1-(benzyloxy)-2-propanone[21] did not give the desired products. Based on the literature precedence we hoped that aldehydes would react better with 2-hydroxyimino esters as compared to ketones. First, methyl L-leucinate[22] (**27**) was oxidized with H_2O_2 in the presence of sodium tungstate[23] to oxime[24] **28**. In the next step, oxime **28** was reacted with acetaldehyde under basic conditions by adding 0.1 M NaOH in portions to the mixture. Using this method saponification of the ester could be largely suppressed. Under these conditions, cyclic nitrone **29** was obtained in 73% yield. The crucial question was now whether the anion of azlactone derivative **29** would react with aldehydes at the 2 or 4 position. Gratifyingly, deprotonation of **29** with lithium hexamethyldisilazide [$LiN(SiMe_3)_2$] at –78 °C followed by addition of acetaldehyde exclusively gave the desired C2 addition product **21**. In this case, also a 1:1 mixture of diastereomers was obtained. The synthesis of MBH-001 (**1**) was completed by reduction of the nitrone to the imine. Preliminary experiments showed that the base can have an influence on the stereoselectivity of the aldol reaction. Thus, if nitrone **29** is deprotonated with the Schwesinger base[25] **30** (*tert*-butylimino-tri(pyrrolidino)phosphorane), the reaction with acetaldehyde gave diastereomer **21a** as the major product (**21a**/**21b** = 3:1). Other bases than Schwesinger base and LiHMDS can be used as well, for example tetramethylguanidine.



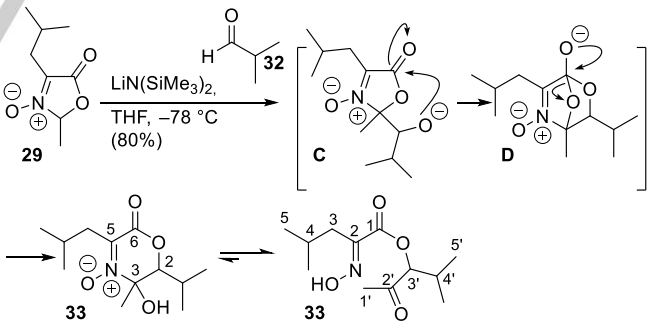
Scheme 6. Alternative route to nitrone **21** and MBH-001 (**1**) via aldol-type reaction of nitrone **29** with acetaldehyde.

We have also found an alternative route (Bode variant) being more flexible to introduce different substituents starting from keto acid **20** directly and condensing first with acetaldehyde oxime[26] (**31**) to get to type nitrone **29** in yields up to 67% after chromatography (Scheme 7).



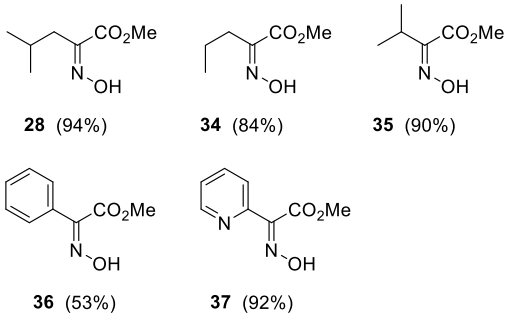
Scheme 7. Alternative route to nitrone **29** from keto acid **20** and acetaldehyde oxime (**31**).

We felt that this strategy – formation of the cyclic nitrones, followed by aldol type reaction with aldehydes – should allow for the synthesis of several MBH-001 analogs. This was largely the case - with certain limitations. For example, if sterically hindered aldehydes are employed in the aldol-like reaction, the primary addition product can undergo rearrangement to the six-membered nitrone as was observed in the reaction of nitrone **29** with isobutyraldehyde (**32**) (Scheme 8). Thus, alkoxide **C** will form tetrahedral intermediate **D** that collapses to the 6-oxo-3,6-dihydro-2*H*-1,4-oxazine 4-oxide **33** and then converts to its ring opened isomer. In this transformation, a formal umpolung of acetaldehyde was realized. The ring opened form is clearly evident from the carbonyl peak at δ = 204.6 ppm in the ^{13}C NMR spectrum.



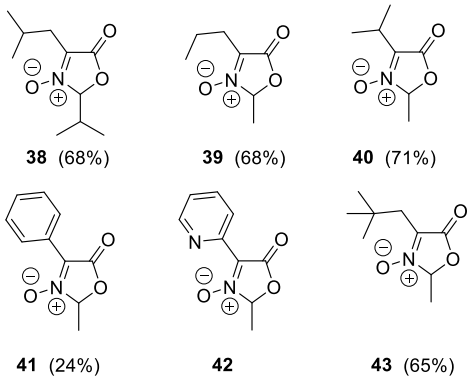
Scheme 8. Reaction of nitrone **29** with isobutyraldehyde (**32**).

According to this plan, various oximes (hydroxyimino esters) **34** – **37** were prepared (Scheme 9). Compounds **34** – **36** were obtained by oxidation of the corresponding amino acid esters (cf. Scheme 6). The yields are listed after the compound numbers. Pyridyloximoester **37** was prepared by nitrosation of the corresponding pyridylacetic acid ester.[27]



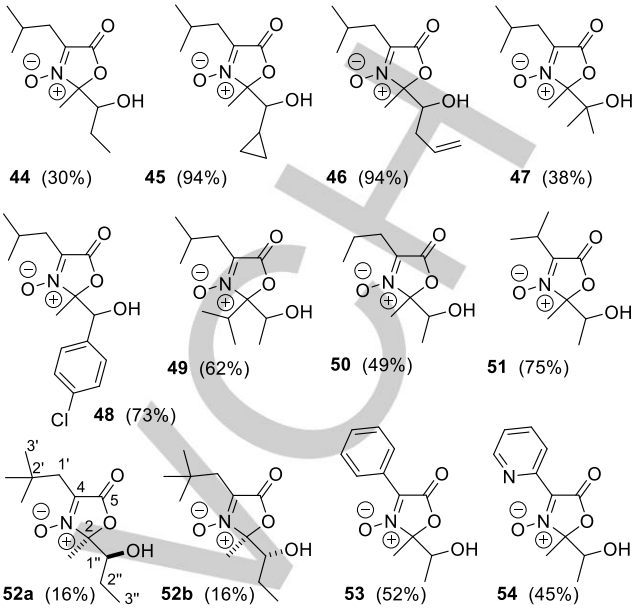
Scheme 9. Collection of hydroxyimino esters used for formation of cyclic nitrones.

The hydroxyimino esters were then condensed with an aldehyde to form the cyclic nitrones shown in Scheme 10. Phenyloxazolone **41** has been prepared from oxime ester **36**, which was generated from methyl phenylglycinate or by the condensation method shown in Scheme 7 using 2-oxo-2-phenylacetic acid and oxime **31**. Nitrone **43** was prepared from 4,4-dimethyl-2-oxopentanoic acid[28] and acetaldehyde oxime (**31**).



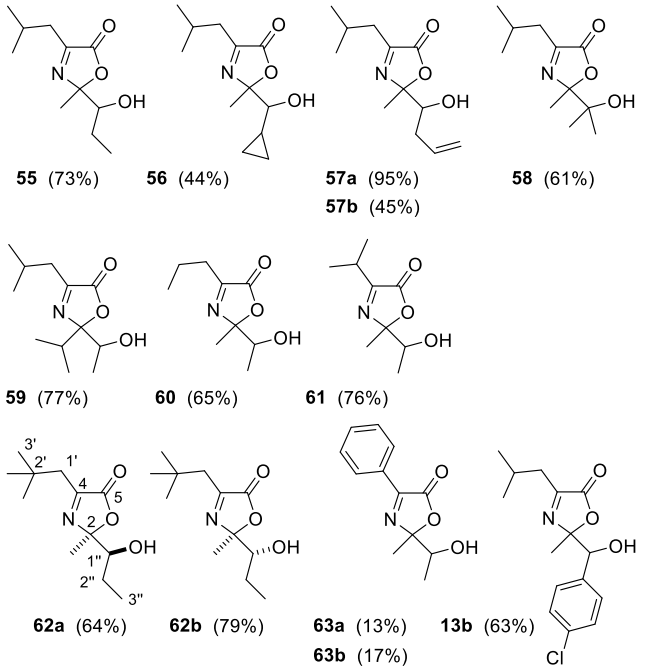
Scheme 10. Collection of 5-oxo-2,5-dihydrooxazole 3-oxides that were used in this study.

Via deprotonation of the cyclic nitrones and reaction of the corresponding anions with aldehydes the compounds **44** – **54** were obtained (Scheme 11). The aldehyde required for the preparation of **46**, but-3-enal was prepared according to a literature procedure.[29] Typically, the aldol-type reaction led to the formation of two diastereomers. In Scheme 11, these are shown for compounds **52a** and **52b**. Their structures were tentatively assigned based on the analysis of **21a** and **21b** (vide supra). The isomers **a** are less polar and move further on the TLC plate (silica gel) than the corresponding **b** isomers. For **44** only isomer **44b** was isolated in pure form. Aldol products **45** and **48** were formed as unseparable mixture of diastereomers. For the nitrones **46**, **50**, **51**, **52**, **53** and **54** the mixtures could be separated by chromatography. In case of nitrone **49** essentially only one isomer was formed.



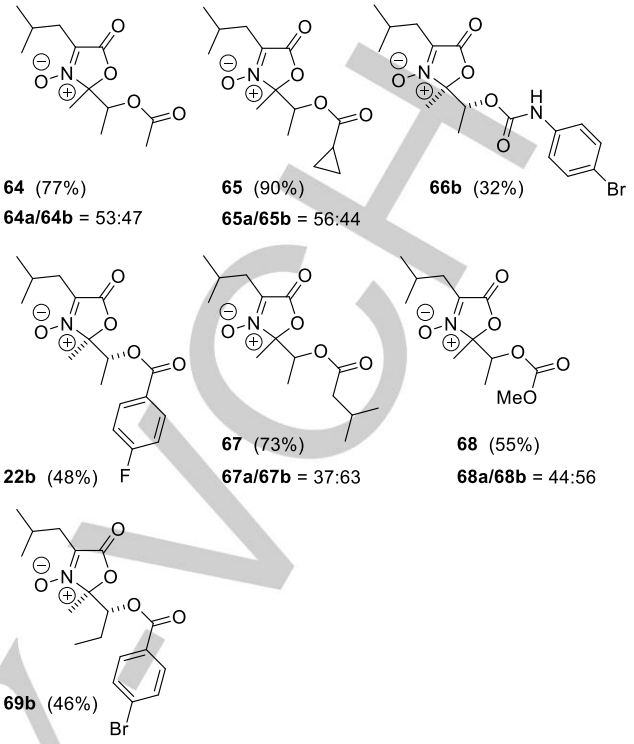
Scheme 11. Collection of aldol-type products obtained by deprotonation of the cyclic nitrones and trapping the anions with carbonyl compounds. The possible diastereomers are shown for nitrone aldol product **52**.

With the nitrone aldol products in hand, a range of MBH-001 analogs could be obtained (Scheme 12). Again, reduction of the nitrone functionality using activated zinc as the reducing agent was the method of choice to obtain the oxazolones **55** – **63**. Unfortunately both diastereoisomers **54** decomposed during reduction to the final compounds. Nitrone **48** was reduced to the oxazolone **13b** (63%) obtained by hydroxyalkylation of azlactone **4b** with 4-chlorobenzaldehyde. The structure was in accordance with the azlactone reaction product described earlier.



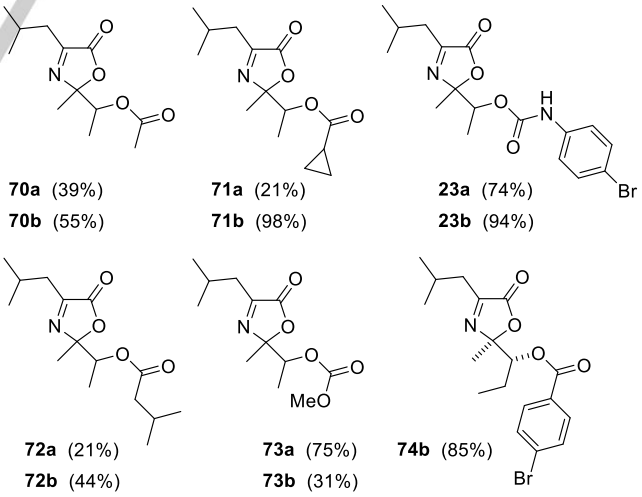
Scheme 12. Selection of prepared MBH-001 analogs that were obtained by reduction of the nitrone functionality. The possible diastereomers are shown for oxazolone **62**.

As mentioned before, in order to analyze the SAR and to explore different prodrug types, the hydroxyl group of the oxazolone side chain has been derivatized under standard conditions, starting from the cyclic nitrones of type **21** or other MBH-001 analogs to form esters (**64**, **65**, **22b**, **67**, **69**), carbonates (**68**) and urethanes (**66b**) (Scheme 13).



Scheme 13. Selection of nitrone derivatives, obtained by converting the side chain hydroxyl group to esters, urethanes and carbonates.

Afterwards the nitrone esters were reduced with zinc to afford the oxazolones **70**–**74**, and **23** in medium to good yields. Some examples can be found in Scheme 14.



Scheme 14. Selection of prepared MBH-001 analogs were the hydroxyl group was derivatized, obtained by reduction of the nitrone functionality.

All prepared ester and carbonate prodrugs (Scheme 14) did not show any significant improved biological activity compared to the

corresponding MBH analogs in the greenhouse. The urethanes were not biologically active at all.

Conclusions

The natural herbicide MBH-001 (**1**) features a 2-methyloxazol-5(2*H*)-one core with a (1-hydroxyethyl) substituent at the 2-position. While it was not possible to access this structure via azlactone precursors, the *N*-oxide of azlactones (cyclic nitrones) served this purpose well. The cyclic nitrones, 2-alkyl-5-oxo-2,5-dihydrooxazole 3-oxides were obtained from 2-hydroxyimino esters, obtained by oxidation of α-amino acid esters, and an aldehyde under basic conditions. It was found that the cyclic nitrones can be deprotonated and the anion trapped with an aldehyde to give the derivatives with the 1-hydroxyalkyl substituent at the 2-position of the 2-alkyl-5-oxo-2,5-dihydrooxazole 3-oxides. A final reduction of the nitrone with activated zinc furnished MBH-001. Using this strategy, several analogs were prepared. It seems that with the nitrone function, the C=N double bond stays in place and the issue of regiocontrol in the reaction with electrophiles, like with the azlactones, was not observed. Further reactions of the cyclic nitrones (cycloaddition[30] or organocatalytic Michael reactions) are under investigation.

Experimental Section

General. HPLC-retention times refer to a Waters Acquity UPLC with Sample Organizer, column: Zorbax Eclipse+ C18, 3 × 50mm; 0.1% aqueous HCO_2H and acetonitrile (ACN, MeCN) as eluent (linear gradient from 10% acetonitrile to 95% acetonitrile). Scheme 6 and Schemes 11–14: To differentiate the diastereomers, the term "upper" and "lower" are used. The term "upper diastereomer" refers to the less polar isomer, whereas "lower diastereomer" refers to the more polar isomer on TLC.

(*S*)-4-Isobutyl-2-methyloxazol-5(4*H*)-one[7] (**4b**). Under a nitrogen atmosphere N-acetyl-L-leucine (**10**) (1000 mg, 5.77 mmol) and EDCl (1107 mg, 5.77 mmol) were dissolved at 0 °C in of diethyl ether (37 mL) and directly hydrolyzed with ice cold water after 15 min. The reaction mixture was washed once with 0 °C cold saturated $NaHCO_3$ solution and twice with ice water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give oxazolone **4b** (250 mg, 27%) as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95, 0.92 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.50–1.55 (m, 1H, 1'-H_A), 1.66–1.72 (m, 1H, 1'-H_B), 1.95 (hept, *J* = 6.8 Hz, 1H, 2'-H), 2.19 (s, 3H, 2-CH_3), 4.13–4.15 (m, 1H, 4-H). The compound should be stored in a deep freezer and directly used for the next steps.

2-(Hydroxy(phenyl)methyl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**13a**). Under nitrogen, azlactone **4b** (2.00 g, 12.8 mmol) in CH_2Cl_2 (8 mL) was cooled down to –20 °C. Then trimethylamine (1.304 g, 1.80 mL, 12.8 mmol) was added followed by benzaldehyde (**12a**) (1.641 g, 1.58 mL, 15.4 mmol). The reaction mixture was stored for 11 d at –18 °C. Then the reaction mixture was diluted with CH_2Cl_2 and washed with KH_2PO_4 buffer and water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by medium pressure column chromatography on silica (Biotage SP1, gradient heptane/EtOAc from 0–50% EtOAc) to give oxazol-5(2*H*)-one **13a** (1.07 g, 32%) as a white solid; mp = 71 °C; R_t = 1.20 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): (isomeric ratio = 93:7) δ = 0.90, 0.92 (2d, *J* = 6.7 Hz, 6H, 3'-H), 2.05–2.14 (m, 1H, 2'-H), 2.34–2.42 (m, 2H, 1'-H), 3.15 (bs, 1H, OH), 7.24–7.39 (m, 5H, Ph); major isomer: 1.53 (s, 3H, 2-CH_3), 4.85 (s, 3H, 1''-H); minor isomer: 1.45 (s, 3H, 2-CH_3), 4.82 (s, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): (isomeric ratio = 93:7) δ = 21.5, 22.3, 22.4 (C-3', 2-CH_3), 26.3 (C-2'), 36.4 (C-1'), 77.1 (C-1''), 106.8 (C-2), 127.9, 128.1, 128.5, 137.3 (Ph), 164.1 (C-4), 164.5 (C-5); minor isomer: 76.5 (C-1'), 106.4 (C-2), 137.3 (Ph), 164.1 (C-4), 165.5 (C-5) ppm.

