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MiPNO, a new chiral cyclic nitronone for enantioselective amino acid synthesis: the cycloaddition approach.

Maryse Thiverny, Christian Philouze, Pierre Yves Chavant and Véronique Blandin*

The resolution of chiral nitronones *via* derivatization of hydroxylamines was applied to MiPNO, a new, stable, easily prepared chiral cyclic nitronone. The application of MiPNO in totally regio- and diastereo- selective 1,3-dipolar cycloaddition reactions provides an expeditious enantioselective access to unusual γ -hydroxy α -aminoacids.

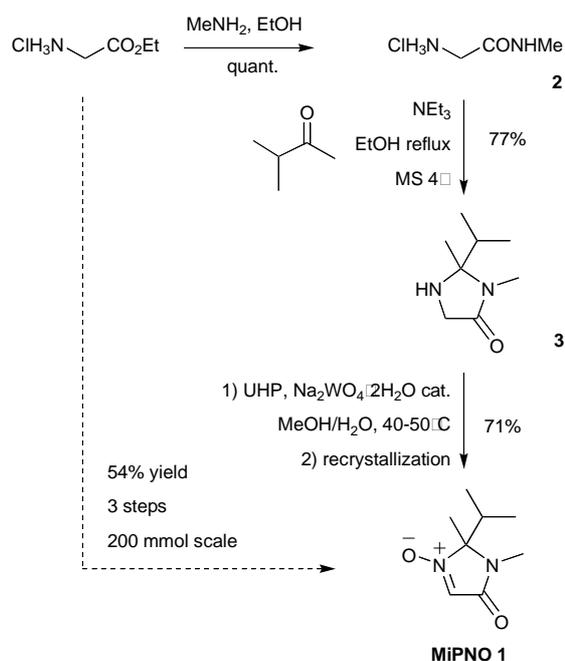
Introduction

The regio- and diastereo- selective 1,3-dipolar cycloaddition reaction of chiral nitronones with dipolarophiles is a powerful tool to obtain chiral nitrogenated compounds.¹ In particular, when α -alkoxycarbonyl or α -alkylaminocarbonyl nitronones are at stake, the cycloaddition reaction with alkenes followed by cleavage of the N–O bond leads to side chain-functionalized chiral α -amino acid derivatives.² In order to gain a high stereoselectivity in the cycloaddition reaction, overcoming the problem of *E/Z* isomerization around the nitronone double bond is important.³ Small-ring endocyclic chiral nitronones are thus good candidates and their more rigid cyclic skeleton compared to acyclic nitronones is another asset to obtain high stereoselectivity. Several five-⁴ and six-⁵ membered chiral cyclic nitronones of this type have been previously designed.⁶

In parallel to our work in the field of *N*-hydroxy peptides synthesis and application,⁷ we sought an access to *N*-hydroxy amino acids via the addition of functionalized organometallic reagents⁸ on to properly designed enantiopure nitronones. To this end, we designed a series of chiral nitronones^{4d,e} obtained by oxydation of imidazolidinones and based on the self-regeneration of stereocenters principle.⁹ In our continuous effort to provide storable reagents and intermediates using inexpensive starting materials and scalable syntheses,¹⁰ we developed the new chiral nitronone **1** (MiPNO), that turned out to feature an excellent thermal stability. This made **1** a good candidate for 1,3-dipolar cycloaddition reactions that usually require prolonged heating. We report herein the synthesis of **1** and its evaluation as a successful substrate for diastereoselective 1,3-dipolar cycloaddition reactions.

Results and discussion

Nitronone **1** was conveniently prepared in three steps according to Scheme 1, starting from glycine ethyl ester hydrochloride. Condensation of amino amide **2** with 3-methyl-butanone led exclusively to the desired cyclic product **3**. Oxidation of **3** was performed using urea-hydrogen peroxide (UHP) complex in the presence of inexpensive sodium tungstate as the catalyst.¹¹ The whole process was routinely carried out on a 200 mmoles scale. After recrystallization the yield of **1**, over three steps, was typically 54%. Nitronone **1** could be stored at room temperature for months without noticeable degradation.

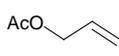
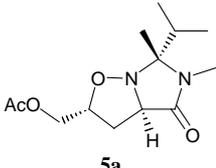
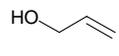
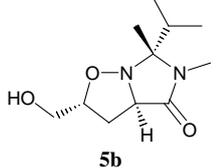
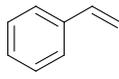
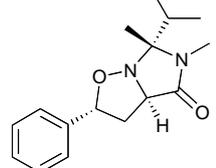


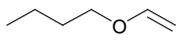
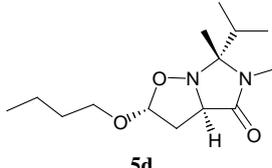
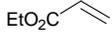
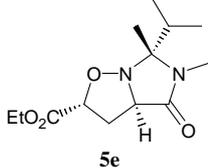
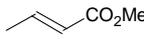
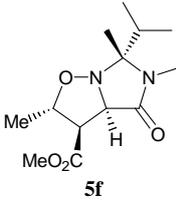
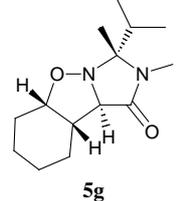
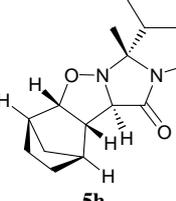
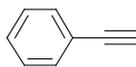
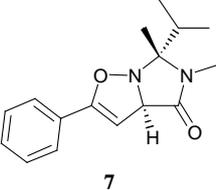
Scheme 1. Preparation of MiPNO 1.

X-ray analysis of **1**¹² showed a planar ring with one side hindered by the isopropyl group. In order to evaluate its level of diastereoselection, nitrone **1** was engaged in 1,3-dipolar cycloaddition reactions with a wide range of alkenes (Table 1), either in neat conditions or using toluene as the solvent.¹³ The reaction was highly regio- and diastereo-selective, the nitrone reacting from the less hindered side in an *exo* mode to give cycloadducts **5a-h**.¹⁴ The NMR and LC/MS analysis of the crude products indicated an isomeric purity of more than 98% in all cases except in case of the acetal **5d** (table 1, entry 4). Nevertheless, after chromatographic purification all compounds were isolated as pure cycloadducts in excellent yield.

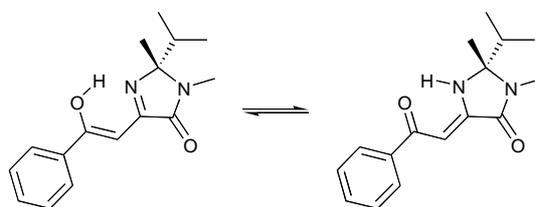
Alkyne dipolarophiles are seldom reported in the reaction with nitrones^{1a} and the cycloadducts are prone to rearrangements.^{5c} In our hands, no reaction occurred between nitrone **1** and propargylic alcohol or protected derivatives thereof. However, phenylacetylene reacted smoothly to give the expected cycloadduct **7** in 73% isolated yield (entry 9). An open-chain enol-imine or keto-enamine by-product **7'** derived from **7** through β -elimination¹⁵ was also isolated in 20% yield (Scheme 2).

Table 1. 1,3-dipolar cycloaddition of racemic nitrone **1** to alkenes **4a-h** and alkyne **6**.

entry	dipolarophile 4 or 6	cycloadduct ^a	yield (%) ^b
1	 4a	 5a	87 (94) ^f
2	 4b	 5b	94 (86) ^f
3	 4c	 5c	90

4			88 ^d
5			84
6			80 (80) ^c
7			74 ^e (65) ^{c, e}
8			90 ^f
9			73 ^g

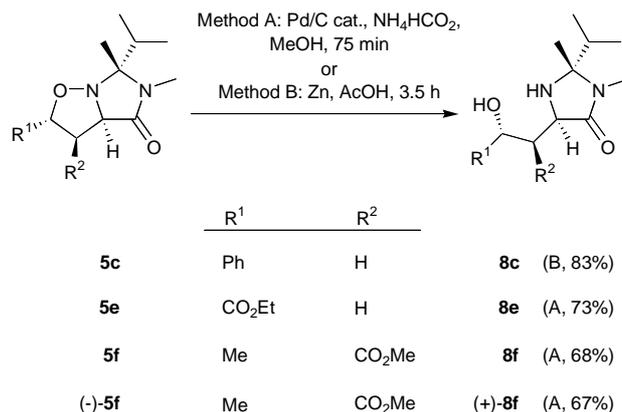
^a Unless otherwise stated, reactions were performed in a sealed vessel at 80 °C for 3-16 h, using 10 equiv **4** or **6** without solvent. The main isomer, representing $\geq 98\%$ of the cycloadducts in the crude product (LC/MS), is shown. ^b Yield of the isolated main isomer. ^c Starting from (-)-(*R*)-**1**. ^d Isomeric purity of the crude product $\geq 95\%$. ^e Toluene was used as a cosolvent. Reaction time: 48h, 90% conversion. ^f 1.2 equiv alkene were used, in toluene. ^g 2 equiv alkyne were used, in toluene. The monocyclic isomer **7'** resulting from β -elimination was isolated in 20% yield.



Scheme 2. Tautomeric structures of by-product **7'**.

To elaborate the amino acid side chain further, reductive cleavage of the N–O bond was investigated (Scheme 3). Hydrogenolysis of **5e** and **5f** under transfer conditions afforded amino alcohols **8e** and **8f** in good isolated yield. In the case of **5f**, a 9:1 mixture of diastereomers was obtained.¹⁶ For the styrene-derived cycloadduct **5c**, the reductive cleavage was performed

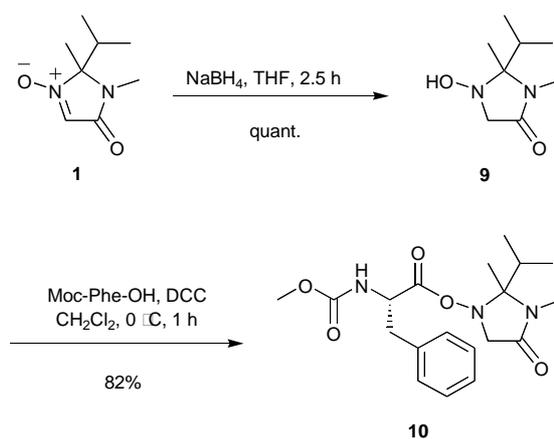
using zinc in acetic acid, leading to amino alcohol **8c** in excellent yield.



Scheme 3. Reductive cleavage of the N–O bond.

In order to obtain MiPNO **1** in enantiomerically pure form, we decided to use a strategy under development in our group, namely the resolution of secondary hydroxylamines *via* *O*-acylation with a chiral carboxylic acid.¹⁷ The nitron **1** was thus converted into the *N*-hydroxy-imidazolidinone **9** by reduction with sodium borohydride (Scheme 4).