2-((4-Chlorophenyl)(hydroxy)methyl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**13b**). Under nitrogen, azlactone **4b** (0.250 g, 1.61 mmol) in CH_2Cl_2 (20 mL) was cooled down to –15 °C. Then, 4-chlorobenzaldehyde (**12b**) (0.238 g, 1.69 mmol) was added followed by catalytic quantities of *N*-ethyldiisopropylamine (21.0 mg, 0.16 mmol). The reaction mixture was stored for 1 d at –18 °C before it was diluted with CH_2Cl_2 and washed with KH_2PO_4 buffer and water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by medium pressure column chromatography on silica (Biotage SP1, gradient heptane/EtOAc from 0–50% EtOAc) to give oxazol-5(2*H*)-one **13b** (0.343 g, 65%, purity 90%) as a colorless oil; R_t = 1.48 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): (isomeric ratio = 64:36) δ = 0.92, 0.94 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.51 (s, 3H, 2-CH_3), 2.09–2.16 (m, 1H, 2'-H), 2.40–2.46 (m, 2H, 1'-H), 4.81 (s, 1H, 1''-H), 7.30–7.34 (m, 4H, Ar-H), minor: 1.46 (s, 3H, 2-CH_3), 4.81 (s, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): (isomeric ratio = 64:36) δ (major) = 21.3, 22.3, 22.5, 26.4 (C-3', C-2', 2-CH_3), 36.6 (C-1'), 76.8 (C-1''), 106.4 (C-2), 128.4, 129.2, 134.6, 135.8, (Ar C), 164.4 (C-4), 165.3 (C-5), minor: 21.3, 22.3, 22.4, 26.3 (C-3', C-2', 2-CH_3), 36.6 (C-1'), 76.2 (C-1''), 106.2 (C-2), 128.5, 129.2, 134.7, 135.7, 164.2 (C-4), 165.3 (C-5) ppm.

Alternative synthesis of oxazolone **13b** via nitrone **48**. According to general procedure 1, nitrone **48** (150 mg, 0.48 mmol) (*low*/*high* = 1:1) was dissolved in THF (11 mL) and water (6 mL) and the resulting solution was treated with activated zinc powder (189 mg, 2.88 mmol). After the addition of NH_4Cl solution (154 mg, 2.88 mmol in 5.4 mL water), the grey suspension was stirred vigorously for 60 min at r. t. Then the reaction mixture was diluted with EtOAc, filtered through a pad of celite, which was rinsed with EtOAc several times. The collected organic phases were extracted with water, dried over Na_2SO_4, filtered, washed and concentrated in vacuo to give oxazolone **13b** (100 mg, 63%, 90% purity). The analytical data were identical with the azlactone procedure; R_t = 1.52 (HPLC); HRMS (ESI-TOF): calcd. for $C_{15}H_{18}ClNO_3$ $[M + H]^+$ 296.1053, found 296.1055.

2-((6-Chloropyridin-3-yl)(hydroxy)methyl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**13c**). Under nitrogen, azlactone **4b** (0.500 g, 3.22 mmol) in CH_2Cl_2 (20 mL) was cooled down to –15 °C. Then, 6-chloronicotinaldehyde (**12c**) (0.479 g (3.38 mmol) was added followed by *N*-ethyldiisopropylamine (0.416 g, 3.22 mmol). The reaction mixture was stored for 2 d at –18 °C before it was diluted with CH_2Cl_2 and washed with KH_2PO_4 buffer and water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by medium pressure column chromatography on silica (Biotage SP1, gradient heptane/EtOAc from 30–100% EtOAc) to give oxazol-5(2*H*)-one **13c** (0.260 g, 26%, purity 95%) as a white solid; R_t = 1.28, 1.28 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): (isomeric ratio = 73:27) δ = 0.92–0.97 (m, 6H, 3'-H), 1.46, 1.49 (s, 3H, 2-CH_3), 2.12–2.22 (m, 1H, 2'-H), 2.41–2.50 (m, 2H, 1'-H), 4.83, 4.89 (s, 1H, 1''-H), 7.32–7.48 (m, 1H, pyridine), 7.72–7.79 (m, 1H, pyridine), 8.35–8.38 (m, 1H, pyridine) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): (isomeric ratio = 73:27) δ (major) = 21.2, 22.4, 22.5, 26.4 (C-3', C-2', 2-CH_3), 36.6 (C-1'), 74.5 (C-1''), 106.0 (C-2), 124.1, 132.3, 138.5, 149.1, 151.6 (Ar C), 164.4 (C-9), 165.2 (C-5), minor: 20.9, 22.3, 22.4, 26.3 (C-3', C-2', 2-CH_3), 36.6 (C-1'), 74.1 (C-1''), 106.0 (C-2), 124.2, 132.3, 138.5, 149.0, 151.7 (Ar C), 164.6 (C-4), 165.1 (C-5) ppm.

rel-*N*-[(2*S*,4*R*,5*R*)-5-Isobutyl-2,4-dimethyl-6-oxo-1,3-dioxan-5-yl]acetamide (**14**). Under nitrogen, azlactone **4b** (1.93 g, 12.4 mmol) in CH_2Cl_2 (8 mL) was cooled down to –20 °C. Then triethylamine (1.29 g, 1.78 mL, 12.4 mmol) was added, followed by acetaldehyde (0.822 g, 1.05 mL, 18.6 mmol). The reaction mixture was stored for 11 d at –18 °C before it was diluted with CH_2Cl_2 and washed with KH_2PO_4 buffer and water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by medium pressure column chromatography on silica (Biotage SP1, gradient heptane/EtOAc from 20% to 40% EtOAc) to give dioxanone **14** (750 mg, 25%) as a white solid; mp = 130.7 °C; R_t = 1.04 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3H, 3'-H), 1.03 (d, *J* = 6.6 Hz, 3H, 3-H), 1.24 (d, *J* = 6.6 Hz, 3H, 4-CH_3), 1.49–1.53 (m, 1H, 1'-H_A), 1.72 (d, *J* = 5.7 Hz, 3H, 2-CH_3), 1.89–1.94 (m, 2H, 1'-H_B, 2'-H), 2.01 (s, 3H, acetyl), 4.94 (q, *J* = 6.4 Hz, 1H, 4-H), 5.74 (bs, 1H, NH), 5.75 (q, *J* = 5.6 Hz, 1H, 2-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.2 (4-CH_3), 20.0 (2-CH_3), 23.2 (CH_3C=O) 23.3 (C-3'), 24.0 (C-2'), 24.6 (C-3'), 40.2 (C-1'), 60.3 (C-N (C-5)), 67.1 (C-4), 99.4 (C-2), 168.7, 170.09 (C-6, C=O acetamide) ppm; HRMS (ESI-TOF): calcd. for $C_{11}H_{19}NO_4$ [M + H]$^+$ 230.1392, found 230.1393.

3-Hydroxybutan-2-one oxime (**15**). A suspension of 3-hydroxy-butan-2-one (5.00 g, 56.7 mmol, 1 equiv), NH_2OH·HCl (9.57 g, 138 mmol, 2.4 equiv) and NaOAc (11.5 g, 140 mmol, 2.5 equiv) in EtOH (120 mL) and H_2O (50 mL) was heated under reflux (90 °C) for 3 h. The mixture was cooled to r.t. and stirred for 1.5 h at r.t. before saturated aqueous $NaHCO_3$ solution (75 mL) was added and the mixture was extracted with CH_2Cl_2/*i*-PrOH 3:1 (4 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting yellow oil can be distilled under reduced pressure (17 mbar, 160 °C) or purified by flash chromatography (EtOAc/petroleum ether, 2:1) to furnish 3-hydroxy-butan-2-one-oxime (**15**) (4.43 g, 43.0 mmol, 76%) as a colorless highly viscous oil which formed a white solid upon cooling. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.13 (d, *J* = 6.5 Hz, 3H, 4-H), 1.69 (s, 3H, 1-H), 4.13 (q, *J* = 6.5 Hz, 1H, 1-H), 4.95 (bs, 1H, OH), 10.34 (bs, 1H, =NOH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 8.7 (C-1), 20.8 (C-4), 67.7 (C-3), 158.4 (C-2) ppm.

(*S*)-2-Hydroxy-4-methylpentanoic acid (**17**). L-Leucine (**16**) (30.0 g, 0.23 mol) was dissolved in H_2SO_4 (2M, 230 mL) and the solution cooled down to 0 °C. Then a solution of $NaNO_2$ (95.0 g, 1.38 mol, 6 equiv) in water (250 mL) was added slowly so that the reaction temperature does not exceed 5 °C (N_2 outgassing). After complete addition, the reaction mixture was left to stir for 3 h at 0 °C before it was allowed to reach r.t. slowly overnight. The mixture was extracted with Et_2O (3 × 1 L) and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was recrystallized from a mixture of petroleum ether/Et_2O to produce hydroxy acid[11] **17** (20.6 g, 68%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.7 Hz, 6H, 5-H), 1.56–1.68 (m, 2H, 3-H), 1.90 (qqdd, *J* = 6.9, 6.9, 6.7, 6.7 Hz, 1H, 4-H), 4.29 (dd, *J* = 8.3, 5.1 Hz, 1H, 2-H), 7.01 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 23.2, 24.4 (C-4, C-5), 43.2 (C-3), 68.9 (C-2), 180.6 (C-1) ppm.

Methyl (*S*)-2-hydroxy-4-methylpentanoate (**18**). To a solution of hydroxy acid **17** (10.0 g, 75.7 mmol) in MeOH (70 mL) was added thionyl chloride (8.4 mL, 0.12 mol) slowly at 0 °C. After complete addition, the ice-bath was removed and the reaction mixture refluxed for 2 h. After the solution had reached r.t., ice-water (500 mL) was added and the mixture extracted with EtOAc (3 × 500 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated in vacuo to provide pure hydroxy ester[11b] **18** (9.08 g, 82%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92, 0.94 (2 d, *J* = 6.7 Hz, 6H, 5-H), 1.49–1.59 (m, 2H, 3-H), 1.87 (qqdd, *J* = 6.9, 6.9, 6.7, 6.7 Hz, 1H, 4-H), 2.74 (br s, 1H, OH), 3.77 (s, 3H, OCH_3), 4.20 (dd, 7.9, 5.4 Hz, 1H, 2-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 23.2, 24.4 (C-4, C-5), 43.5 (C-3), 52.4 (OCH_3), 69.0 (C-2), 176.3 (C-1) ppm.

Methyl 4-methyl-2-oxopentanoate (**19**). NaOH (6.45 g, 0.16 mol) was dissolved in water (80 mL) and then the solution was cooled to –5 °C. Bromine (4.15 mL, 80.8 mmol) was added dropwise within 2 h so that the temperature did not exceed 0 °C. Subsequently, a solution of hydroxy ester **18** (9.07 g, 62.1 mmol) in CH_2Cl_2 (80 mL) was added to the generated NaOBr solution dropwise while keeping the temperature below 0 °C. Thereafter, concentrated HCl solution (1.56 mL, 18.7 mmol) was added within a 15 min period at the same temperature. The ice-bath was removed and the resulting two-phase orange solution was stirred overnight before it was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was distilled at 30 °C under reduced pressure (1 mbar) to give α-keto ester[13] **19** (6.0 g, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.7 Hz, 6H, 5-H), 2.18 (qqt, *J* = 6.7, 6.7, 6.7 Hz, 1H, 4-H), 2.70 (d, *J* = 6.7 Hz, 2H, 3-H), 3.84 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (C-5), 24.1 (C-4), 47.9 (OCH_3), 52.9 (C-3), 161.7 (C-1), 194.0 (C-2) ppm.

4-Methyl-2-oxopentanoic acid (**20**). To a solution of α-keto ester **19** (2.0 g, 13.9 mmol) in MeOH (5 mL) was added a solution of NaOH (555 mg, 13.9 mmol) in water (10 mL) at 0 °C. Thereafter, the ice-bath was removed, and the solution was stirred at 60 °C for 1.5 h. When TLC analysis showed full conversion, the mixture was cooled down to 0 °C and acidified to pH = 1 using 15% HCl solution before it was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give α-keto acid[14] **20** (1.75 g, 97%) as a slightly yellowish oil of sufficient purity to be used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.7 Hz, 6H, 5-H), 2.21 (qqt, *J* = 6.7, 6.7, 6.7 Hz, 1H, 4-H), 2.82 (d, *J* = 6.8 Hz, 2H, 3-H), 8.32 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (C-5), 24.4 (C-4), 45.9 (C-3), 160.2 (C-1), 195.4 (C-2) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydro-oxazole-3-oxide (**21a**) and rel-(*S*)-2-((*R*)-1-Hydroxyethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole-3-oxide (**21b**). A mixture of 4-methyl-2-oxopentanoic acid (**20**) (470 mg, 3.6 mmol) and 3-hydroxybutan-2-one oxime (**15**) (560 mg, 5.4 mmol, 1.5 equiv) in dichloroethane (10 mL) was refluxed for 3 d before it was cooled to r.t. and all volatiles were removed under reduced pressure. After purification by flash chromatography (petroleum ether/EtOAc, 3:1) the heterocycles **21a** and **21b** were obtained in a ratio of 1:1 as a colorless oils, which solidified upon standing (240 mg, 31%).

Upper diastereomer **21a**. R_f = 0.39 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (2 d, *J* = 6.7 Hz, 6H, 3''-H), 1.29 (d, *J* = 6.4 Hz, 3H, 2'-H), 1.77 (s, 3H, 2-CH_3), 2.18 (qqdd, *J* = 7.1, 7.1, 6.7, 6.7 Hz, 1H, 2''-H), 2.45 (dd, *J* = 13.9, 7.1 Hz, 2H, 1''-H), 3.18 (d, *J* = 3.9 Hz, 1H, OH), 3.94 (qd, *J* = 6.4, 3.9 Hz, 1H, 1'-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 18.4, 22.4, 22.5, 26.3, 30.7 (2-CH_3, C-1'', C-2'', C-2', C-3''), 71.6 (C-1'), 104.5 (C-2), 131.3 (C-4), 164.3 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{10}H_{17}NO_4$ [M + Na]$^+$ 238.10498, found 238.10519.

Lower diastereomer **21b**. R_f = 0.31 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (2 d, *J* = 6.7 Hz, 6H, 3''-H), 1.34 (d, *J* = 6.6 Hz, 3H, 2'-H), 1.71 (s, 3H, 2-CH_3), 2.12 (d, *J* = 8.2 Hz, 1H, OH), 2.18 (qqdd, *J* = 6.9, 6.9, 6.8, 6.8 Hz, 1H, 2''-H), 2.45 (dd, *J* = 13.8, 7.4 Hz, 2H, 1''-H), 4.17 (qd, *J* = 8.1, 6.6 Hz, 1H, 1'-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0, 20.6, 22.4, 22.5, 26.2, 30.7 (2-CH_3, C-1'', C-2'', C-2', C-3''), 68.6 (C-1'), 105.6 (C-2), 131.8 (C-4), 165.0 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{10}H_{17}NO_4$ [M + Na]$^+$ 238.10498, found 238.10531.

rel-(*S*)-2-((*R*)-1-((4-Fluorobenzoyl)oxy)ethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**22b**). To a solution of nitrone **21b** (1.30 g, 6.04 mmol) in dry acetonitrile (6 mL) under nitrogen atmosphere were

consecutively added at 0 to –10 °C, *N*,*N*-diisopropylethylamine (1.51 g, 12.00 mmol), DMAP (0.221 g, 1.81 mmol) and then 4-fluorobenzoyl chloride (1.053 g, 6.64 mol). The reaction was held for 2 h at 0 °C and warmed up to room temperature. After 2 d, the reaction mixture was diluted with EtOAC and extracted with water. The organic layer was dried over Na_2SO_4, filtered, rinsed and concentrated in vacuo. The residue was purified by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc) to give fluorobenzoate **22b** (0.970 g, 48%) as a white solid (mp = 80.5 °C); R_t = 1.61 min (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.76, 0.80 (2d, *J* = 6.7 Hz, 6H, 3'-H), 1.53 (d, *J* = 6.6 Hz, 3H, 2''-H), 1.79 (s, 3H, 2-CH_3), 1.94–2.04 (m, 1H, 2'-H), 2.33, 2.36 (2 dd, *J* = 13.6, 7.0 Hz, 2H, 1'-H), 5.57 (q, *J* = 6.6 Hz, 1H, 1''-H), 7.05–7.10 (m, 2H, Ar-H), 7.87–7.92 (m, 2H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.6 (C-2'), 21.0 (2-CH_3), 22.50, 22.53, 26.5 (C-3'', C-2''), 30.7 (C-1''), 69.7 (C-1'), 104.8 (C-2), 115.7, 115.8, 125.30, 125.32, 125.30, 125.32 (Ar-F), 131.1 (C-4), 132.25, 132.27 (Ar-F), 163.4, 164.8, 165.3, 166.9 (C-5, Ester-CO, C-F) ppm; HRMS (ESI-TOF): calcd. for $C_{17}H_{20}FNO_5$ $[M + H]^+$ 338.1404, found 338.1402.

rel-(*S*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl (4-bromophenyl)carbamate (**23a**). Under nitrogen atmosphere MBH-001 high **1a** (100 mg, 0.50 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL). Afterwards 4-bromophenylisocyanate (0.149 g, (0.75 mmol) in CH_2Cl_2 (2.5 mL) and *N*,*N*-diisopropylethylamine (71.4 mg, 0.55 mmol) were added. The reaction mixture was stirred for 4 d at room temperature. After evaporation of the solvent, the crude reaction mixture was directly purified by by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc) to give of pure carbamate **23a** (125 mg, 60%, purity 95%) as a white solid; R_t = 1.66 min (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.0 Hz, 6H, 3'-H), 1.31 (d, *J* = 6.6 Hz, 3H, 2''-H), 1.62 (s, 3H, 2-CH_3), 2.18–2.22 (m, 1H, 2'-H), 2.50 (bd, *J* = 5.1 Hz, 1'-H), 5.20 (q, *J* = 6.6 Hz, 1H, 1''-H), 6.56 (bs, 1H, NH), 7.23–7.30 (bm, 2H, Ar-H), 7.40–7.45 (m, 2H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.0 (C-2'), 21.9, 22.35, 22.45 (C-3', 2-CH_3), 26.2 (C-2'), 36.6 (C-1'), 72.6 (C-1''), 105.6 (C-2), 120.4 (Ar C), 132.1 (Ar C), 136. 5 (Ar C), 151.9 (O-(C=O)-N), 164.2 (C-4), 165.2 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{17}H_{21}BrN_2O_4$ $[M + H]^+$ 200.1287, found 200.1286.