Interestingly, this reduction was clean when THF was the solvent, whereas the reduction in MeOH was accompanied by the formation in large amount (30%) of the imine resulting from dehydration of **9**. Moc-Phe-OH¹⁸ was chosen as the chiral derivatizing agent for its ability to provide chromatographically separable diastereomers. The 1:1 mixture of diastereomers **10** was obtained in high yield.



Scheme 4. Resolution of MiPNO: derivatization of hydroxylamine **9**.

Unfortunately, the *O*-acylated hydroxylamine proved to be very sensitive to silica gel and partially decomposed into Moc-Phe-OH and imine. Nevertheless, submitting the mixture of diastereomers to medium pressure liquid chromatography allowed the isolation of the first eluted diastereomer **10a** as a solid in 32% yield. On the basis of the relative configuration obtained by X-ray analysis of recrystallized **10a** (Figure 1),¹⁹ the stereochemistry of the imidazolidinone moiety is (*R*).

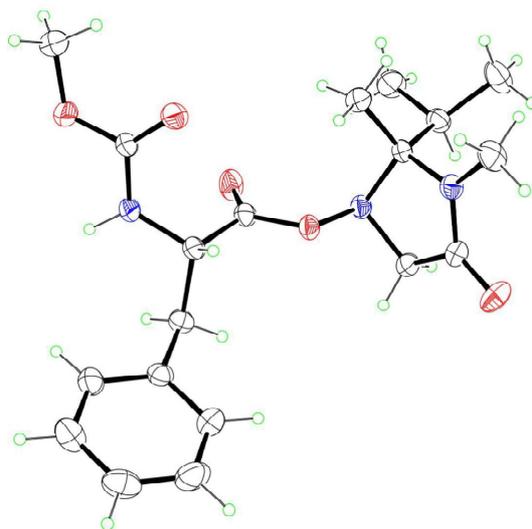
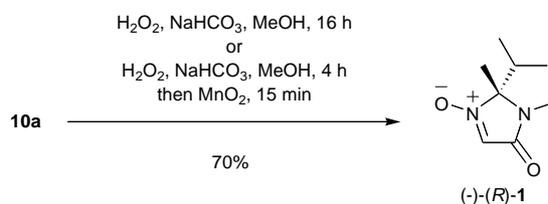


Figure 1. ORTEP drawing of **10a**. The ellipsoids are plotted at the 25% probability level.

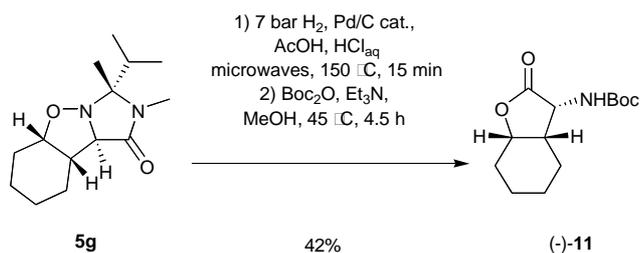
Treatment of **10a** with basic aqueous hydrogen peroxide overnight allowed the one-pot liberation of the hydroxylamine and its oxidation into the nitrone (-)-**1**. More efficiently, MnO_2 may be added as soon as the first step is completed in order to accelerate the process (Scheme 5).



Scheme 5. Resolution of MiPNO: one-pot removal of resolving agent and oxidation.

The enantiomeric excess of (-)-**1** was above 99% as determined by chiral HPLC analysis. The nitrone (-)-**1** proved to be configurationally stable when purified by chromatography on silica gel^{4c} or when heated in toluene at 80 °C for 16h.

The 1,3-dipolar cycloaddition of enantiopure MiPNO (-)-**1** with several alkenes gave results consistent with those obtained for the racemic series (Table 1, entries 1, 2, 6 and 7). The N–O bond of (-)-**5f** was cleaved using method A (Scheme 2) and (+)-**8f** was obtained in 67% yield. Next, the tricyclic compound (+)-**5g** was chosen to investigate the transformation of cycloadducts into conveniently *N*-protected amino acids (Scheme 6). We developed a microwave-assisted procedure where acidic hydrogenolytic conditions allow the one-pot cleavage of the N–O, amide, and N–C–N bonds.²⁰ The crude α -amino- γ -lactone²¹ was Boc-protected to give after chromatography (-)-**11** as a single isomer in 42% yield from (+)-**5g**. This is to our knowledge the first preparation of **11** in enantiopure form.



Scheme 6. One-pot conversion of cycloadduct **5g** to *N*-protected α -amino γ -lactone (-)-**11**.

Conclusion

The new nitrone MiPNO **1**, easily prepared on large scale in three inexpensive steps and one recrystallization, has proven to exhibit a high degree of facial differentiation, making it a promising new building block for the synthesis of α -amino acids. The cycloaddition reaction with alkenes features excellent regio- and stereo- selectivity, affording a single enantiopure isomer in high yields. From there, one operation provides α -amino γ -lactones, a masked form of γ -hydroxy α -amino acids. We are currently studying improved resolutions of MiPNO, as well as its applications to other addition reactions.

Experimental

General

THF was freshly distilled from sodium benzophenone ketyl. Styrene, cyclohexene, methyl crotonate and phenylacetylene were distilled before use, other purchased reagents were used without purification. Unless otherwise stated, the indicated reaction temperatures are external ones (oil bath). Reactions were monitored by thin layer chromatography (TLC) using commercial aluminium-backed silica gel plates (Merck, Kieselgel 60 F₂₅₄). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with an appropriate staining solution (KMnO₄, ninhydrine for amines, basic TTC (2,3,5-triphenyltetrazolium chloride) for hydroxylamines). Product purification by column chromatography were performed using Macherey Nagel Silica Gel 60M (230-400 mesh). Microwave irradiation experiments were conducted in a CEM Discover S-Class apparatus (single mode technology), equipped with a gas addition kit. Melting points were determined in capillary tubes with a Büchi B-540 apparatus. Optical rotations were measured on a Perkin Elmer 341 polarimeter, the corresponding concentration is given in g/100 cm⁻³. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on a Varian 400MR spectrometer in CDCl₃ (δ_{H} 7.26 ppm; δ_{C} 77.2 ppm; standard for ¹H spectra: tetramethylsilane δ_{H} 0.0 ppm). NOESY experiments were run on a Unity Plus 500 MHz Varian. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, hept = heptuplet, m = multiplet, br = broad, coupling constants *J* are reported in Hz. ¹H and ¹³C resonance assignments were performed using conventional 1D and 2D techniques (DEPT, COSY, HMQC and HMBC experiments). Relative stereochemistry was assigned using NOESY experiments. Infrared spectra (IR) were obtained either from a thin film or from a dispersion of the compound in a KBr pellet. IR spectra were recorded on a Nicolet Impact-400 FT-IR spectrometer and the data are reported as absorption maxima in cm⁻¹. Mass spectra (LRSM) were recorded on an Esquire 300 Plus Bruker Daltonics spectrometer (ESI). High resolution mass spectra (HRMS) were recorded on a Thermoquest Orbitrap spectrometer at the LCOSB, UMR 7613, Université Pierre et Marie Curie, Paris, France. Experimental errors for HRMS data are estimated between 1 and 2 ppm.

(*rac*)-2-Isopropyl-2,3-dimethyl-imidazolidin-4-one **3**

The aminoamide **2** was prepared according to ref. 22: in a 250-mL Erlenmeyer flask under magnetical stirring, methylamine (125 mL, 8M in ethanol, 1.0 mol) was added to glycine ethyl ester hydrochloride (27.92 g, 200 mmol) in ethanol (80 mL). After stirring for 16h at room temperature, and concentration, the crude product was taken up in ethanol (200 mL) and the solvent and excess methylamine were removed under vacuum. This operation was repeated twice to give pure **2** (24.91 g, 200 mmol, quantitative yield) as an amorphous solid.

In a 500-mL flask fitted with a reflux condenser were introduced the aminoamide hydrochloride **2** (24.91 g, 200 mmol), ethanol (200 mL), 3-methyl-2-butanone (42.8 mL, 400 mmol), triethylamine (28.1 mL, 200 mmol) and activated 4Å molecular sieves (beads, 60 g). The reaction mixture was heated for 16 h at reflux without stirring, then the sieves were filtered off and the solvent was evaporated under reduced pressure. The crude white slurry was taken up in ethyl acetate (150 mL), the precipitated triethylamine hydrochloride was filtered off and the solvent evaporated under reduced pressure to yield 24.15 g of crude material **3** (theoretical: 31.25 g; *R_f* = 0.33 (ethyl acetate/ethanol - 80:20); ν_{max} (KBr pellet): 3327, 2970, 2942, 2876, 1685, 1432, 1404 and 1124; δ_{H} (400 MHz; CDCl₃; Me₄Si) 3.53 (d, *J* 16.0, 1H), 3.42 (d, *J* 16.0, 1H), 2.74 (s, 3H), 1.91 (qq, *J* 6.4 and 6.8, 1H), 1.71 (br s, 1H), 1.34 (s, 3H), 0.96 (d, *J* 6.4, 3H), 0.79 (d, *J* 6.8, 3H); δ_{C} (100 MHz, CDCl₃) 172.7, 82.0, 49.4, 34.7, 25.2, 24.2, 16.6, 16.2 ppm; MS (ES⁺): *m/z* 335 (2M + Na⁺, 30%), 179 (M + Na⁺, 55), 157 (M + H⁺, 100); HRMS: *m/z* 157.13329 (M + H) C₈H₁₇N₂O requires 157.13354.

(*rac*)-2-Isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one **1**

In a 500-mL flask fitted with a reflux condenser the crude amine **3** (24.15 g, 154.58 mmol) was dissolved in methanol (200 mL) and the reaction mixture was heated at 40 °C. Sodium tungstate dihydrate (5.09 g, 15.46 mmol) suspended in water (1.99 g) was added, followed by the urea-hydrogen peroxide complex (72.71 g, 772.90 mmol) in two portions. The internal temperature of the flask was maintained below 50°C (water bath). The reaction was monitored by TLC (silica gel, ethyl acetate) and was completed after 3 h. The reaction flask was cooled in an ice bath and MnO₂ (Fluka, ref 63548, 10.0 g) was added in three portions to destroy the excess of hydrogen peroxide. The reaction mixture was vigorously stirred until the end of dioxygen evolution (15 min) and the solvent was removed under vacuum. The residue was taken up in dichloromethane (100 mL), anhydrous Na₂SO₄ (40 g) was added, and the reaction mixture was filtered over Celite. After concentration, the crude product was refluxed in ethyl acetate (32 mL), the hot reaction mixture was filtered and cyclohexane (29 mL) was added portionwise to the boiling solution. The reaction mixture was allowed to cool slowly and after 4 h at room temperature, filtration yielded the nitrone **1** as white crystals (18.56 g, 109.04 mmol, 54 % from glycine ethyl ester hydrochloride); mp 113.0-113.1 °C; *R_f* = 0.32 (ethyl acetate); ν_{max} (KBr pellet): 2972, 2803, 1701, 1561, 1259 and 1046; δ_{H} (400 MHz; CDCl₃; Me₄Si) 7.06 (s, 1H), 2.99 (s, 3H), 2.30 (qq, *J* 7.2 and 6.8, 1H), 1.66 (s, 3H), 1.00 (d, *J* 7.2, 3H), 0.97 (d, *J* 6.8, 3H) ppm; δ_{C} (100 MHz, CDCl₃) 162.8, 124.9, 94.1, 34.4, 26.0, 21.5, 16.1, 15.4 ppm; MS (ES⁺): *m/z* 363 (2M + Na⁺, 23%), 341 (2M + H⁺, 29), 193 (M + Na⁺, 57), 171 (M + H⁺, 100); Anal. Found: C, 56.08; H, 8.26; N, 16.59; Calc. for C₈H₁₄N₂O₂: C, 56.45; H, 8.29; N, 16.46%.