(*R*)-1''-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl 4-bromobenzoate (**24b**). Under a nitrogen atmosphere of (*2S,1''R*)-**1b** (50.0 mg, 0.251 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. Then triethylamine (38.1 mg, 0.376 mmol) and DMAP (6.1 mg, 0.05 mmol) were added. Next, 4-bromobenzoyl chloride (60.6 mg, 0.276 mmol) in CH_2Cl_2 (2 mL) was added at that temperature and the mixture warmed up to r.t. After 12 h stirring at r.t., additional trimethylamine (38.1 mg, 0.376 mmol), DMAP (6.1 mg, 0.05 mmol) and 4-bromobenzoyl chloride (60.6 mg, 0.276 mmol) in CH_2Cl_2 (2 mL) were added. After 12 h the reaction mixture was concentrated in vacuo and purified directly by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 0% – 30% EtOAc) to give pure benzoate *(2S,1''R)*-**24b** (50.0 mg, 52%) as colorless solid; R_t = 1.75 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.01, 1.02 (2d, *J* = 6.6 Hz, 6H, 3'-H), 1.36 (d, *J* = 6.4 Hz, 2''-H), 1.64 (s, 3H, 2-CH_3), 2.21 (sept, *J* = 6.7 Hz, 1H, 2'-H), 2.52 (d, *J* = 7.0 Hz, 2H, 1'-H), 5.44 (q, *J* = 6.6 Hz, 1H, 1''-H), 7.57 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.80 (d, *J* = 8.6 Hz, 2H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.9 (C-2''), 22.0, 22.4, 22.5, 26.1 (C-2'), 36.6 (C-1'), 72.1 (C-1''), 105.6 (C-2), 128.5, 128.6, 131.1, 131.8 (Ar C), 164.2, 165.5, 165.2 (C-4, C-5, ester C=O) ppm; HRMS (ESI-TOF): calcd. for $C_{17}H_{20}BrNO_4$ $[M + H]^+$ 382.0654, found 382.0655.

Benzoate *ent*-**24b** was prepared in a similar way.

Reduction of the cyclic nitrones with zinc. General procedure 1.

To a solution of nitrone **21** in THF (≈ 2.5 mL per 1 mmol) activated zinc powder[31] (5 equiv) was added, followed by addition of saturated aqueous NH_4Cl solution (1:1 solvent ratio). The resulting grey suspension was stirred vigorously for 40 min. Thereafter, the reaction mixture was filtered through a pad of celite, which was rinsed with Et_2O. The filtrate was treated with water, and extracted thrice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. This way pure oxazolone **1** was obtained.

Upper diastereomer **1a**. R_f = 0.44 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98, 0.99 (2 d, *J* = 6.6 Hz, 6H, 3'-H), 1.29 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.58 (s, 3H, 2-CH_3), 1.86 (br s, 1H, OH), 2.19 (qqdd, *J* = 6.8, 6.8, 6.7, 6.7 Hz, 1H, 2'-H), 2.48 (dd, *J* = 14.8, 6.8 Hz, 2H, 1'-H), 3.90 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 20.7, 22.3, 22.4, 26.2, 36.6 (2-CH_3, C-1', C-2', C-2'', C-3'), 71.3 (C-1''), 107.3 (C-2), 163.8, 165.4 (C-4, C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{10}H_{17}NO_3$ $[M + Na]^+$ 222.11006, found 222.11030.

Lower diastereomer **1b**. R_f = 0.40 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98, 0.99 (2 d, *J* = 6.6 Hz, 6H, 3'-H), 1.32 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.56 (s, 3H, 2-CH_3), 1.72 (br s, 1H, OH), 2.19 (qqdd, *J* = 6.8, 6.8, 6.7, 6.7 Hz, 1H, 2'-H), 2.48 (dd, *J* = 15.0, 6.8 Hz, 2H, 1'-H), 3.83 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 20.1, 22.3, 22.4, 26.2, 36.5 (2-CH_3, C-1', C-2', C-2'', C-3'), 71.1 (C-1''), 107.6 (C-2), 163.5, 165.5 (C-4, C-5) ppm; HRMS (ESI-TOF): calcd for $C_{10}H_{17}NO_3$ $[M + Na]^+$ 222.11006, found 222.11031.

rel-(*S*)-1-((*S*)-2-(1-Hydroxyethyl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**1a**). According to general procedure 1, cyclic nitrone **21a** (158 mg, 0.73 mmol) in THF (2 mL) was reduced with activated zinc powder (240 mg, 3.7 mmol, 5 equiv), in the presence of saturated aqueous NH_4Cl solution (2 mL). The resulting grey suspension was stirred vigorously for 40 min. Thereafter, the mixture was filtered through a pad of celite, which was rinsed with Et_2O (20 mL). The filtrate was treated with water (20 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. This way pure oxazol-5(2*H*)-one **1a** (120 mg, 82%) was obtained as a colorless oil.

Preparation of pure enantiomers **1b** *(RS/SR)*

a) Racemic **1b** (300 mg, 1.39 mmol) was separated into its enantiomers by chiral chromatography on Chiralpak IC (heptane/propanol, 90:10) to give (*2R,1''S*)-**1b** *(*132 mg,44%) and (*2S,1''R*)-**1b** (174 mg, 57%).

b) Alternatively, nitrone **21b** (300 mg, 1.39 mmol) was separated into its enantiomers by chiral chromatography on CHIRALCEL OX (Sepiatec, 80 mL, 10% B ACN + 0.1% HCOOH) to give pure nitrone *(2R,1''S)*-**21b** [100 mg, 33%, R_t = 1.0 min (HPLC); R_t = 1.57 min (chiral HPLC on Chiralpak OX, MeCN)] and pure nitrone *(2S,1''R)*-**21b** [105 mg, 35%, R_t = 0.99 min (HPLC), R_t = 1.88 min (chiral HPLC on Chiralpak OX, MeCN].

c1) According to general procedure 1, nitrone *(2R,1''S)*-**21b** (100 mg, 0.46 mmol) was dissolved in THF (6 mL) and the resulting solution was treated with activated zinc powder (182 mg, 2.78 mmol). After the addition of NH_4Cl solution (149 mg, 2.78 mmol, in 3 mL water), the grey suspension was stirred vigorously for 60 min at r.t. Then the reaction mixture was diluted with EtOAc, filtered through a pad of celite, which was rinsed with EtOAc several times. The collected organic phases were washed with water, dried over Na_2SO_4, filtered, the filter cake rinsed with EtOAc and the filtrate concentrated in vacuo to give *(2R,1''S)*-**1b** (85.0 mg, 89%, 97% purity) as a colorless oil; R_t = 1.06 min (HPLC); R_t = 6.53 (Chiralpak IC; heptane/*i*PrOH, 90:10); HRMS (ESI-TOF): calcd. for $C_{10}H_{17}NO_3$ $[M + H]^+$ 200.1287, found 200.1287; $[\alpha]_{20}^{D}$ = –23.62 (*c* = 2.405 in $CHCl_3$).

c2) According to general procedure 1, nitrone *(2S,1''R)*-**21b** (105 mg, 0.48 mmol) was dissolved in THF (6 mL) and the resulting solution was treated

with activated zinc powder (191 mg, 2.92 mmol). After the addition of NH_4Cl solution (157 mg, 2.92 mmol, in 3 mL water), the grey suspension was stirred vigorously for 60 min at r.t. Then the reaction mixture was diluted with EtOAc, filtered through a pad of celite, which was rinsed with EtOAc several times. The collected organic phases were washed with water, dried over Na_2SO_4, filtered, the filter cake rinsed with EtOAc, and the filtrate concentrated in vacuo to give *(2S,1''R)*-**1b** (80.0 mg, 78%, 95% purity) as a colorless oil; R_t = 1.06 (HPLC); R_t = 8.56 (Chiralpak IC; heptane/*i*PrOH, 90:10); HRMS (ESI-TOF): calcd. for $C_{10}H_{17}NO_3$ $[M + H]^+$ 200.1287, found 200.1289; $[\alpha]_{20}^D$ = +22.76 (*c* = 2.46 in $CHCl_3$).

3-Methyl-2-oxo-1-oxa-4-azaspiro[4.5]dec-3-ene 4-oxide (**26**). To a suspension of methyl 2-(hydroxyimino)propanoate[19] (**25**) (400 mg, 3.05 mmol) and cyclohexanone (1.37 mL, 1.3 g, 123.3 mmol, 4.3 equiv) in water (10 mL) was added NaOH solution (0.1M, 10 mL, 1 mmol, 0.33 equiv) at 0 °C in portions (2 mL every 30 min). After being stirred for 12 h at 0 °C and 24 h at room temperature, the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 4:1) gave cyclic nitrone **26** (317 mg, 57%) as a white solid, m.p. = 115 °C. R_f = 0.39 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.37 (m, 1H), 1.63–1.82 (m, 5H), 1.85–1.94 (m, 2H), 2.11 (s, 3H, CH_3), 2.18–2.26 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6 (CH_3), 22.1, 23.7, 34.1 (CH_2), 105.9 (C-5, spiro C), 127.3 (C-3), 164.7 (C-2) ppm; HRMS (EI): calcd. for $C_9H_{13}NO_3$ $[M - e^-]^+$ 183.08899, found 183.09045.

Methyl 2-amino-4-methylpentanoate (**27**). Thionyl chloride (30.5 mL, 0.42 mol, 1.1 equiv) was added dropwise within 20 min to methanol (400 mL) at 0 °C, followed by addition of L-leucine (50.0 g, 0.38 mol, 1 equiv) in portions. The resulting solution was left to stir at r.t. overnight. After that, all volatiles were removed by evaporation and the white solid (hydrochloride salt) was suspended in chloroform (270 mL). To this suspension a solution of triethylamine (54.0 mL, 0.39 mol) in chloroform (270 mL) was added dropwise at r.t. After 4 h of stirring at r.t., the mixture was refluxed for 1 h. Then it was cooled again to r.t. and concentrated in vacuo to a white solid, which was diluted with Et_2O (0.5 – 1 L) and filtered. The white solid (Et_3N·HCl) was washed with of Et_2O (500 mL). The combined filtrates were concentrated and the resulting oil was distilled under vacuum (oil pump, bath temperature < 50 °C). The colorless free amino acid ester[22] **27** (49.8 g, 90%) was kept in a fridge (–18 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88, 0.90 (2 d, *J* = 6.7 Hz, 6H, 5-H), 1.34–1.43 (m, 1H, 3-H), 1.45–1.51 (m, 2H, NH_2), 1.49–1.57 (m, 1H, 3-H), 1.74 (qqdd, *J* = 6.7, 6.7, 6.7, 6.7 Hz, 1H, 4-H), 3.41–3.47 (m, 1H, 2-H), 3.68 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 22.9, 24.7 (C-4, C-5), 44.0 (C-3), 51.8 (C-2), 52.7 (OCH_3), 177.0 (C-1) ppm.

Oxidation of amino acid methyl esters to the 2-hydroxyimino esters. General procedure 2.

To a solution of the amino acid methyl ester (1 equiv) in ethanol (1.6 mL per mmol of ester) was added sodium tungstate dihydrate (0.1 equiv). After stirring of the solution for 30 min at 0 °C, hydrogen peroxide solution (31% in H_2O, 1 mL per mmol, 13 equiv) was added dropwise over a period of 20 min. Thereafter, water (1.6 mL per mmol) was added and the mixture stirred overnight with concomitant warming to r.t. The mixture was poured into a separation funnel containing saturated NH_4Cl solution (15 mL per mmol) and EtOAc (6 ml per mmol). After separation of the layers, the aqueous layer was extracted thrice with EtOAc. The combined organic layers were washed with sodium thiosulfate solution (1M, 15 mL per mmol) and saturated NaCl solution (15 mL per mmol). They were dried over Na_2SO_4 or $MgSO_4$, filtered and concentrated in vacuo to give the pure 2-(hydroxyimino)ester.

Methyl 2-(hydroxyimino)-4-methylpentanoate **(28)**. According to general procedure 2, methyl leucinate (**27**) (10.0 g, 0.07 mol, 1 equiv) was oxidized to pure oxime[24] **28** (10.3 g, 94%), white powder. R_f = 0.23 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 6H, 5-H), 2.04 (qqt, *J* = 6.9, 6.9, 6.8 Hz, 1H, 4-H), 2.53 (d, *J* = 7.5 Hz, 2H, 3-H), 3.83 (s, 3H, OCH_3), 8.70 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (C-5), 26.5 (C-4), 33.3 (C-3), 52.6 (OCH_3), 152.5 (C-2), 164.2 (C-1) ppm; HRMS (ESI-TOF): calcd. for $C_7H_{13}NO_3$ $[M + Na]^+$182.07876, found 182.07897.

Synthesis of cyclic nitrones, General procedure 3.

A solution of the oxime **28** (1 equiv) in toluene or as suspension in distilled water (≈ 2.5 mL per 1 mmol, 0.4M) was cooled down to 5 °C before the addition of the aldehyde (4 equiv) under N_2 atmosphere. The resulting mixture was treated with a freshly prepared NaOH solution (0.1M, 0.05 equiv). The same amount of the NaOH solution (0.1M, 0.05 equiv) was added every 90 min after the reaction was started at 5 °C (5 portions altogether) and the resulting suspension was stirred at the same temperature overnight. Thereafter, the reaction mixture was transferred to a separation funnel and extracted thrice with Et_2O. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oxazolone 3-oxides were purified by flash chromatography using a petroleum ether/EtOAc system to give the oxazolone **29** as colorless oil.

4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**29**). According to general procedure 3, oxime **28** (1.0 g, 6.3 mmol) was dissolved in toluene (15 mL) and cooled down to 5 °C. Then acetaldehyde (1.4 mL, 25.1 mmol) was added at once following by the addition of aqueous NaOH solution (0.1M, 3 mL). The remaining four portions of NaOH solution (0.1M) were added every 90 min at the same temperature. After being stirred overnight, the reaction mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give oxazolone **29** as colorless oil (790 mg, 73%). R_f = 0.33 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94, 0.95 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.77 (d, *J* = 6.0 Hz, 3H, 2-CH_3), 2.18 (qqdd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 1H, 2'-H), 2.45 (dd, *J* = 13.9, 7.0 Hz, 2H, 1'-H), 5.60 (q, *J* = 6.0 Hz, 1H, 2-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 22.4, 22.5, 26.2, 30.6 (2-CH_3, C-1', C-2', C-3'), 95.1 (C-2), 131.1 (C-4), 164.9 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_8H_{13}NO_3$ $[M + Na]^+$ 194.07876, found 194.07895.

Condensation of α-ketoacid **20** with aldoximes to oxazolone-*N*-oxides. General procedure 4.

4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**29**). A solution of acetaldehyde oxime[26] (**31**) (2.72 g, 46.1 mmol) in CH_2Cl_2 (6 mL) was added to a solution of 4-methyl-2-oxopentanoic acid (**20**) (4.00 g, 30.7 mmol) in CH_2Cl_2 (5 mL) at r.t. After stirring overnight, the solvent was evaporated and the residue directly purified by chromatography on a diol column Chromabond 40, with a flow rate of 25 mL/min, heptane/EtOAc with a gradient from 3-30% EtOAc to give oxazolone **29** (3.30 g, 63%) as a colorless oil. HPLC retention time = 1.04 min. The spectral data were in full agreement with the above data.