(*rac*)- and (2*R*,3*aR*,6*R*) acetic acid (6-isopropyl-5,6-dimethyl-4-oxo-hexahydro-imidazo[1,5-*b*]isoxazol-2-yl)methyl ester **5a** and (-)-**5a**

The preparation of **5a** is typical: The reaction was performed in a sealed vessel. A mixture of nitron **1** (340 mg, 2.00 mmol) and allyl acetate (2.16 mL, 20.00 mmol) was heated at 80 °C for 16 h. The major part of the alkene was removed under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane - 70:30) to yield isoxazolidine **5a** (468 mg, 1.73 mmol, 87 %) as a yellow oil; R_f = 0.35 (ethyl acetate); ν_{\max} (KBr pellet): 2973, 2935, 2890, 1735, 1696, 1407, 1382, 1260, 1235, 1084 and 1047; δ_{H} (400 MHz; CDCl₃; Me₄Si) 4.16-3.98 (m, 4H), 2.77 (s, 3H), 2.65 (ddd, J 1.2, 6.4 and 12.4, 1H), 2.24 (td, J 8.8 and 12.4, 1H), 2.05 (s, 3H), 1.83 (qq, J 6.8 and 7.2, 1H), 1.45 (s, 3H), 1.02 (d, J 6.8, 3H), 0.78 (d, J 7.2, 3H) ppm; δ_{C} (100 MHz, CDCl₃) 172.1, 170.7, 88.6, 74.5, 66.1, 64.1, 36.4, 35.2, 26.5, 20.9, 17.9, 17.0; MS (ES⁺): m/z 563 (2M + Na⁺, 11), 293 (M + Na⁺, 100), 271 (M + H⁺, 32); HRMS: m/z 293.14756 (M + Na); C₁₃H₂₂N₂O₄Na requires 293.14718.

(-)-**5a** (60 mg, 222 μ mol, 94%) was obtained starting from (*R*)-**1** (40 mg, 235 μ mol) and allyl acetate (254 μ L, 2.35 mmol) as a pale yellow oil which solidified upon standing; mp 87.9-88.0 °C; $[\alpha]_{\text{D}}^{20}$ -37.9 (*c* 1.06, CHCl₃); Anal. Found: C, 57.47; H, 8.43; N, 10.25; Calc. for C₁₃H₂₂N₂O₄: C, 57.76; H, 8.20; N, 10.36%. The enantiomeric purity of (-)-**5a** (\geq 97% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 x 100 mm, eluent water/acetonitrile - 60:40, 0.5 mL/min, retention time for (-)-**5a** 7.67 min and for (+)-**5a** 6.76 min.

(rac)- and (2*R*,3*aR*,6*R*)-2-Hydroxymethyl-6-isopropyl-5,6-dimethyl-tetrahydro-imidazo[1,5-*b*]isoxazol-4-one **5b** and (-)-**5b**

5b was prepared as described for **5a** using **1** (851 mg, 5.00 mmol) and allyl alcohol (3.4 mL, 50.00 mmol). The reaction mixture was heated at 80 °C for 3.5 h. Purification by column chromatography (silica gel, ethyl acetate/ethanol - 90:10) gave **5b** (1.07 g, 4.69 mmol, 94%) as a pale yellow oil which solidified upon standing. An analytic sample crystallized from *t*-butyl methyl ether had a mp of 85.0-85.1 °C; R_f = 0.42 (ethyl acetate/ethanol - 80:20); ν_{\max} (KBr pellet): 3360, 2974, 2924, 2883, 1685, 1451, 1409, 1381, 1089, 1049 and 881; δ_{H} (400 MHz; CDCl₃; Me₄Si) 4.07 (br d, J 9.2, 1H), 4.04-4.00 (m, 1H), 3.78 (ddd, J 2.8, 5.2 and 12.0, 1H), 3.59 (ddd, J 2.0, 6.8 and 12.0, 1H), 2.80 (s, 3H), 2.63 (ddd, J 1.6, 6.4 and 12.4, 1H), 2.39 (ddd, J 7.2, 9.2 and 12.4, 1H), 2.20 (br t, J 6.0, 1H), 1.86 (hept, J 6.8, 1H), 1.48 (s, 3H), 1.04 (d, J 6.8, 3H), 0.83 (d, J 6.8, 3H); δ_{C} (100 MHz, CDCl₃) 172.4, 88.4, 77.3, 66.3, 63.7, 36.5, 33.9, 26.7, 17.8, 17.3, 17.1; MS (ES⁺): m/z 479 (2M + Na⁺, 42%), 251 (M + Na⁺, 100), 229 (M + H⁺, 54); HRMS: m/z 251.13580 (M + Na); C₁₁H₂₀N₂O₃Na: requires 251.13661.