Reaction of cyclic nitrones with aldehydes using $LiN(SiMe_3)_2$ as base, General procedure 5.

A solution of cyclic nitrone (1 equiv) in THF (≈ 3.5 mL per 1 mmol) was cooled down to –78 °C and treated with a LiHMDS solution in THF (1M, 1.05 equiv) in a dropwise fashion under N_2 atmosphere. The resulting

yellow suspension was left to stir for 1 h at –78 °C. The corresponding aldehyde (1.5 equiv) was added and stirring was continued for 0.5 h at –78 °C. Thereafter, the reaction mixture was quenched with saturated NH_4Cl solution, brought to ambient temperature and extracted thrice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/EtOAc or petroleum ether/Et_2O) the 2-(1-hydroxyalkyl) substituted cyclic nitrone was isolated.

2-(1-Hydroxyethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole-3-oxide (**21**). a) Using LiHMDS as base: According to general procedure 5, a solution of nitrone **29** (1.46 g, 8.5 mmol) in THF (30 mL) was cooled to –78 °C. To the resulting suspension a solution of LiHMDS in THF (1M, 8.95 mL, 8.95 mmol) was added dropwise. After 1 h of stirring, acetaldehyde (0.72 mL, 12.81 mmol) was added and stirring was continued for 0.5 h at –78 °C. Then saturated NH_4Cl solution (50 mL) was added and the resulting two-layer mixture was allowed to reach r.t. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/EtOAc, 3:1) both diastereoisomers **21a** and **21b** were isolated in 1:1 ratio as colorless oils, which solidified while kept in a freezer (1.47 g, 80%). The spectral data were in full agreement with the previously described ones.

b) Using Schwesinger base **30**: To a –78 °C cooled solution of nitrone **29** (357 mg, 2.08 mmol) in THF (10 mL) Schwesinger base (**30**) (0.475 mL, 2.3 mmol) was added. Thereafter, acetaldehyde (0.175 mL, 3.13 mmol) was added and the resulting reaction mixture was left to stir at this temperature overnight. Next day, saturated NH_4Cl solution (50 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 2:1) gave **21a** (248 mg, 55%) and **21b** (80 mg, 18%).

2-Methyl-4-oxopentan-3-yl-2-(hydroxyimino)-4-methylpentanoate (**33**). Nitrone **29** (1.65 g, 9.63 mmol) was dissolved in THF (45 mL) and cooled to –78 °C. Then, LiHMDS in THF (1M, 11.6 mL, 11.6 mmol, 1.2 equiv) was added dropwise under N_2 atmosphere. The resulting yellow suspension was left to stir for 1 h at –78 °C, before isobutyraldehyde (1.32 mL, 1.042 g, 14.45 mmol, 1.5 eq) was added. After being stirred for 1 h at –78 °C, the reaction mixture was quenched with sat. NH_4Cl solution (220 mL) and extracted with diethyl ether (3 x 300 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/Et_2O, 4:1) ester **33** was isolated as a colorless oil (1.041 g, 44%). R_f = 0.33 (petroleum ether/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (2 d, *J* = 6.6 Hz, 6H, 5-H), 0.96 (d, *J* = 6.9 Hz, 3H, 5'-H), 1.03 (d, *J* = 6.9 Hz, 3H, 5'-H), 2.03–2.10 (m, 1H, 4-H), 2.16 (s, 3H, 1'-H), 2.27–2.35 (m, 1H, 4'-H), 2.54 (d, *J* = 7.5 Hz, 2H, 3-H), 5.0 (d, *J* = 4.2 Hz, 1H, 3'-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (C-5'), 19.1 (C-5'), 22.7, 22.7 (C-5), 26.5 (C-4), 26.9 (C-1'), 29.6 (C-4'), 33.4 (C-3), 83.9 (C-3'), 151.8 (C-2), 163.4 (C-1), 204.6 (C-1') ppm.

Methyl 2-(hydroxyimino)pentanoate (**34**). According to general procedure 2, methyl norvalinate (0.50 g, 3.81 mmol, 1 equiv) in ethanol (6 mL) was oxidized with hydrogen peroxide solution (31% in H_2O, 3.8 mL, 13 equiv) in the presence of sodium tungstate dihydrate (0.126 g, 0.381 mmol, 0.1 equiv) to oxime **34** (0.464 g, 84%) which was obtained as a white solid. R_f = 0.47 (petroleum ether/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, 3H, CH_3CH_2), 1.57 (m, 2H, $CH_3CH_2CH_2$), 2.60 (m, 2H, CH_2C=NOH), 3.85 (s, 3H, OCH_3), 8.20–10.80 (b, 1H, C=N-O*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3CH_2), 19.4 (CH_3CH_2), 26.6 ($CH_3CH_2CH_2$), 52.6 (OCH_3), 152.9 (*C*=NOH), 164.0 (CO_2CH_3) ppm.

Methyl 2-(hydroxyimino)-3-methylbutanoate (**35**). According to general procedure 2, methyl valinate (5.0 g, 38.1 mmol, 1 equiv) in ethanol (60 mL) was oxidized with hydrogen peroxide solution (31% in H_2O, 38 mL, 13 equiv) in the presence of sodium tungstate dihydrate (1.26 g, 3.81 mmol, 0.1 equiv) to oxime **35** (4.98 g, 90%) which was obtained as a white solid. In this case, both oxime isomers are visible in the ^{1}H NMR spectrum. R_f = 0.45 (petroleum ether/Et_2O, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.8 Hz, 0.6H (minor isomer), $(CH_3)_2CH$), 1.23 (d, *J* = 7.1 Hz, 6H, $(CH_3)_2CH$), 2.79 (sept, *J* = 6.8 Hz, 0.08H (minor isomer), $(CH_3)_2CH$), 3.48 (sept, *J* = 7.1 Hz, 1H, $(CH_3)_2CH$), 3.82 (s, 3H, OCH_3), 3.87 (s, 0.28H (minor isomer), OCH_3), 9.11 (s, br, 1H, C=NOH) ppm.

Methyl 2-(hydroxyimino)-2-phenylacetate (**36**). According to general procedure 2, to a solution of (*S*)-methyl 2-amino-2-phenylacetate hydrochloride (1.20 g, 5.95 mmol) in H_2O (16.8 mL) was added at 0 °C a sodium hydroxide solution in H_2O (2M, 2.975 mL, 239 mg, 5.95 mmol) and then after 5 min tungstate dihydrate (198 mg, 0.59 mmol) in one portion. After stirring the mixture for 30 min at 0 °C, aqueous hydrogen peroxide (35%, 1.735 g, 17.8 mmol) was added, the mixture was warmed-up to room temperature and then stirred 2 h at this temperature. The reaction mixture was diluted with CH_2Cl_2 and extracted thrice with CH_2Cl_2 (20 mL). The combined organic phases were stirred with sodium thiosulfate solution (1M, 30 mL) for 30 min, causing disappearance of the yellow color. The phases were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The organic residue was purified by flash chromatography on silica (25 g, Biotage Isolera, gradient heptane/EtOAc from 0 – 100% EtOAc, 75mL/min) to give pure oxime ester **36** (560.0 mg, 53%) as a slightly yellow oil. R_t = 0.75 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3H, OCH_3), 7.42–7.50 (m, 5H, Ph) ppm.

Methyl (2-(hydroxyimino)-2-(pyridin-2-yl)acetate[27b] (**37**). To a solution of methyl pyridin-2-ylacetate (4.54 g, 30.0 mmol) in acetic acid (33 mL) at 0 °C was added a solution of sodium nitrite (2.07 g, 30.0 mmol) in water (27 mL). The resulting mixture was warmed to r.t. and stirred for 1 h upon which time water (90 mL) was added and stirring continued for an additional 1 h. The reaction mixture was concentrated under reduced pressure to remove most of the AcOH, then basified to pH 8-9 with saturated aqueous Na_2CO_3 and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with saturated NaCl solution (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (Biotage Isolera, gradient heptane/EtOAc from gradient 0 – 75% EtOAc, 50mL/min) afforded oxime ester **37** (5.001 g, 92%) in different fractions: fraction 1 single stereoisomer as a colorless oil (1.533 g, 28% yield), fraction 2 as a mixture of stereoisomers as a pale yellow gum (1.241 g, 23% yield); fraction 3 single (other) stereoisomer as a white solid (2.227 g, 41% yield); R_t = 0.54/0.65 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): major isomer: δ = 3.99 (s, OCH_3), 7.30 (ddd, *J* = 7.5, 5.0, 1.3 Hz, 1H, pyridine), 7.72 (td, *J* = 7.8, 1.8 Hz, 1H, pyridine), 7.79 (bs, 1H, OH), 7.84 (dt, *J* = 8.0, 1.1 Hz, 1H, pyridine), 8.60–8.62 (m, 1H, pyridine) ppm; minor isomer: δ = 3.95 (s, OCH_3), 7.50 (ddd, *J* = 7.5, 5.0, 1.3 Hz, 1H, pyridine), 7.96 (td, *J* = 7.8, 1.8 Hz, 1H, pyridine), 7.79 (bs, 1H, OH), 8.15 (dt, *J* = 8.4, 1.1 Hz, 1H, pyridine), 8.53–8.55 (m, 1H, pyridine) ppm.

4-Isobutyl-2-isopropyl-5-oxo-2,5-dihydrooxazole 3-oxide (**38**). According to general procedure 3, oxime **28** (600 mg, 3.77 mmol) was dissolved in toluene (10 mL) and cooled down to 5 °C. Then, isobutyraldehyde (**32**) (1.4 mL, 15.34 mmol) was added at once following by the addition of aqueous NaOH solution (0.1M, 1.8 mL). The remaining four portions of NaOH solution (0.1M) were added every 90 min at the same temperature. After

being stirred overnight, the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (1 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 6:1) to give oxazolone **38** as colorless oil (510 mg, 68%). R_f = 0.5 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz, 3H, 2''-H or 3'-H), 0.93 (2 d, *J* = 6.7 Hz, 6H, 2''-H or 3'-H), 1.14 (d, *J* = 7.1 Hz, 3H, 2''-H or 3'-H), 2.15 (qqdd, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 1H, 2'-H), 2.38 (ddd, *J* = 13.8, 7.3, 1.0 Hz, 1H, 1'-H), 2.48 (dd, *J* = 13.8, 7.1 Hz, 1H, 1'-H), 2.57 (qqd, *J* = 7.0, 7.0, 2.4 Hz, 1H, 1''-H), 5.42 (d, *J* = 2.2 Hz, 1H, 2-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 17.2, 22.5, 22.6, 26.0, 30.0, 30.6 (C-1'', C-1', C-2'', C-2', C-3'), 100.7 (C-2), 132.1 (C-4), 165.4 (C-5) ppm.

2-Methyl-5-oxo-4-propyl-2,5-dihydrooxazole 3-oxide (**39**). According to general procedure 3, oxime **34** (10.0 g, 68.9 mmol) was suspended in distilled water (160 mL) and cooled down to 5 °C. Then acetaldehyde (15.4 mL, 0.27 mol) was added at once following by the addition of aqueous NaOH solution (0.1M, 32.9 mL).The remaining four portions of NaOH solution (0.1M) were added every 90 min at the same temperature. After being stirred overnight, the reaction mixture was extracted with Et_2O (3 × 500 mL). The combined organic layers washed with saturated NaCl solution (1 × 500 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give oxazolone **39** as colorless oil (7.35 g, 68%). R_f = 0.52 (petroleum ether/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3H, 3'-H), 1.67 (qdd, *J* = 15.1, 7.4, 7.4 Hz, 2H, 2'-H), 1.76 (d, *J* = 6.1 Hz, 3H, 2-CH_3), 2.54 (dd, *J* = 15.2, 7.5 Hz, 2H, 1'-H), 5.58 (q, *J* = 6.1 Hz, 1H, 2-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 18.3, 19.1, 23.8 (2-CH_3, C-1', C-2', C-3'), 95.1 (C-2), 131.4 (C-4), 164.7 (C-5) ppm.

4-Isopropyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**40**). According to general procedure 3, oxime **35** (4.74 g, 32.65 mmol) was suspended in distilled water (80 mL) and cooled down to 5 °C. Then acetaldehyde (7.4 mL, 0.13 mol) was added at once following by the addition of aqueous NaOH solution (0.1M, 16.3 mL).The remaining four portions of NaOH solution (0.1M) were added every 90 min at the same temperature. After being stirred overnight, the reaction mixture was extracted with Et_2O (3 × 250 mL). The combined organig layers were washed with saturated NaCl solution (1 × 250 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give oxazolone **40** as colorless oil (3.62 g, 71%). R_f = 0.38 (petroleum ether/Et_2O, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 7.1 Hz, 6H, 2'-H), 1.73 (d, *J* = 6.1 Hz, 3H, 2-CH_3), 3.17 (qq, *J* = 7.1, 7.1 Hz, 1H, 1'-H), 5.52 (q, *J* = 6.1 Hz, 1H, 2-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3, 19.0 (2-CH_3, C-2'), 23.6 (C-1'), 94.5 (C-2), 134.7 (C-4), 163.7 (C-5) ppm.

2-Methyl-5-oxo-4-phenyl-2,5-dihydrooxazole 3-oxide (**41**). a) From oxime **36**: According to general prodedure 3, a solution of oxime **36** (450 mg, 2.51 mmol) in toluene (6.1 mL) was cooled down to 5 °C before the addition of acetaldehyde (443 mg, 10.0 mmol) under nitrogen atmosphere. The resulting mixture was treated with a freshly prepared NaOH solution (0.1M, 1.2 mL, 0.12 mmol). The same amount of the NaOH solution (0.1M) was added every 90 min after the reaction was started at 5 °C (5 portions altogether) and the resulting suspension was stirred at the same temperature overnight. Thereafter, the reaction mixture was transferred to a separation funnel and extracted thrice with Et_2O. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. The yellow crude product (500 mg, >100%) was purified by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 0 – 20% EtOAc; 25mL/min) to give pure nitrone **41** (180.0 mg, 38%) as an oil.

b) From keto acid: According to general procedure 4, phenylglyoxylic acid (441 mg, 2.94 mmol) was dissolved in dry CH_2Cl_2 (5 mL) before acetaldehyde oxime[26] **31** (260.3 mg, 4.41 mmol) in CH_2Cl_2 (5 mL) was added and the mixture stirred for 3 d at r.t. After evaporation of the solvent, the crude product was directly purified by flash chromatography on Chromabond Diol (15 g, Biotage Isolera, gradient heptane/EtOAc 20mL/min, 0 – 30% EtOAc) to give pure nitrone **41** (140.0 mg, 24%) as an oil; R_t = 1.16 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.87 (d, *J* = 6.0 Hz, 3H, 2-CH_3), 5.69 (q, *J* = 6.0 Hz, 1H, 2-H), 7.50-7.55 (m, 3H, Ph), 8.64-8.65 (m, 2H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (2-CH_3), 94.3 (C-2), 124.3 (Ph), 126.9 (Ph), 128.6 (Ph), 132.0 (C-4), 163.7 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{10}H_9NO_3$ $[M + H]^+$ 192.0661, found 192.0663.

2-Methyl-5-oxo-4-(pyridin-2-yl)-2,5-dihydrooxazole 3-oxide (**42**). The crude product from the reaction was directly used for the preparation of **54**.

2-Methyl-4-neopentyl-5-oxo-2,5-dihydrooxazole 3-oxide (**43**). Under a nitrogen atmosphere 4,4-dimethyl-2-oxopentanoic acid[28] (3.00 g, 20.8 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and stirred at room temperature. Then acetaldehyde oxime (**31**) (1.844 g, 31.2 mmol), dissolved in dry CH_2Cl_2 (10 mL) was added dropwise. The reaction was stirred overnight and after concentration in vacuo, purified by flash chromatography on a diol phase (Chromabond 40, Biotage Isolera, gradient heptane/EtOAc, 25mL/min, from 3 – 30% EtOAc) to give nitrone **43** (2.80 g, 65%, 90% pure) as an oil; R_t = 1.32 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.01 (s, 9H, 3'-H), 1.78 (d, *J* = 6.0 Hz, 2-CH_3), 2.47, 2.54 (2 d, *J* = 13.2 Hz, 2H, 1'-H), 5.61 (q, *J* = 6.0 Hz, 2-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.4 (2-CH_3), 30.0 (C-3'), 35.4 (C-1'), 48.0 (C-2'), 95.2 (C-2), 159.4 (C-4), 165.4 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_9H_{15}NO_3$ $[M + H]^+$ 186.1130, found 186.1131.

rel-(*S*)-2-((*R*)-1-Hydroxypropyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydro-oxazole 3-oxide (**44b**). According to general procedure 5, nitrone **29** (0.59 g, 3.45 mmol) was dissolved in THF (12 mL) and cooled to –78 °C. To the resulting suspension a solution of LiHMDS in THF (1M, 3.6 mL, 3.6 mmol) was added dropwise. After 1 h of stirring, propionaldehyde (0.37 mL, 5.16 mmol) was added and stirring was continued for 0.5 h at –78 °C before saturated NH_4Cl solution (20 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After careful purification by flash chromatography (petroleum ether/EtOAc, 4:1) only the lower diastereoisomer **44b** was isolated in a pure form as colorless oil (0.24 g, 30%). R_f = 0.38 (lower diastereomer) (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95, 0.96 (2 d, *J* = 6.7 Hz, 3H each, 3'-H), 1.06 (t, *J* = 7.4 Hz, 3H, 3''-H), 1.49 (qd, *J* = 10.5, 7.4 Hz, 1H, 2''-H), 1.71 (s, 3H, 2-CH_3), 1.72 (qdd, *J* = 10.2, 7.4, 2.6 Hz, 1H, 2''-H), 2.04 (br s, 1H, OH), 2.18 (qqdd, *J* = 6.8, 6.8, 6.7, 6.7 Hz, 1H, 2'-H), 2.41, 2.48 (2 dd, *J* = 13.9, 7.4 Hz, 2H, 1'-H), 3.89 (dd, *J* = 10.5, 2.6 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.2 (C-3''), 20.7, 22.4, 22.5, 23.6, 26.2, 30.8 (2-CH_3, C-1', C-2', C-2'', C-3'), 73.6 (C-1''), 105.6 (C-2), 131.7 (C-4), 165.0 (C-5) ppm.