(-)-**5b** (46 mg, 201 μ mol, 86%) was obtained starting from (*R*)-**1** (40 mg, 235 μ mol) and allyl alcohol (160 μ L, 2.35 mmol) as a pale yellow oil which solidified upon standing; mp 99.5-99.6 °C; $[\alpha]_{\text{D}}^{20}$ -32.7 (*c* 1.08 in CHCl₃); Anal. Found: C, 57.55; H, 9.00; N, 12.27; Calc. for C₁₁H₂₀N₂O₃: C, 57.87; H, 8.83; N, 12.27%. The enantiomeric purity of (-)-**5b** (\geq 91% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 x 100 mm, eluent water/acetonitrile - 60:40, 0.5 mL/min, retention time for (-)-**5b** 5.39 min and for (+)-**5b** 4.54 min.

(rac)-(2*R**,3*aR**,6*R**)-6-Isopropyl-5,6-dimethyl-2-phenyl-tetrahydro-imidazo[1,5-*b*]isoxazol-4-one **5c**

5c was prepared as described for **5a** using **1** (340 mg, 2.00 mmol) and styrene (2.3 mL, 20.00 mmol). The reaction mixture was heated at 80 °C for 3 h. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 70:30) gave **5c** (494 mg, 1.80 mmol, 90%) as a colourless oil; R_f = 0.48 (ethyl acetate); ν_{\max} (KBr pellet): 3084, 3067, 3028, 2974, 2939, 2885, 1696, 1452, 1404, 1082, 1049, 760, 700; δ_{H} (400 MHz; CDCl₃; Me₄Si) 7.38-7.30 (m, 5H), 4.73 (dd, J 5.0 and 10.6, 1H), 4.20 (br d, J 8.6, 1H), 2.95 (dd, J 5.0 and 12.2, 1H), 2.85 (s, 3H), 2.52 (ddd, J 8.6, 10.6 and 12.2, 1H), 1.92 (hept, J 6.8, 1H), 1.55 (s, 3H), 1.09 (d, J 6.8, 3H), 0.83 (d, J 6.8, 3H); δ_{C} (100 MHz, CDCl₃) 172.1, 137.8, 128.7, 128.4, 126.7, 89.3, 79.1, 67.6, 41.4, 36.3, 26.4, 18.6, 17.0, 16.8; MS (ES⁺): m/z 571 (2M + Na⁺, 57%), 297 (M + Na⁺, 100), 275 (M + H⁺, 54); HRMS: m/z 297.15803 (M + Na); C₁₆H₂₂N₂O₂Na requires 297.15735.

(rac)-(2*R**,3*aR**,6*R**)-2-Butoxy-6-isopropyl-5,6-dimethyl-tetrahydro-imidazo[1,5-*b*]isoxazol-4-one **5d**

5d was prepared as described for **5a** using **1** (340 mg, 2.00 mmol) and *n*-butyl vinyl ether (2.6 mL, 20.00 mmol). The reaction mixture was heated at 80 °C for 16 h. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 70:30) gave **5d** (476 mg, 1.76 mmol, 88%) as a colourless oil which solidified upon standing; mp 54.7-54.8 °C; R_f = 0.40 (ethyl acetate/cyclohexane - 70:30); ν_{\max} (KBr pellet): 2958, 2921, 2873, 1691, 1458, 1432, 1401, 1386; δ_{H} (400 MHz; CDCl₃; Me₄Si) 5.01 (dd, J 1.4 and 6.2, 1H), 4.06 (dd, J 2.8 and 9.6, 1H), 3.68 (td, J 6.8 and 10.0, 1H), 3.40 (td, J 6.8 and 10.0, 1H), 2.80 (s, 3H), 2.76 (ddd, J 2.8, 6.2 and 13.4, 1H), 2.46 (ddd, J 1.4, 9.6 and 13.4, 1H), 1.85 (hept, J 7.2, 1H), 1.56 (quint, J 6.8, 2H), 1.43 (s, 3H), 1.42-1.35 (m, 2H), 1.03 (d, J 7.2, 3H), 0.91 (d, J 7.2, 3H), 0.91 (t, J 7.4, 3H); δ_{C} (100 MHz, CDCl₃) 173.5, 99.8, 87.3, 67.6, 64.1, 39.0, 37.0, 31.8, 27.3, 19.4, 18.1, 17.3, 17.0, 13.9; MS (ES⁺): m/z 563 (2M + Na⁺, 68%), 293 (M + Na⁺, 100), 271 (M + H⁺, 30); Anal. Found: C, 62.36; H, 9.78; N, 10.40; Calc. for C₁₄H₂₆N₂O₃: C, 62.20; H, 6.70; N, 10.37%.