2-(Cyclopropyl(hydroxy)methyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**45a/b**). A solution of cyclic nitrone **29** (400 mg, 2.33 mmol) in THF (5.6 mL) was cooled down to –78 °C and treated with a LiHMDS solution (1M, 2.45 mL, 2.45 mmol, 411 mg) in THF in a dropwise fashion under nitrogen atmosphere. The resulting yellow suspension was left to stir for 1 h at –78 °C before cyclopropylcarbaldehyde (180 mg, 2.57 mmol) was added and stirring continued for 1 h at –78 °C. Thereafter, additional cyclopropylcarbaldehyde was added (180 mg, 2.57 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution (17 mL), brought to ambient temperature and extracted thrice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. After

purification by flash chromatography on a diol phase (Chromabond, Biotage Isolera, gradient heptane/EtOAc, 20ml/min, 3 – 30%EtOAc) pure nitrone **45** (560 mg, 94%) was isolated as an oil (mixture of diastereoisomers 56:44 = *low/high*); R_t = 1.17 (*low*), 1.20 (*high*) (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers): δ = 0.39–0.80 (m, 4H, cyclopropyl), 0.94–0.96 (m, 6H, 3'-H), 1.05–1.18 (m, 1H, cyclopropyl), 1.80, 1.84 (s, 3H, 2-CH_3), 2.19 (sept, *J* = 6.8 Hz, 1H, 2'-H), 2.39–2.52 (m, 2H, 1'-H), 3.24 (d, *J* = 8.3 Hz, "1H", 1"-H), 3.29 (d, *J* = 9.2 Hz, "1H", 1"-H) ppm.

Preparation of homoallylaldehyde (but-3-enal)

a) Preparation of octa-1,7-diene-4,5-diol.[29] To a solution of allyl bromide (1.25 g, 10.3 mmol), potassium iodide (2.86 g, 17.2 mmol) and tin(II)dichloride dihydrate (2.33 g, 10.3 mmol) in water (12.5 mL), a solution of glyoxal in water (40%, 500 mg, 3.44 mmol) was added, followed by stirring of the mixture for 2 h at 40 °C and 15 h at r.t. The reaction mixture was quenched with aqueous HCl (1M, 5 mL) and extracted with EtOAc. The organic phase was then washed with aqueous sodium bisulfite ($NaHSO_3$) solution to achieve decoloration. The water phase again was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give the title diol (375 mg, 76%). The analytical data were in accordance with literature data.

b) Preparation of homoallylaldehyde (but-3-enal). A solution of octa-1,7-diene-4,5-diol (316 mg, 2.2 mmol) in CH_2Cl_2/H_2O (1:1, 5.0 mL) was treated with $NaIO_4$ (468 mg, 2.2 mmol) at 0 °C. After stirring of the mixture for 2.5 h at 0 °C, the organic phase was separated, dried over Na_2SO_4, filtered, and the filter cake washed with CH_2Cl_2. This solution was directly used without further purification for the next step.

rel-(*S*)-2-((*S*)-1-Hydroxybut-3-en-1-yl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**46a**) and rel-(*S*)-2-((*R*)-1-hydroxybut-3-en-1-yl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**46b**). According to general procedure 5, a solution of cyclic nitrone **29** (500 mg, 2.92 mmol) in THF (3 mL) was cooled down to –78 °C and treated with a LiHMDS solution (1M in THF, 3.06 mL, 513 mg, 3.06 mmol) in a dropwise fashion under N_2 atmosphere. The resulting yellow suspension was left to stir for 1 h at –78 °C. Then homoallylaldehyde (but-3-enal, 308 mg, 4.40 mmol) in CH_2Cl_2 (about 10 mL) was added and stirring was continued for 4 h at –78 °C. Thereafter, the reaction mixture was quenched with saturated NH_4Cl solution, brought to ambient temperature and extracted thrice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give 660 mg (94%) of a mixture of nitrones **46**. The crude product was purified by flash chromatography on preparative HPLC (Luna C18; neutral, MeCN/H_2O) to give pure **46a** (100.0 mg, 14%) and pure **46b** (100.0 mg, 14%) as colorless oils.

Upper diastereomer **46a**: R_t = 1.19 (HPLC); R_f = 0.52 (Petrolether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.80 (s, 3H, 2-CH_3), 2.13–2.24 (m, 1H, 2'-H), 2.27–2.50 (m, 4H, 2"-H, 1'-H), 3.08 (bs, 1H, OH), 3.84 (dd, *J* = 8.8, 4.1 Hz, 1H, 1"-H), 5.14–5.21 (m, 2H, 4"-H), 5.83 (ddt, *J* =17.1, 10.2, 6.9, 6.9 Hz, 1H, 3"-H) ppm.

Lower diastereomer **46b**: R_t = 1.14 (HPLC); R_f = 0.42 (Petrolether/EtOAc, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.97 (2 d, *J* = 6.7 Hz, 3'-H), 1.73 (s, 3H, 2-CH_3), 2.14–2.54 (m, 5H, 2"-H, 1'-H, 2'-H), 4.04–4.09 (m, 1H, 1"-H), 5.20–5.24 (m, 2H, 4"-H), 5.77–5.88 (m, 1H, 3'-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 22.4, 22.5 (2-CH_3, C-3'), 26.2 (C-2'), 30.0 (C-1'), 35.3 (C-2"), 70.7 (C-1"), 105.2 (C-2), 120.0 (C-4"), 131.6 (C-4), 132.5 (C-3"), 165.0 (C-5) ppm.

2-(2-Hydroxypropan-2-yl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**47**). According to general procedure 5, to a solution of nitrone **29** (500.0 mg, 2.92 mmol) in dry THF (10 mL) was added LiHMDS solution (1M in THF, 2.78 mL, 464.3 mg, 2.78 mmol) at –78 °C under nitrogen atmosphere. After stirring of the mixture for 1 h at –78 °C, acetone (204 mg, 260 μL, 3.50 mmol) was added and the mixture was left overnight at –78 °C. The reaction was quenched at this temperature with saturated NH_4Cl solution (20 mL), and after warm-up to r.t., additional NH_4Cl solution (19 mL) was added. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, the filter cake washed with EtOAc, and evaporated in vacuo to give nitrone **47** (330 mg, 37%, purity 75%) as an oil, which was purified by flash chromatography on a Chromabond diol phase (Biotage Isolera, gradient heptane/EtOAc from 3% – 30% EtOAc) to give **47** (38%, 90% pure) as a colorless oil; R_t = 1.14 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96, 0.98 (2 d, *J* = 6.8 Hz, 6H, 3'-H), 1.16 (s, 3H, 2"-H), 1.35 (s, 3H, 2"-H), 1.59 (bs, 1H, OH), 1.84 (s, 3H, 2-CH_3), 2.13–2.25 (m, 1H, 2'-H), 2.41–2.51 (m, 2H, 1'-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.6 (2-CH_3), 22.5, 22.8 (C-2"), 23.5, 23.9 (C-3'), 26.1 (C-2'), 30.8 (C-1'), 73.6 (C-1"), 106.1 (C-2), 132.2 (C-4), 164.4 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{11}H_{19}NO_4$ $[M + H]^+$ 230.1392, found 230.1393.

rel-(*S*)-2-((*S*)-(4-Chlorophenyl)(hydroxy)methyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**48a**) and rel-(*S*)-2-((*R*)-(4-chlorophenyl)(hydroxy)methyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**48b**). According to general procedure 5, a solution of cyclic nitrone **29** (400 mg, 2.33 mmol) in THF (3 mL) was cooled down to –78 °C and treated with a LiHMDS solution (1M in THF, 411.0 mg, 2.45 mL, 2.45 mmol) in a dropwise fashion under N_2 atmosphere. The resulting yellow suspension was left to stir for 1 h at –78 °C. Then 4-chlorobenzaldehyde (361 mg, 2.57 mmol) was added and stirring was continued for 2 h at –78 °C. Thereafter, the reaction mixture was quenched with saturated NH_4Cl solution, brought to ambient temperature and extracted thrice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification by flash chromatography on a Chromabond diol phase (Biotage Isolera, gradient heptane/EtOAc, 20mL/min, 3-30% EtOAc) of pure nitrone **48** (560 mg, 73%) as a mixture of 25% *low* and 75% *high*) was obtained; R_t = 1.48 high, 1.43 low (HPLC).

Upper diastereomer **48a**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.86, 0.92 (2d, *J* = 6.7 Hz, 6H, 3'-H), 1.62 (s, 3H, 2-CH_3), 2.34–2.47 (m, 2H, 1'-H), 2.94 (bd, 1H, *J* = 6.5 Hz, OH), 5.01 (bd, *J* = 6.5 Hz, 1H, 2"-H), 7.26–7.39 (m, 4H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.32, 22.31 (C-3'), 22.40 (2-CH_3), 26.36 (C-2'), 31.0 (C-1'), 74.4 (C-1"), 106.41 (C-2), 128.50, 129.24 (Ar CH), 134.59, 135.75 (Ar C), 164.41, 165.31 (C-4, C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{15}H_{18}ClNO_4$ $[M + H]^+$ 312.1003, found 312.1003.

Lower diastereomer **48b**, minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.71, 0.83 (2d, 6H, *J* = 6.7 Hz, 3'-H), 1.58 (s, 3H, 2-CH_3) 1.91–1.96 (m, 1H, 2'-H), 2.22–2.32 (m, 2H, 1'-H), 3.45 (bd, *J* = 3.2 Hz, 1H, OH), 4.96 (bd, *J* = 3.2 Hz, 1H, 1"-H), 7.30–7.38 (m, 4H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.34, 22.33, 22.46 (2-CH_3), 26.31 (C-2'), 36.58 (C-1'), 76.17 (C-1"), 106.18 (C-2), 128.42, 129.23, 134.65, 135.72, 164.21, 165.27 ppm.

2-(1-Hydroxyethyl)-4-isobutyl-2-isopropyl-5-oxo-2,5-dihydrooxazole 3-oxide (**49**). To a cooled (–78 °C) solution of nitrone **38** (415 mg, 2.08 mmol) in THF (7 mL), Schwesinger base **30** (0.7 mL, 2.29 mmol) was added. Thereafter, acetaldehyde (0.18 mL, 3.2 mmol) was added and the resulting reaction mixture was left to stir at this temperature overnight. Then saturated NH_4Cl solution (50 mL) was added, and when the resulting two-layer mixture had reached r.t., the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) gave aldol product **49** (314 mg, 62%) as a single diastereomer. R_f = 0.11 (petroleum

ether/EtOAc, 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3H, 2'-H or 2'''-H or 3''-H), 0.96, 0.97 (2 d, *J* = 6.6 Hz, 3H each, 2'-H or 2'''-H or 3''-H), 1.08 (d, *J* = 7.0 Hz, 3H, 2'-H or 2'''-H or 3''-H), 1.42 (d, *J* = 6.7 Hz, 3H, 2'-H or 2'''-H or 3''-H), 2.04 (br s, 1H, OH), 2.18 (qq, *J* = 6.9, 6.9 Hz, 1H, 1'-H), 2.44 (d, *J* = 7.3 Hz, 2H, 1''-H), 2.63 (qqdd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 1H, 2''-H), 4.29 (q, *J* = 6.7 Hz, 1H, 1'''-H) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-2-methyl-5-oxo-4-propyl-2,5-dihydro-oxazole 3-oxide (**50a**) and rel-(*S*)-2-((*R*)-1-hydroxyethyl)-2-methyl-5-oxo-4-propyl-2,5-dihydrooxazole 3-oxide (**50b**). According to general procedure 5, the nitrone **39** (2.0 g, 12.7 mmol) was dissolved in THF (40 mL) and cooled to –78 °C. To the resulting suspension a solution of LiHMDS in THF (1M, 13.4 mL, 13.4 mmol) was added dropwise. After 1 h of stirring, acetaldehyde (1.1 mL, 19.6 mmol) was added and stirring was continued for 0.5 h at –78 °C. Then saturated NH_4Cl solution (70 mL) was added, and when the resulting two-layer mixture had reached r.t., the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/Et_2O, 2:1) both diastereoisomers **50** were isolated in 1.2:1 ratio (the upper and the lower one respectively) as white crystals (1.25 g, 49%).

Upper diastereomer **50a**: R_f = 0.31 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3H, 3'-H), 1.27 (d, *J* = 6.4 Hz, 3H, 2''-H), 1.67 (qdd, *J* = 15.0, 7.4, 7.4 Hz, 2H, 2'-H), 1.77 (s, 3H, 2-CH_3), 2.54 (dd, *J* = 15.2, 7.4 Hz, 2H, 1'-H), 3.02 (br s, 1H, OH), 3.94 (q, *J* = 6.4 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 18.3, 23.8 (2-CH_3, C-2'', C-3'), 16.5, 18.3 (C-1', C-2'), 71.5 (C-1''), 104.5 (C-2), 131.7 (C-4), 164.1 (C-5) ppm.

Lower diastereomer **50b**: R_f = 0.22 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3H, 3'-H), 1.33 (d, *J* = 6.6 Hz, 3H, 2''-H), 1.68 (qdd, *J* = 14.9, 7.5, 7.5 Hz, 2H, 2'-H), 1.71 (s, 3H, 2-CH_3), 2.16 (br s, 1H, OH), 2.51 (dd, *J* = 14.2, 7.5 Hz, 1H, 1'-H), 2.58 (dd, *J* = 14.2, 7.6 Hz, 1H, 1'-H), 4.15 (qd, *J* = 6.7, 6.6 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 18.3, 23.8 (2-CH_3, C-2'', C-3'), 16.9, 20.5 (C-1', C-2'), 68.6 (C-1''), 105.5 (C-2), 132.2 (C-4), 164.7 (C-5) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-4-isopropyl-2-methyl-5-oxo-2,5-dihydro-oxazole 3-oxide (**51a**) and rel-(*S*)-2-((*R*)-1-hydroxyethyl)-4-isopropyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**51b**). According to general procedure 5, the nitrone **40** (0.5 g, 3.2 mmol) was dissolved in THF (10 mL) and cooled to –78 °C. To the resulting suspension a solution of LiHMDS in THF (1M, 3.4 mL, 3.4 mmol) was added dropwise. After 1 h of stirring, acetaldehyde (0.27 mL, 4.81 mmol) was added and stirring was continued for 0.5 h at –78 °C. Then saturated NH_4Cl solution (20 mL) was added, and when the resulting two-layer mixture had reached r.t., the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/EtOAc, 5:2) both diastereoisomers **51** were isolated in 2:1 ratio (the upper and the lower one respectively) as white crystals (0.48 g, 75%).

Upper diastereomer **51a**: R_f = 0.42 (petroleum ether/Et_2O, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.4 Hz, 3H, 2''-H), 1.29, 1.30 (2 d, *J* = 7.1 Hz, 6H, 2'-H), 1.76 (s, 3H, 2-CH_3), 3.07 (br s, 1H, OH), 3.17 (qq, 7.1 Hz, 1H, 1'-H), 3.93 (q, *J* = 6.4 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 17.2, 17.3, 18.3, 23.7 (2-CH_3, C-1', C-2', C-2''), 71.5 (C-1''), 103.7 (C-2), 135.0 (C-4), 163.2 (C-5) ppm.

Lower diastereomer **51b**: R_f = 0.33 (petroleum ether/Et_2O, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28, 1.30 (2 d, *J* = 7.1 Hz, 6H, 2'-H), 1.31 (d, *J* = 6.6 Hz, 3H, 2''-H), 1.70 (s, 3H, 2-CH_3), 2.07 (br s, 1H, OH), 3.18 (qq, 7.1 Hz, 1H, 1'-H), 4.13 (q, *J* = 6.6 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 17.3, 17.5, 20.4, 23.7 (2-CH_3, C-1', 2 × C-2', C-2''), 68.8 (C-1''), 104.6 (C-2), 135.6 (C-4), 163.7 (C-5) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxypropyl)-2-methyl-4-neopentyl-5-oxo-2,5-dihydrooxazole 3-oxide (**52a**) and rel-(*S*)-2-((*R*)-1-hydroxypropyl)-2-methyl-4-neopentyl-5-oxo-2,5-dihydrooxazole 3-oxide (**52b**). According to general procedure 5, a solution of cyclic nitrone **43** (1.00 g, 5.39 mmol) in THF (12 mL) was cooled down to –78 °C and treated with a LiHMDS solution (1M in THF, 5.67 mL, 5.66 mmol, 949.0 mg) in a dropwise fashion under nitrogen atmosphere. The resulting yellow suspension was left to stir for 1 h at –78 °C. Then, propionaldehyde (345 mg, 5.93 mmol) was added and stirring was continued for 1 h at –78 °C. Thereafter, the reaction mixture was quenched with saturated NH_4Cl solution (44 mL), brought to ambient temperature and extracted thrice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give nitrone **52** (770 mg, 59%). The crude product was purified by flash chromatography on Chromabond Diol (40 g, Biotage Isolera, gradient heptane/EtOAc, 25mL/min from 0 – 30% EtOAc) to obtain the two diastereoisomers, **52a** (210.0 mg, 16%) as an oil and **52b** (210.0 mg, 16%) as a white solid.

Upper diastereomer **52a**: R_t = 1.24 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 9H, 3'-H), 1.05 (t, *J* = 7.5 Hz, 3H, 3''-H), 1.60–1.68 (m, 2H, 2''-H), 1.78 (s, 3H, 2-CH_3), 2.49 (br s, 2H, 1'-H), 3.21 (bd, *J* = 2.8 Hz, 1H, OH), 3.63 (dt, *J* = 10.4, 2.8 Hz, 1''-H) ppm.

Lower diastereomer **52b**: R_t = 1.18 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 9H, 3'-H), 1.08 (t, *J* = 7.5 Hz, 3H, 3''-H), 1.46–1.52, 1.69–1.78 (2 m, 2H, 2''-H), 1.73 (s, 3H, 2-CH_3), 1.88 (bd, 1H, OH), 2.45, 2.53 (2 d, *J* = 13.2 Hz, 1'-H), 3.91 (m, 1H, 1''-H) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-2-methyl-5-oxo-4-phenyl-2,5-dihydrooxazole 3-oxide (**53a**) and rel-(*S*)-2-((*R*)-1-hydroxyethyl)-2-methyl-5-oxo-4-phenyl-2,5-dihydrooxazole 3-oxide (**53b**). In analogy to general procedure 5, cyclic nitrone **41** (200 mg, 1.11 mmol) was dissolved in acetonitrile (1.1 mL) and cooled down to 0 °C. Then acetaldehyde (295 mg, 6.69 mmol) and K_2CO_3 (154 mg, 1.11 mmol) were added and the reaction mixture was left at ambient temperature for 44 h. The reaction mixture was diluted with H_2O (5 mL) and extracted thrice with DCM (7 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 380 mg of a yellow oil, which was purified by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 0% – 20% EtOAc, 25 mL/min). The two diastereomers **53a** (28.0 mg, 11%) and **53b** (110.0 mg, 42%) could be isolated as colorless oils.

Upper diastereomer **53a**: R_t = 1.07 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.4 Hz, 3H, 2'-H), 1.88 (s, 3H, 2-CH_3), 3.12 (d, *J* = 4.3 Hz, 1H, OH), 4.07 (dd, *J* = 6.4, 4.2 Hz, 1H, 1'-H), 7.48–7.57, 8.62–8.67 (2 m, 5 H, Ph) ppm.

Lower diastereomer **53b**: R_t = 1.03 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.5 Hz, 3H, 2'-H), 1.82 (s, 3H, 2-CH_3), 2.10 (d, *J* = 8.0 Hz, 1H, OH), 4.23–4.30 (m, 1H, 1'-H), 7.45–7.55, 8.54–8.76 (2 m, 5H, Ph) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-2-methyl-5-oxo-4-(pyridin-2-yl)-2,5-dihydrooxazole 3-oxide (**54a**) and rel-(*S*)-2-((*R*)-1-hydroxyethyl)-2-methyl-5-oxo-4-(pyridin-2-yl)-2,5-dihydrooxazole 3-oxide (**54b**). In analogy to general procedure 5, cyclic nitrone **42** (540.5 mg, 3.0 mmol) was dissolved

in acetonitrile (30 mL) and cooled down to 0 °C. Then acetaldehyde (793.0 mg, 18.0 mmol) and K_2CO_3 (414.6 mg, 3.00 mmol) were added and the reaction mixture was left at ambient temperature for 4 h. The reaction mixture was diluted with EtOAc (100 mL), filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (Biotage Isolera, gradient heptane/EtOAc from 0% – 75% EtOAc) afforded the two diastereomers of the desired product, nitrone **54a** as a pale yellow solid [167 mg, 24% yield, dr = 95:5 (*high/low*)] and nitrone **54b** (146 mg, 21%) as a white solid [dr = 93:7 (*low/high*)].

Upper diastereomer **54a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.5 Hz, 3H, 2'-H), 1.89 (s, 3H, 2-CH_3), 3.04 (bs, 1H, OH), 4.12 (q, *J* = 6.5 Hz, 1H, 1'-H), 7.41 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H, pyridyl), 7.86 (ddd, *J* = 7.8, 7.8, 1.9 Hz, 1H, pyridyl), 8.45 (ddd, *J* = 7.9, 0.9, 0.9 Hz, 1H, pyridyl), 8.86 (ddd, *J* = 4.8, 1.8, 0.8 Hz, 1H, pyridyl) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.5, 18.7 (2-CH_3, C-2'), 71.5 (C-1'), 104.6 (C-2), 120.3, 127.9, 136.9 (pyridyl), 143.8 (C-4), 150.2 (pyridyl), 152.1 (C-4), 161.9 (C-5) ppm.

Lower diastereomer **54b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.6 Hz, 3H, 2'-H), 1.79 (s, 3H, 2-CH_3), 2.50–3.50 (bs, 1H, OH), 4.34 (q, 1H, *J* = 6.7 Hz, 1'-H), 7.35 (dd, *J* = 7.6, 4.8 Hz, 1H, pyridyl), 7.77–7.80 (m, 1H, pyridyl), 8.33–8.35 (m, 1H, pyridyl), 8.77–8.79 (m, 1H, pyridyl) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = low: 17.0, 20.3 (2-CH_3, C-2'), 68.9 (C-1'), 106.0 (C-2), 123.9, 125.2, 136.8 (pyridyl) 143.8 (C-4), 145.0 (pyridyl), 162.7 (C-5), ppm; HRMS (ESI-TOF): calcd. for $C_{11}H_{12}N_2O_4$ $[M + H]^+$ 237.0875, found 237.0876.

rel-(*S*)-2-((*R*)-1-Hydroxypropyl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**55b**). According to general procedure 1, nitrone **44** (220 mg, 0.96 mmol) was dissolved in THF (2.5 mL) and the resulting solution was treated with activated zinc powder (315 mg, 4.82 mmol). After the addition of saturated NH_4Cl solution (2.5 mL), the grey suspension was stirred vigorously for 40 min at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed with Et_2O (10 mL). The filtrate was treated with water (15 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to provide oxazol-5(2*H*)-one **55b** (150 mg, 73%) as colorless oil. Lower diastereomer **55b**: R_f = 0.42 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.03 (t, *J* = 7.4 Hz, 3H, 3''-H), 1.46 (qd, *J* = 10.3, 7.2 Hz, 1H, 2''-H), 1.55 (s, 3H, 2-CH_3), 1.78 (qdd, *J* = 10.0, 7.6, 2.5 Hz, 1H, 2''-H), 2.07 (br s, 1H, OH), 2.18 (qqdd, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 1H, 2'-H), 2.47 (dd, *J* = 14.8, 6.9 Hz, 2H, 1'-H), 3.51 (dd, *J* = 10.3, 2.5 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6 (C-3''), 20.3, 22.4, 24.4, 26.2, 36.6 (2-CH_3, C-1', C-2', C-2'', C-3'), 107.7 (C-2), 163.4, 165.5 (C-4, C-5) ppm; The signal for C-1'' is obscured.

2-(Cyclopropyl(hydroxy)methyl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**56**). According to general procedure 1, nitrone **45** (560 mg, 2.32 mmol) was dissolved in THF (17.8 mL) and the resulting solution was treated with activated zinc powder (910.6 mg, 13.9 mmol). After the addition of NH_4Cl (745 mg, 13.9 mmol) in H_2O (8.9 mL), the grey suspension was stirred vigorously for 1 h at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed three times with EtOAc. The combined organic filtrates were washed with water, the layers were separated, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give oxazolone **56** (240 mg, 44%) as colorless oil (isomeric mixture = 58:42) after purification on a diol phase (Chromabond, Biotage Isolera, gradient heptane/EtOAc, 20mL/min, 3 – 30%EtOAc); R_t = 1.24, 1.25 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.36–0.47 (m, 2H, cyclopropyl), 0.55–0.75 (m, 2H, cyclopropyl), 0.98–1.01 (m, 6H, 3'-H), 1.02–1.12 (m, 1H, cyclopropyl), 1.66, 1.67 (2 s, 3H, 2-CH_3), 2.16–2.25 (m, 1H, 2'-H), 2.46–2.52 (m, 2H, 1'-H), 3.08–3.13 (m, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = (ca 58:42 ratio) 2.1, 2.4, 4.3, 4.5 (cyclopropyl CH_2), 12.9, 13.0, 21.3, 21.6, 22.4, 22.4, 22.48, 22.50, 26.3 (2-CH_3, 3'-H, 2'-H, cyclopropyl CH), 36.6, 36.7 (C-1'), 78.3, 78.8 (C-1''), 107.4, 107.5 (C-2), 163.4, 164.0 (C-4), 165.5, 165.9 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{12}H_{19}NO_3$ $[M + H]^+$ 226.1443, found 226.1445.

rel-(*S*)-2-((*S*)-1-Hydroxybut-3-en-1-yl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**57a**). According to general procedure 1, nitrone **46a** (75.0 mg, 0.31 mmol) was dissolved in THF (3 mL) and the resulting solution was treated with activated zinc powder (102 mg, 1.55 mmol). After the addition of NH_4Cl (83 mg, 1.55 mmol) in H_2O (1.5 mL), the grey suspension was stirred vigorously for 1 h at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed three times with Et_2O. The combined filtrates were washed with water, the layers were separated, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give to give oxazolone **57a** (70 mg, 95%) as colorless oil; R_t = 1.31 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.60 (s, 3H, 2-CH_3), 1.90 (bd, *J* = 4.9 Hz, OH), 2.23–2.30 (m, 2H, 2''-H), 2.42–2.57 (m, 3H, 1'-H, 2'-H), 3.71–3.77 (m, 1H, 1''-H), 5.13–5.20 (m, 2H, 4''-H), 5.79–5.89 (m, 1H, 3''-H) ppm.

rel-(*S*)-2-((*R*)-1-Hydroxybut-3-en-1-yl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**57b**). According to general procedure 1, nitrone **46b** (90 mg, 0.37 mmol) was dissolved in THF (3.5 mL) and the resulting solution was treated with activated zinc powder (122 mg, 1.86 mmol). After the addition of NH_4Cl (100 mg, 1.86 mmol) in H_2O (1.75 mL), the grey suspension was stirred vigorously for 1 h at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed three times with Et_2O. The combined filtrates were washed with water, the layers were separated, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give to give oxazolone **57b** (60.0 mg, 68%) as colorless oil; R_t = 1.26 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.59 (s, 3H, 2-CH_3), 1.81 (bd, *J* = 4.9 Hz, 1H, OH), 2.24–2.28 (m, 2H, 2''-H), 2.48 (dd, *J* = 7.3, 3.0 Hz, 1H), 2.51–2.57 (m, 3H, 1'-H, 2'-H), 3.72 (dd, *J* = 10.0, 3.0 Hz, 1H, 1''-H), 5.13–5.21 (m, 2H, 4''-H), 5.79–5.89 (m, 1H, 3''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.5, 22.4 (2-CH_3, C-3'), 26.2 (C-2'), 36.1, 36.6 (C-2'', C-1'), 73.6 (C-1''), 106.9 (C-2), 118.8 (C-4''), 133.7 (C-3''), 163.6 (C-4), 165.5 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{12}H_{19}NO_3$ $[M + H]^+$ 226.1443, found 226.1443.

2-(2-Hydroxypropan-2-yl)-4-isobutyl-2-methyloxazol-5(2*H*)-one (**58**). According to general procedure 1, a solution of nitrone **47** (100 mg, 0.43 mmol) in THF (12 mL) was treated with activated zinc powder (171 mg, 2.61 mmol). After the addition of NH_4Cl solution (140 mg, 2.61 mmol, in 6 mL water), the grey suspension was stirred vigorously for 60 min at r.t. Then the reaction mixture was diluted with EtOAc, filtered through a pad of celite, which was rinsed with EtOAc several times. The collected organic phases were extracted with water, dried over Na_2SO_4, filtered, the filter cake washed with EtOAc, and concentrated in vacuo to give oxazolone **58** (60.0 mg, 61%, 95% purity) as a colorless oil; R_t = 1.17 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.00 ("t", *J* = 6.7 Hz, 6H, 3'-H), 1.29 (s, 3H, 2''-H), 1.33 (s, 3H, 2''-H), 1.61 (s, 3H, 2-CH_3), 2.06 (bs, 1H, OH), 2.16–2.22 (m, 1H, 2'-H), 2.49 (d, *J* = 7.2 Hz, 2H, 1'-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.8 (2-CH_3), 22.4, 22.5, (C-2''), 24.7, 25.0, (C-3'), 26.3 (C-2'), 36.6 (C-1'), 73.8 (C-1''), 109.3 (C-2), 163.4 (C-4), 165.7 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{11}H_{19}NO_3$ $[M + H]^+$ 214.1443, found 214.1443.

rel-(*S*)-2-((*R*)-1-Hydroxyethyl)-4-isobutyl-2-isopropyloxazol-5(2*H*)-one (**59b**). According to general procedure 1, nitrone **49b** (165 mg, 0.68 mmol) was dissolved in THF (1.5 mL) and the resulting solution was treated with activated zinc powder (222 mg, 3.4 mmol). After the addition of saturated NH_4Cl solution (1.5 mL), the grey suspension was stirred vigorously for 40 min at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed with Et_2O (10 mL). The filtrate was treated with water (10 mL), the layers were separated and the aqueous layer was extracted with

Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give oxazol-5(2*H*)-one **59** (118 mg, 77%) as colorless oil. R_f = 0.15 (petroleum ether/EtOAc, 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, 3H, 2'-H or 2'''-H or 3''-H), 0.95 (d, *J* = 6.9 Hz, 3H, 2'-H or 2'''-H or 3''-H), 1.00 (d, *J* = 6.7 Hz, 6H, 2'-H or 2'''-H or 3''-H), 1.23 (d, *J* = 6.5 Hz, 3H, 2'-H or 2'''-H or 3''-H), 1.78 (br s, 1H, OH), 2.19 (qq, *J* = 6.8, 6.8 Hz, 1H, 1'-H), 2.50 (dd, *J* = 14.9, 6.9 Hz, 2H, 1''-H), 2.52 (qqdd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 1H, 2''-H), 4.29 (q, *J* = 6.5 Hz, 1H, 1'''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 17.4, 22.4, 22.5, 26.4, 31.1, 36.6 (C-1', C-1'', C-2', C-2'', C-2''', C-3''), 67.8 (C-1'''), 110.8 (C-2), 164.4, 165.8 (C-4, C-5) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-2-methyl-4-propyloxazol-5(2*H*)-one (**60a**) and rel-(*S*)-2-((*R*)-1-hydroxyethyl)-2-methyl-4-propyloxazol-5(2*H*)-one (**60b**). According to general procedure 1, nitrone **50** (0.5 g, 2.5 mmol) was dissolved in THF (6 mL) and the resulting solution was treated with activated zinc powder (0.81 g, 12.4 mmol). After the addition of saturated NH_4Cl solution (6 mL), the grey suspension was stirred vigorously for 40 min at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed with Et_2O (20 mL). The filtrate was treated with water (30 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give oxazol-5(2*H*)-one **60** (0.30 g, 65%) as colorless oil.

Upper diastereomer **60a**: R_f = 0.32 (petroleum ether/Et_2O, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3H, 3'-H), 1.26 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.57 (s, 3H, 2-CH_3), 1.74 (qdd, *J* = 14.9, 7.4, 7.4 Hz. 2H, 2'-H), 2.17 (br s, 1H, OH), 2.57 (dd, *J* = 14.9, 7.4 Hz, 2H, 1'-H), 3.88 (q, *J* = 6.4 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 17.4, 19.1, 20.6, 29.8 (2-CH_3, C-1', C-2', C-2'', C-3'), 71.2 (C-1''), 107.4 (C-2), 164.3, 165.3 (C-4, C-5) ppm.