(rac)-(2*R**,3*aS**,6*R**)-6-Isopropyl-5,6-dimethyl-4-oxo-hexahydro-imidazo[1,5-*b*]isoxazole-2-carboxylic acid ethyl ester **5e**

5e was prepared as described for **5a** using **1** (340 mg, 2.00 mmol) and ethyl acrylate (2.2 mL, 20.00 mmol). The reaction mixture was heated at 80 °C for 4 h. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 70:30) gave **5e** (454 mg, 1.68 mmol, 84%) as a colourless oil; R_f = 0.42 (ethyl acetate); ν_{\max} (KBr pellet): 2973, 2918, 2883, 1740, 1686, 1459, 1399, 1378, 1088, 1049 and 881; δ_{H} (400 MHz; CDCl₃; Me₄Si) 4.33 (t, J 6.8, 1H), 4.24-4.10 (m, 2H), 4.04 (dd, J 1.8 and 9.2, 1H), 2.83 (ddd, J 1.8, 7.2 and 12.6, 1H), 2.78 (s, 3H), 2.74 (ddd, J 2.2, 9.2 and 12.6, 1H), 1.82 (qq, J 6.8 and 7.2, 1H), 1.47 (s, 3H), 1.26 (t, J 6.8, 3H), 1.01 (d, J 6.8, 3H), 0.82 (d, J 7.2, 3H); δ_{C} (100 MHz, CDCl₃) 172.1, 170.4, 88.2, 74.3, 65.3, 61.5, 36.7, 35.8, 26.9, 17.6, 17.5, 17.1, 14.2; MS (ES⁺): m/z 563 (2M + Na⁺, 16%), 293 (M + Na⁺, 100), 271 (M + H⁺, 21); HRMS: m/z 293.14783 (M +

Na); C₁₃H₂₂N₂O₄Na requires 293.14718.

(rac)- and (2S,3R,3aR,6R)-6-isopropyl-2,5,6-trimethyl-4-oxo-hexahydro-imidazo[1,5-b]isoxazole-3-carboxylic acid methyl ester 5f and (-)-5f

5f was prepared as described for **5a** using **1** (340 mg, 2.00 mmol) and *trans*-methyl crotonate (2.1 mL, 20.00 mmol). The reaction mixture was heated at 80 °C for 16 h. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 70:30) gave **5f** as a colourless oil (435 mg, 1.61 mmol, 80%); *R_f* = 0.41 (ethyl acetate); *v*_{max} (KBr pellet): 2971, 2934, 2885, 1743, 1697, 1437, 1403, 1374, 1086 and 1050; δ_H (400 MHz; CDCl₃; Me₄Si) 4.27 (d, *J* 9.2, 1H), 4.08 (qd, *J* 6.0 and 10.4, 1H), 3.78 (s, 3H), 3.20 (t, *J* 9.2, 1H), 2.75 (s, 3H), 1.86 (qq, *J* 6.4 and 6.8, 1H), 1.49 (s, 3H), 1.28 (d, *J* 6.0, 3H), 1.03 (d, *J* 6.4, 3H), 0.73 (d, *J* 6.8, 3H); δ_C (100 MHz, CDCl₃) 169.2, 168.9, 89.1, 74.9, 68.0, 56.1, 52.2, 36.1, 26.2, 18.5, 16.9, 16.6, 16.5; MS (ES⁺): *m/z* 563 (2M + Na⁺, 26%), 293 (M + Na⁺, 100), 271 (M + H⁺, 16); HRMS: *m/z* 293.14770 (M + Na); C₁₃H₂₂N₂O₄Na requires 293.14718.

(-)-**5f** (84 mg, 311 μmol, 80%) was obtained starting from (*R*)-**1** (66 mg, 388 μmol) and *trans*-methyl crotonate (411 μL, 3.88 mmol) as a colourless oil; [α]_D²⁰ -96.1 (*c* 1.00, CHCl₃).

The enantiomeric purity of (-)-**5f** (≥ 99% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 x 100 mm, eluent water/acetonitrile - 60:40, 0.5 mL/min, retention time for (+)-**5f** 8.21 min and for (-)-**5f** 7.47 min.

(rac)- and (1R,3aR,3bS,7aS)-1-Isopropyl-1,2-dimethyl-octahydro-8-oxa-2,8a-diaza-cyclopenta[a]inden-3-one 5g and (+)-5g

5g was prepared as described for **5a** using **1** (340 mg, 2.00 mmol), cyclohexene (2.0 mL, 20.00 mmol) and toluene (0.5 mL). The reaction mixture was heated at 80 °C for 48 h (90% conversion). Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 65:35) gave **5g** as a pale yellow oil (376 mg, 1.48 mmol, 74% yield); *R_f* = 0.29 (ethyl acetate/cyclohexane - 70:30); *v*_{max} (KBr pellet): 2973, 2939, 2883, 1685, 1449, 1406, 1084 and 1050; δ_H (400 MHz; CDCl₃; Me₄Si) 3.78-3.76 (m, 1H), 3.66 (br s, 1H), 2.75 (s, 3H), 2.63 (ddd, *J* 2.4, 6.4 and 12.0, 1H), 1.99-1.96 (m, 1H), 1.83 (qq, *J* 6.4 and 7.2, 1H), 1.80-1.76 (m, 1H), 1.70-1.66 (m, 1H), 1.55-1.41 (m, 4H), 1.46 (s, 3H), 1.24-1.13 (m, 1H), 1.04 (d, *J* 6.4, 3H), 0.74 (d, *J* 7.2, 3H); δ_C (100 MHz, CDCl₃) 172.1, 89.3, 74.8, 73.7, 45.1, 36.4, 27.3, 26.1, 25.5, 24.3, 19.8, 18.7, 17.1, 16.7; MS (ES⁺): *m/z* 527 (2M + Na⁺, 26%), 275 (M + Na⁺, 42), 253 (M + H⁺, 100); HRMS: *m/z* 275.17304 (M + Na); C₁₄H₂₄N₂O₂Na requires 275.17300.