Lower diastereomer **60b**: R_f = 0.25 (petroleum ether/Et_2O, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3H, 3'-H), 1.30 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.54 (s, 3H, 2-CH_3), 1.74 (qdd, *J* = 14.9, 7.4, 7.4 Hz. 2H, 2'-H), 2.40 (br s, 1H, OH), 2.56 (dd, *J* = 15.0, 7.4 Hz, 2H, 1'-H), 3.82 (q, *J* = 6.4 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 17.5, 19.1, 20.1, 29.8 (2-CH_3, C-1', C-2', C-2'', C-3'), 71.0 (C-1''), 107.6 (C-2), 164.1, 165.3 (C-4, C-5) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-4-isopropyl-2-methyloxazol-5(2*H*)-one (**61a**) and rel-(*S*)-2-((*R*)-1-Hydroxyethyl)-4-isopropyl-2-methyloxazol-5(2*H*)-one (**61b**). According to general procedure 1, nitrone **51** (0.30 g, 1.5 mmol) was dissolved in THF (4 mL) and the resulting solution was treated with activated zinc powder (0.49 g, 7.5 mmol). After the addition of saturated NH_4Cl solution (4 mL), the grey suspension was stirred vigorously for 40 min at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed with Et_2O (15 mL). The filtrate was treated with water (20 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to provide oxazol-5(2*H*)-one **61** (209 mg, 76%) as colorless oil.

Upper diastereomer **61a**: R_f = 0.35 (petroleum ether/Et_2O, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.27 (d, *J* = 6.9 Hz, 6H, 2'-H), 1.56 (s, 3H, 2-CH_3), 2.14 (br s, 1H, OH), 2.96 (qq, *J* = 6.9, 6.9 Hz, 1H, 1'-H), 3.86 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3, 19.1, 19.2, 20.6, 28.1 (2-CH_3, C-1', C-2', C-2''), 71.3 (C-1''), 106.9 (C-2), 164.7, 168.3 (C-4, C-5) ppm.

Lower diastereomer **61b**: R_f = 0.31 (petroleum ether/Et_2O, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.9 Hz, 6H, 2'-H), 1.29 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.55 (s, 3H, 2-CH_3), 2.25 (br s, 1H, OH), 2.97 (qq, *J* = 6.9, 6.9 Hz, 1H, 1'-H), 3.82 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 19.1, 19.2, 20.2, 28.1 (2-CH_3, C-1', C-2', C-2''), 71.0 (C-1''), 107.2 (C-2), 164.7, 168.3 (C-4, C-5) ppm.

rel-(*S*)-2-((*S*)-1-Hydroxypropyl)-2-methyl-4-neopentyloxazol-5(2*H*)-one (**62a**). According to general procedure 1, nitrone **52a** (210 mg, 0.86 mmol) was dissolved in THF (2.5 mL) and the resulting solution was treated with activated zinc powder (339 mg, 5.17 mmol). After the addition of NH_4Cl (277 mg, 5.17 mmol) in H_2O (1.30 mL), the grey suspension was stirred vigorously for 1 h at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed three times with EtOAc. The combined organic filtrates were washed with water. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give pure oxazolone **62a** (155 mg, 79%) as white solid; R_t = 1.34 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.04 (s, 9H, 3'-H), 1.05 (t, *J* = 7.4 Hz, 3H, 3''-H), 1.47–1.52, 1.70–1.76 (2 m, 2H, 2''-H), 1.60 (s, 3H, 2-CH_3), 1.90 (bs, 1H, OH), 2.47, 2.56 (2 d, *J* = 13.2 Hz, 2H, 1'-H), 3.61 (dd, *J* = 10.3, 2.1 Hz, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 10.6 (C-3''), 21.0 (2-CH_3), 24.7 (C-1'), 29.4 (C-3'), 32.2 (C-2'), 40.1 (C-2''), 76.8 (C-1''), 107.1 (C-2), 163.1 (C-4), 166.0 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{12}H_{21}NO_3$ $[M + H]^+$ 228.1600, found 228.1600.

rel-(*S*)-2-((*R*)-1-Hydroxypropyl)-2-methyl-4-neopentyloxazol-5(2*H*)-one (**62b**). According to general procedure 1, nitrone **52b** (210 mg, 0.86 mmol) was dissolved in THF (2.5 mL) and the resulting solution was treated with activated zinc powder (339.0 mg, 5.17 mmol). After the addition of NH_4Cl (277 mg, 5.17 mmol) in H_2O (1.30 mL), the grey suspension was stirred vigorously for 1 h at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed three times with EtOAc. The combined organic filtrates were washed with water, the layers were separated the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give oxazolone **62b** (130.0 mg, 64%, 95% pure) as an oil; R_t = 1.32 (HPLC). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.04 (s, 9H, 3'-H), 1.05 (t, *J* = 7.4 Hz, 3H, 3''-H), 1.44–1.52, 1.76–1.85 (2 m, 2H, 2''-H), 1.56 (s, 3H, 2-CH_3), 1.76 (bs, 1H, OH), 2.48, 2.54 (2 d, *J* = 13.4 Hz, 1'-H), 3.53 (bd, *J* = 10.1 Hz, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 10.6 (C-3''), 20.3 (2-CH_3), 24.5 (C-1'), 29.4 (C-3'), 32.1 (C-2'), 40.01 (C-2''), 76.7 (C-1''), 107.5 (C-2), 162.7 (C-4), 166.0 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{12}H_{21}NO_3$ $[M + H]^+$ 228.1600, found 228.1600.

rel-(*S*)-2-((*S*)-1-Hydroxyethyl)-2-methyl-4-phenyloxazol-5(2*H*)-one (**63a**). According to general procedure 1, nitrone **53a** (80 mg, 0.34 mmol) was dissolved in THF (2.0 mL) and the resulting solution was treated with activated zinc powder (111.0 mg, 1.70 mmol). After the addition of NH_4Cl (245 mg, 4.58 mmol)) in H_2O (2.0 mL), the grey suspension was stirred vigorously for 10 min at r.t. Then the reaction mixture was filtered and washed three times with CH_2Cl_2. The combined organic filtrates were washed with water, the layers were separated, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give after purification by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc/2%NEt_3 from 0% – 100% EtOAc) oxazolone **63a** (10 mg, 13%) as a slightly yellow oil; R_t = 1.11 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.4 Hz, 3H, 2'-H), 1.70 (s, 3H, 2-CH_3), 1.88 (bs, 1H, OH), 3.97 (q, *J* = 6.4 Hz, 1H, 1'-H,), 7.50–7.60, 8.37–8.41 (2 m, 5H, Ph) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, contains some DMSO): δ = 17.6 (C-2'), 20.7 (2-CH_3), 71.7 (C-1'), 107.5 (C-2), 128.6 (Ph), 128.7 (Ph), 128.8 (Ph), 132.6 (Ph), 157.1 (C-4), 164.2 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{12}H_{13}NO_3$ $[M + H]^+$ 220.0974, found 220.0976.

rel-(*S*)-2-((*R*)-1-Hydroxyethyl)-2-methyl-4-phenyloxazol-5(2*H*)-one (**63b**). According to general procedure 1, nitrone **53b** (300 mg, 1.27 mmol) was dissolved in THF (5.5 mL) and the resulting solution was treated with activated zinc powder (417 mg, 6.37 mmol). After the addition of NH_4Cl

(428.5 mg, 8.01 mmol) in H_2O (5.5 mL), the grey suspension was stirred vigorously for 10 min at r.t. Then the reaction mixture was filtered and washed three times with CH_2Cl_2. The combined organic filtrates were washed with water, the layers were separated, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give, after purification by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc/2%NEt_3 from 0% - 100% EtOAc), oxazolone **63b** (49 mg (17%) in a ratio *low*/*high* = 88:12; R_t = 1.11 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.4 Hz, 3H, 2'-H), 1.67 (s, 3H, 2-CH_3), 19.7 (bs, 1H, OH), 3.95 (q, *J* = 6.4 Hz, 1H, 1'-H), 7.45–7.60 (m, 5H, Ph) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.6 (C-2'), 20.2 (2-CH_3), 71.4 (C-1'), 106.7 (C-2), 128.5 (Ph), 128.8 (Ph), 132.6 (Ph), 156.9 (C-4), 164.3 (C-5) ppm; HRMS (ESI-TOF): calcd. for $C_{12}H_{13}NO_3$ $[M + H]^+$ 220.0974, found 220.0972.

rel-(*S*)-2-((*S*)-1-Acetoxyethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**64a**) and rel-(*S*)-2-((*R*)-1-Acetoxyethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**64b**). Under an argon atmosphere hydroxynitrone **21** (400.0 mg, 1.85 mmol) was diluted with dry CH_2Cl_2 (18.6 mL), then triethylamine (282.1 mg, 2.78 mmol), DMAP (45.4 mg, 0.37 mmol) and at last acetyl chloride (160.5 mg, 2.04 mmol) were added in small portions followed by stirring of the mixture for 2 h at r.t. Thereafter, the reaction mixture was poured on saturated aqueous $NaHCO_3$ solution (15 mL). After separation of the organic layer, the aqueous layer was extracted thrice with CH_2Cl_2 (30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 5% – 100% EtOAc, 50 g SiO_2, 100 mL/min) to give acetate derivatives **64a** (210 mg, 54%) and **64b** (188 mg, 39%) as slightly yellow oils.

Upper diastereomer **64a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97, 0.98 (2 d, *J* = 6.7 Hz, 3H each, 3'-H), 1.30 (d, *J* = 6.7 Hz, 3H, 2''-H), 1.77 (s, 3H, 2-CH_3), 2.07 (s, 3H, Ac), 2.15–2.23 (m, 1H, 2'-H), 2.43 (dd, *J* = 13.8, 7.3 Hz, 1H, 1'-H_A), 2.51 (dd, *J* = 13.8, 7.0 Hz, 1H, 1'-H_B), 5.32 (q, *J* = 6.7 Hz, 1H, 1''-H) ppm.

Lower diastereomer **64b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.43 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.73 (s, 3H, 2-CH_3), 1.96 (s, 3H, Ac), 2.12–2.19 (m, 1H, 2'-H), 2.37–2.53 (m, 2H, 1'-H), 5.28 (q, *J* = 6.50 Hz, 1H, 1''-H) ppm.)

rel-(*S*)-2-((*S*)-1-((Cyclopropanecarbonyl)oxy)ethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**65a**) and rel-(*S*)-2-((*R*)-1-((Cyclopropanecarbonyl)oxy)ethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**65b**). Under an argon atmosphere hydroxynitrone **21** (50.0 mg, 0.23 mmol) was diluted with dry CH_2Cl_2 (2.3 mL), then triethylamine (35.3 mg, 0.34 mmol), DMAP (5.7 mg,0.04 mmol) and at last cyclopropanecarbonyl chloride (26.7 mg, 0.25 mmol) were added and the mixture stirred for 6 h at r.t. The reaction mixture was poured on saturated aqueous $NaHCO_3$ solution (5 mL). After separation of the layers, the aqueous layer was extracted thrice with CH_2Cl_2 (10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 0% – 20% EtOAc, 15 g SiO_2, 25 ml/min) to give nitrone ester **65a** (14.0 mg, 21%) and nitrone ester **65b** (45.0 mg, 69%), both as slightly yellow oils.

Upper diastereomer **65a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.94 (m, 2H, cyclopropyl), 0.99 (t, *J* = 6.3 Hz, 6H, 3'-H), 1.01–1.05 (m, 2H, cyclopropyl), 1.28 (d, *J* = 6.6 Hz, 3H, 2''-H), 1.55–1.59 (m, 1H, cyclopropyl), 1.77 (s, 3H, 2-CH_3), 2.15–2.22 (m, 1H, 2'-H), 2.44 (dd, *J* = 14.1, 7.5 Hz, 1H, 1'-H), 2.50 (dd, *J* = 14.1, 7.2 Hz, 1H, 1'-H), 5.35 (q, *J* = 6.6 Hz, 1H, 1''-H) ppm.

Lower diastereomer **65b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.96 (m, 4H, cyclopropyl), 0.97 (d, *J* = 6.7 Hz, 6H, 3'-H), 1.42 (d, *J* = 6.8 Hz, 3H, 1''-H), 1.43–1.49 (m, 1H, cyclopropyl), 1.73 (s, 3H, 2-CH_3), 2.17 (m, 1H, 2'-H), 2.42 (dd, *J* = 13.4, 7.6 Hz, 1H, 1'-H_A), 2.51 (dd, *J* = 13.5, 6.8 Hz, 1H, 1'-HB), 5.31 (q, *J* = 6.5Hz, 1H, 1''-H) ppm.

rel-(*S*)-2-((*R*)-1-(((4-Bromophenyl)carbamoyl)oxy)ethyl)-4-isobutyl-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**66b**). Under a nitrogen atmosphere nitrone **21b** (75.9 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) and 4-bromophenylisocyanate (36.3 mg, 0.28 mmol) were treated with *N*,*N*-diisopropylethylamine (36.3 mg, 0.28 mmol) and the mixture was stirred at room temperature for 1 d. After evaporation of the solvents in vacuo, the crude mixture was directly purified by flash chromatography on a diol phase (Biotage Isolera, gradient heptane/EtOAc from 3% – 30% EtOAc) and then on silica (gradient heptane/EtOAc from 3% – 30% EtOAc) and on Luna C18 (Gilson GX; acetonitrile/water) to give nitrone **66b** (35.0 mg, 32%, purity 95%) as a white solid; R_t = 1.56 min (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91, 0.93 (2 d, *J* = 6.4 Hz, 6H, 3'-H), 1.49 (d, *J* = 6.7 Hz, 3H, 2''-H), 1.76 (s, 3H, 2-CH_3), 2.10–2.17 (bm, 1H, 2'-H), 2.37–2.45 (bm, 2H, 1'-H), 5.37 (q, *J* = 6.8 Hz, 1H, 1''-H); 6.55 (bs, 1H, NH), 7.21 (bd, *J* = 8.1 Hz, 2H, Ar-H), 7.38–7.41 (m, 2H, Ar-H) ppm.

rel-(*S*)-4-Isobutyl-2-methyl-2-((*S*)-1-((3-methylbutanoyl)oxy)ethyl)-5-oxo-2,5-dihydrooxazole 3-oxide (**67a**) and rel-(*S*)-4-Isobutyl-2-methyl-2-((*R*)-1-((3-methylbutanoyl)oxy)ethyl)-5-oxo-2,5-dihydrooxazole 3-oxide (**67b**). Under an argon atmosphere hydroxynitrone **21** (250.0 mg, 1.16 mmol) was diluted with dry CH_2Cl_2 (11.6 mL), then triethylamine (176.3 mg, 1.74 mmol), DMAP (28.4 mg, 0.23 mmol) and at last 3-methylbutanoyl chloride (154.1 mg, 1.27 mmol) were added and the mixture was stirred for 1 h at r.t. Thereafter, the reaction mixture was poured on saturated aqueous $NaHCO_3$ solution (15 mL). After separation of the organic layer, the aqueous layer was extracted thrice with CH_2Cl_2 (30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 5% – 40% EtOAc, 40 g SiO_2, 50 mL/min) to give nitrone ester **67a** (95.0 mg, 27%) and nitrone ester **67b** (159.0 mg, 46%) as colorless oils.

Upper diastereomer **67a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–0.99 (m, 12H, 3'-H, 3'''-H), 1.30 (d, *J* = 6.7 Hz, 3H, 2''-H), 1.77 (s, 3H, 2-CH_3), 2.03–2.10 (m, 1H, 2'''-H), 2.15–2.22 (m, 3H, 1'''-H, 2'-H), 2.43 (dd, *J* = 14.1, 7.5 Hz, 1H, 1'-H_A), 2.50 (dd, *J* = 14.1, 6.8 Hz, 1H, 1'-H_B), 5.33 (q, *J* = 6.7 Hz, 1H, 1''-H) ppm.

Lower diastereomer **67b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88, 0.89, 0.95, 0.96 (4 d, 12H, 3'-H, 4'''-H), 1.40 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.73 (s, 3H, 2-CH_3), 1.94–2.02 (m, 1H, 3'''-H), 2.05–2.07 (m, 2H, 2'''-H), 2.12–2.19 (m, 1H, 2'-H), 2.38-2.47 (m, 2H, 1'-H), 5.29 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm.

rel-(*S*)-4-Isobutyl-2-((*S*)-1-((methoxycarbonyl)oxy)ethyl)-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**68a**) and rel-(*S*)-4-Isobutyl-2-((*R*)-1-((methoxycarbonyl)oxy)ethyl)-2-methyl-5-oxo-2,5-dihydrooxazole 3-oxide (**68b**). Under an argon atmosphere, hydroxynitrone **21** (1.00 g, 4.64 mmol) was diluted with dry CH_2Cl_2 (46.5 mL), then triethylamine (705 mg, 6.96 mmol) and DMAP (114 mg, 0.92 mmol), and at last methylchloroformate (483 mg, 5.11 mmol) were added. The mixture was stirred overnight, then additional trimethylamine (1.410 g, 13.92 mmol), DMAP (228 mg, 1.84 mmol) and methylchloroformate (966 mg, 10.22 mmol) were added in two portions during about 36 h. The reaction mixture was poured on saturated

aqueous $NaHCO_3$ solution (50 mL). After separation of the organic layer, the aqueous layer was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 0% – 100% EtOAc, 40 g SiO_2, 100 mL/min) to give carbonate **68a** (344 mg, 27%) as an oil (dr = 85:15 (*high:low*) and **68b** (410 mg, 32%) as an oil.

Upper diastereomer **68a**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.97 ("t", *J* = 6.3 Hz, 6H, 3'-H), 1.38 (d, *J* = 6.6 Hz, 3H, 2''-H), 1.80 (s, 3H, 2-CH_3), 2.15–2.22 (m, 1H, 2'-H), 2.42 (dd, *J* = 13.8, 7.4 Hz, 1H, 1'-H_A), 2.51 (dd, *J* = 13.8, 7.2 Hz, 1H, 1'-H_B), 3.80 (s, 3H, OCH_3), 5.15 (q, *J* = 6.6 Hz, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.3 (C-2''), 20.7, 22.4, 22.6, 26.3 (2-CH_3, C-2', C-3'), 30.8 (C-1'), 55.3 (OCH_3), 74.4 (C-1''), 103.4 (C-2), 131.8 (C-4), 154.6 (OC=O), 164.5 (C-5) ppm.

Lower diastereomer **68b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94, 0.96 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.49 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.73 (s, 3H, 2-CH_3), 2.11–2.21 (m, 1H, 2'-H), 2.39 (dd, *J* = 13.8, 7.5 Hz, 1H, 1'-H_A), 2.51 (dd, *J* = 13.8, 7.15 Hz, 1H, 1'-H_B), 3.73 (s, 3H, OCH_3), 5.16 (q, 1H, *J* = 6.5 Hz, 1''-H) ppm.

para-Bromobenzoate **69b**. Under a nitrogen atmosphere, nitrone **44b** (200 mg, 0.87 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Then trimethylamine (183 μL, 133 mg, 1.30 mmol) and 4-dimethylaminopyridine (DMAP) (21.3 mg, 0.17 mmol) and at last 4-bromobenzoyl chloride (211 mg, 0.96 mmol) were added followed by stirring of the mixture overnight at ambient temperature. After treatment with additional trimethylamine (133 mg, 1.30 mmol) and 4-bromobenzoyl chloride (211 mg, 0.96 mmol), the reaction was concentrated after 3 d and the residue purified without further work-up by flash chromatography on silica (Biotage Isolera, gradient heptane/EtOAc from 0–30% EtOAc) to give pure benzoate **69b** (175 mg, 46%) as an oil. R_t = 1.80 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.7 Hz, 6H, 3'-H), 1.00 (t, *J* = 7.5 Hz, 3H, 3''-H), 1.80 (s, 3H, 2-CH_3), 1.87–1.99 (m, 3H, 2'-H, 2''-H), 2.28 (dd, *J* = 7.2, 2.5 Hz, 1'-H), 5.63 (dd, *J* = 9.3, 3.7 Hz, 1''-H), 7.20-7.62 (m, 2H, Ar-H), 7.78-7.84 (m, 2H, Ar-H) ppm.

rel-(*S*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl acetate (**70a**). According to general procedure 1, nitrone **64a** (217.0 mg, 0.84 mmol) was dissolved in THF (5.5 mL) and the resulting solution was treated with activated zinc powder (276.0 mg, 4.21 mmol). After the addition of saturated aqueous NH_4Cl solution (5.5 mL), the grey suspension was stirred vigorously for 30 min at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed with CH_2Cl_2 (15 mL). The combined organic filtrates were washed with water (10 mL). After separation of the layers, the water layer was re-extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give oxazolone acetate **70a** (193.0 mg, 95%, purity 84%), which was purified by flash chromatography on spherical silica (Biotage Isolera, 2% NEt_3/heptane, then gradient heptane/EtOAc from 0% – 100% EtOAc, 36 mL/min) to give oxazolone **70a** (79.0 mg, 39%) as an oil; R_t = 1.40 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.00 (2 d, *J* = 6.7 Hz, 6H, 1.07 Hz, 3'-H), 1.30 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.58 (s, 3H, 2-CH_3), 1.99 (s, 3H, Ac), 2.16–2.23 (m, 1H, 2'-H), 2.45, 2.53 (2 dd, *J* = 14.7, 7.2 Hz, 2H, 1'-H), 5.2 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.2 (C-2''), 20.9, 21.3, 22.4, 26.3 (2-CH_3, C-3', Ac), 36.6 (C-1'), 71.3 (C-1''), 105.4 (C-2), 164.3 (C-4), 165.1 (C-5), 169.56 (acetate C=O) ppm.

rel-(*R*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl acetate (**70b**). According to general procedure 1, nitrone **64b** (188.0 mg, 0.73 mmol) was dissolved in THF (4.5 mL) and the resulting solution was treated with activated zinc powder (239 mg, 3.65 mmol). After the addition of saturated aqueous NH_4Cl solution (4.5 mL), the grey suspension was stirred vigorously for 30 min at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed with CH_2Cl_2 (15 mL). The combined organic filtrates were washed with water (10 mL). After separation of the layers, the water layer was re-extracted twice with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give oxazolone acetate **70b** (135.0 mg, 77%, purity 65%), which was purified by flash chromatography on spherical silica (Biotage Isolera, 2% NEt_3/heptane, then gradient heptane/EtOAc from 0% – 100% EtOAc, 36 mL/min) to give **70b** (97 mg, 55%) as an oil; R_t = 1.39 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.5 Hz, 3H, 3'-H), 0.99 (d, *J* = 6.7 Hz, 6H, 3'-H), 1.35 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.57 (s, 3H, 2-CH_3), 1.990 (s, 3H, Ac), 2.13–2.20 (m, 1H, 2'-H), 2.46–2.48 (m, 2H, 1'-H), 5.10 (q, *J* = 6.5 Hz 1H, 1''-H) ppm.

rel-(*S*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl cyclopropanecarboxylate (**71a**). According to general procedure 1, a solution of nitrone **65a** (62.0 mg, 0.21 mmol) in THF (1.5 mL) was treated with activated zinc powder (72.0 mg, 1.09 mmol). After the addition of saturated aqueous NH_4Cl solution (1.5 mL) the grey suspension was stirred vigorously for 30 min at r.t. Then the reaction mixture was filtered and the filter washed with CH_2Cl_2 (10 mL). The combined organic filtrates were washed with water (10 mL). After separation of the layers, the water layer was re-extracted twice with CH_2Cl_2 (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give, after purification by flash chromatography on silica (15 g) (Biotage Isolera, 2% NEt_3/heptane, then gradient heptane/EtOAc from 5% – 40% EtOAc, 25 mL/min) pure oxazolone ester **71a** (23.0 mg, (39%) as a colorless oil; R_t = 1.43 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–1.01 (m, 4H, cyclopropyl), 1.02 (2 d, *J* = 6.7 Hz, 6H, 3'-H), 1.30 (d, *J* = 6.4 Hz, 3H, 2''-H), 1.47–1.53 (m, 1H, cyclopropyl), 1.60 (s, 3H, 2-CH_3), 2.17–2.23 (m, 1H, 2'-H), 2.47 (dd, *J* = 14.6, 6.4 Hz, 1H, 1'-H_A), 2.40 (dd, *J* = 14.6, 7.5 Hz, 1H, 1'-H_B), 5.21 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm.

rel-(*R*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl cyclopropanecarboxylate (**71b**). According to general procedure 1, a solution of nitrone **65b** (400 mg, 1.41 mmol) in THF (10 mL) was treated with activated zinc powder (462 mg, 7.05 mmol). After the addition of saturated aqueous NH_4Cl solution (10 mL) the grey suspension was stirred vigorously for 2 h at r.t. Then the reaction mixture was filtered and the filter washed with CH_2Cl_2 (20 mL). The combined organic filtrates were washed with water (10 mL). After separation of the layers the water layer was re-extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give, after purification by flash chromatography on silica (15 g) (Biotage Isolera, gradient heptane/EtOAc from 0% – 100% EtOAc, 75 mL/min) pure oxazolone ester **71b** (370.0 mg, 98%) as a colorless oil; R_t = 1.50 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.83-0.97 (m, 4H, cyclopropyl), 1.00 (2d, *J* = 6.8 Hz, 6H, 3'-H), 1.36 (d, *J* = 6.5 Hz, 3H, 1''-H), 1.48–1.52 (m, 1H, cyclopropyl), 1.57 (s, 3H, 2-CH_3), 2.14–2.21 (m, 1H, 2-H), 2.48 (d, *J* = 6.8 Hz, 2H, 1'-H), 5.15 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 8.75, 8.82, (cyclopropyl CH_2), 12.8, 15.3, 21.3, 22.4, 22.5, 26.1 (C-2'', 2-CH_3, C-3', cyclopropyl CH, C-2'), 36.5 (C-1'), 70.8 (C-1''), 105.8 (C-2), 163.8 (C-4), 165.4 (C-5), 173.3 (cyclopropyl-C=O) ppm.

rel-(*S*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl 3-methylbutanoate (**72a**). According to general procedure 1, nitrone **67a** (74.0 mg, 0.24 mmol) was dissolved in THF (2.0 mL) and the resulting solution was treated with activated zinc powder (81.0 mg, 1.23 mmol). After the addition of saturated aqueous NH_4Cl solution (2.0 mL), the grey suspension was stirred vigorously for 30 min at r.t. Then the reaction mixture was filtered and the filter washed with CH_2Cl_2 (10 mL). The combined organic filtrates were washed with water (10 mL). After separation of the layers, the water layer was re-extracted twice with CH_2Cl_2

(5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give, after purification by flash chromatography on silica (Biotage Isolera, 2% NEt_3/heptane, then gradient heptane/EtOAc from 5% – 40% EtOAc, 25 mL/min) pure oxazolone ester **72a** (21.0 mg, 30%) as a slightly yellow oil; R_t = 1.68 (HPLC);^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92, 1.01 (2d, *J* = 6.7 Hz, 12H, 3'-H, 4'''-H), 1.31 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.59 (s, 3H, 2-CH_3), 1.98–2.07 (m, 1H, 2'''-H), 2.10 (s, br, 1H, 3'''-H), 2.12 (d, *J* = 1.6 Hz, 1H, 2'-H), 2.16–2.23 (m, 1H, 2'''-H), 2.46 (dd, *J* = 14.8, 7.0 Hz, 1H, 1'-H_A), 2.54 (dd, *J* = 14.8, 7.3 Hz, 1H, 1'-H_B), 5.20 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm.

rel-(*R*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl 3-methylbutanoate (**72b**). According to general procedure 1, nitrone **67b** (155.0 mg, 0.51 mmol) was dissolved in THF (3.5 mL) and the resulting solution was treated with activated zinc powder (169.0 mg, 2.58 mmol). After the addition of saturated aqueous NH_4Cl solution (3.5 mL), the grey suspension was stirred vigorously for 2 h at r.t. Then the reaction mixture was filtered and the filter washed with CH_2Cl_2 (20 mL). The combined organic filtrates were washed with water (10 mL). After separation of the layers, the water layer was re-extracted twice with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give after purification by flash chromatography on silica (Biotage Isolera, 2% NEt_3/heptane, then gradient heptane/EtOAc from 5% – 40% EtOAc, 15 g SiO_2, 25 mL/min) oxazolone ester **72b** (64.0 mg, 44%) (*low/high* = 83:17); R_t = 1.67 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.6 Hz, 6H, 4'''-H), 0.99 (2d, *J* = 6.8 Hz, 6H, 3'-H), 1.36 (d, *J* = 6.4 Hz, 3H, 2''-H), 1.57 (s, 3H, 2-CH_3), 2.00–2.05 (m, 1H, 2'''-H), 2.09–2.12 (m, 2H, 2'''-H), 2.14–2.19 (m, 1H, 2'-H), 2.45 (dd, *J* = 15.0, 7.3 Hz, 1H, 1'-H_A), 2.49 (dd, *J* = 15.1, 6.8 Hz, 1H, 1'-H_B), 5.11 (q, *J* = 6.4 Hz, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.3 (C-2''), 21.3, 22.25, 22.32, 22.5, 25.7, 26.1, 30.3 (C-2', C-2''', C-3', C-3''', 2-CH_3), 36.5 (C-1'), 43.3 (C-1'''), 74.6 (C-1''), 105.8 (C-2), 163.9 (C-4), 165.3 (C-5), 171.5 (ester) ppm.

rel-(*S*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl methyl carbonate (**73a**). According to general procedure 1, nitrone **68a** (77.0 mg, 0.28 mmol) was dissolved in THF (1.5 mL) and the resulting solution was treated with activated zinc powder (92.0 mg, 1.40 mmol). After the addition of saturated aqueous NH_4Cl solution (1.5 mL), the grey suspension was stirred vigorously for 30 min at r.t. Then the reaction mixture was filtered and the filter residue rinsed with CH_2Cl_2 (10 mL). The combined organic filtrates were washed with water and the water layer was re-extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give pure oxazolone carbonate **73a** (54 mg, 75%) as an oil; R_t = 1.39 (HPLC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, 6H, *J* = 6.7 Hz, 3'-H), 1.39 (d, *J* = 6.5 Hz, 3H, 2''-H), 1.59 (s, 3H, 2-CH_3), 2.14–2.24 (m, 1H, 2'-H), 2.47 (dd, *J* = 14.6, 6.8 Hz, 1H, 1'-H_A), 2.47 (dd, *J* = 14.6, 7.2 Hz, 1H, 1'-H_B), 3.76 (s, 3H, OCH_3), 5.02 (q, *J* = 6.5 Hz, 1H, 1''-H) ppm.

rel-(*R*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)ethyl methyl carbonate (**73b**). According to general procedure 1, nitrone **68b** (410 mg, 1.50 mmol) was dissolved in THF (10.0 mL) and the resulting solution was treated with activated zinc powder (491 mg, 7.50 mmol). After the addition of saturated aqueous NH_4Cl solution (10.0 mL), the grey suspension was stirred vigorously for 2 h at r.t. Then the reaction mixture was filtered through a pad of celite, which was rinsed with CH_2Cl_2 (20 mL). The combined organic filtrates were washed with water (10 mL). After separation of the layers, the water layer was re-extracted twice with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO4, filtered, and concentrated in vacuo to give pure pure oxazolone carbonate **73b** (364 mg, 94%) as an oil; R_t = 1.38 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.97 (2d, *J* = 6.7 Hz, 6H, 3'-H), 1.434 (d, *J* = 6.6 Hz, 3H, 2''-H), 1.57 (s, 3H, 2-CH_3), 2.13–2.00 (m, 1H, 2''-H), 2.43–2.50 (m, 2H, 1''-H), 3.73 (s, 3H, OCH_3), 4.93 (q, *J* = 6.6 Hz, 1H, 1''-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.3 (C-2''), 21.1, 22.2, 22.4 (2-CH_3, C-3'), 26.1 (C-2'), 36.5 (C-1'), 75.1 (C-1''), 105.4 (C-2), 154.8 (O-CO), 164.12 (C-4), 165.2 (C-5) ppm.

rel-(*R*)-1-((*S*)-4-Isobutyl-2-methyl-5-oxo-2,5-dihydrooxazol-2-yl)propyl 4-bromobenzoate (**74b**). According to general procedure 1, nitrone **69b** (110 mg, 0.26 mmol) was dissolved in THF (2.5 mL) and the resulting solution was treated with activated zinc powder (105 mg, 1.60 mmol). After the addition of NH_4Cl solution (86 mg, 1.60 mmol, in 1.3 mL water), the grey suspension was stirred vigorously for 60 min at r.t. Then the reaction mixture was diluted with EtOAc, filtered through a pad of celite, which was rinsed with EtOAc several times. The collected organic phases were extracted with water, dried over Na_2SO_4, filtered, and concentrated in vacuo to give pure oxazolone **74b** (95 mg, 90%); R_t = 2.02 (HPLC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.83 (2 d, *J* = 6.6 Hz, 6H, 3'-H), 0.96 (t, *J* = 7.5 Hz (x2), 3H, 3''-H), 1.64 (s, 3H, 2-CH_3), 1.80–1.88 (m, 1H, 2'-H), 1.95–2.03 (m, 2H, 2''-H), 2.26 (dd, *J* = 15.3, 7.3 Hz, 1H, 1'-H_A), 2.36 (dd, *J* = 15.3, 6.7 Hz, 1H, 1'-H_B), 5.34 (dd, *J* = 10.3, 3.0 Hz, 1H, 1''-H), 7.57 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.80 (d, *J* = 8.6 Hz, 2H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 10.0 (C-3''), 21.5, 22.2, 22.4 (2-CH_3, C-3'), 23.0 (C-2''), 25.9 (C-2'), 36.4 (C-1'), 75.8 (C-1''), 105.9 (C-2), 128.2, 128.6, 131.1, 132.9 (Ar C) 163.9, 164.6, 165.4 (C-4, C-5, ArCO) ppm; HRMS (ESI-TOF): calcd. for $C_{18}H_{22}BrNO_4$ $[M + H]^+$ 396.0810, found 396.0809.

Acknowledgements ((optional))

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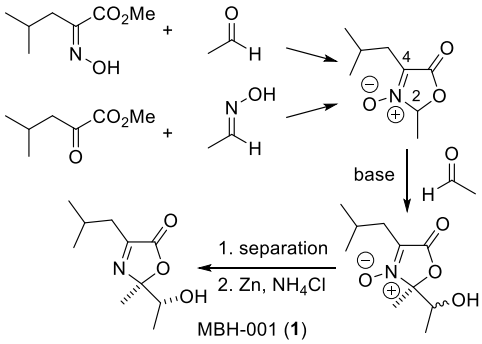

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