(+)-**5g** (72 mg, 285 μmol, 65% yield) was obtained starting from (*R*)-**1** (75 mg, 441 μmol) and cyclohexene (447 μL, 4.41 mmol) as a pale yellow oil; [α]_D²⁰ +8.9 (*c* 1.04 in CHCl₃). The enantiomeric purity of (+)-**5g** (≥ 99% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 x 100 mm, eluent water/acetonitrile - 68:32, 0.5 mL/min, retention time for (-)-**5g** 19.30 min and for (+)-**5g** 17.70 min.

(rac)-(1R*,3aR*,3bS*,4S*,7R*,7aS*)-1-Isopropyl-1,2-dimethyl-octahydro-4,7-methano-8-oxa-2,8a-diaza-cyclopenta[a]inden-3-one 5h

5h was prepared as described for **5a** using **1** (170 mg, 1.00 mmol), 2-norbornene (113 mg, 1.20 mmol) and toluene (1 mL). The reaction mixture was heated at 80 °C for 16 h. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 65:35) gave **5h** as a white solid (238 mg, 900 μmol, 90%); mp 79.7-79.8 °C; *R_f* = 0.32 (ethyl acetate/cyclohexane - 65:35); *v*_{max} (KBr pellet): 2958, 2873, 2360, 2339 and 1685; δ_H (400 MHz; CDCl₃; Me₄Si) 3.99 (br d, *J* 6.8, 1H), 3.61 (d, *J* 2.4, 1H), 2.76 (s, 3H), 2.72-2.70 (m, 1H), 2.27-2.25 (m, 2H), 1.87-1.85 (m, 1H), 1.78 (hept, *J* 6.8, 1H), 1.47-1.42 (m, 2H), 1.39 (s, 3H), 1.18-1.13 (m, 1H), 1.10-1.07 (m, 1H), 1.01 (d, *J* 6.8, 3H), 0.99-0.94 (m, 1H), 0.83 (d, *J* 6.8, 3H); δ_C (100 MHz, CDCl₃) 171.8, 87.8, 86.0, 70.8, 55.8, 41.9, 41.0, 36.6, 33.0, 27.5, 26.7, 23.5, 17.8, 17.5, 17.1; MS (ES⁺): *m/z* 551 (2M + Na⁺, 42), 287 (M + Na⁺, 20), 265 (M + H⁺, 100); Anal. Found: C, 68.12; H, 9.25; N, 10.58; Calc. for C₁₅H₂₄N₂O₂: C, 68.15; H, 9.15; N, 10.60%.

(rac)-(3aR*,6R*)-6-isopropyl-5,6-dimethyl-2-phenyl-5,6-dihydro-3aH-imidazo[1,5-b]isoxazol-4-one 7

7 was prepared as described for **5a** using **1** (170 mg, 1.00 mmol), phenylacetylene (220 μL, 2.00 mmol) and toluene (1 mL). The reaction mixture was heated at 80 °C for 16 h. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 75:25) gave **7** as a beige solid (199 mg, 730 μmol, 73%); mp 146.8-146.9 °C; *R_f* = 0.33 (ethyl acetate); *v*_{max} (KBr pellet): 3089, 3067, 3037, 2963, 2937, 2898, 2872, 1702, 1451, 1422, 1391, 823 and 733; δ_H (400 MHz; CDCl₃; Me₄Si) 8.04 (dd, *J* 1.2 and 7.2, 2H), 7.61 (tt, *J* 1.2 and 7.2, 1H), 7.51 (t, *J* 7.2, 2H), 3.52 (d, *J* 5.2, 1H), 3.18 (d, *J* 5.2, 1H), 2.64 (s, 3H), 1.92 (qq, *J* 6.4 and 6.8, 1H), 1.16 (s, 3H), 1.10 (d, *J* 6.4, 3H), 0.90 (d, *J* 6.8, 3H); δ_C (100 MHz, CDCl₃) 194.2, 168.9, 137.8, 134.0, 129.0, 128.7, 84.1, 45.3, 42.3, 38.7, 26.0, 20.7, 16.4, 16.2; MS (ES⁺): *m/z* 567 (2M + Na⁺, 52%), 545 (2M + H⁺, 32), 295 (M + Na⁺, 100), 273 (M + H⁺, 65); Anal. Found: C, 70.17; H, 7.58; N, 10.29; Calc. for C₁₆H₂₀N₂O₂: C, 70.57; H, 7.41; N, 10.29%.

A monocyclic isomer **7'** with two possible tautomeric structures was isolated in 20% yield (yellow oil, 55 mg, 202 μmol); *R_f* = 0.52 (ethyl acetate); δ_H (400 MHz; CDCl₃; Me₄Si) 7.97 (d, *J* 6.8, 2H), 7.48-7.41 (m, 3H), 6.51 (s, 1H), 2.95 (s, 3H), 2.10 (qq, *J* 6.4 and 6.8, 1H), 1.54 (s, 3H), 1.10 (d, *J* 6.8, 3H), 0.67 (d, *J* 6.4, 3H); δ_C (100 MHz, CDCl₃) 191.2, 162.6, 150.4, 138.9, 131.8, 128.5, 127.5, 86.8, 80.6, 34.7, 25.0, 23.9, 17.1, 15.4; MS (ES⁺): *m/z* 567 (2M + Na⁺, 100%), 295 (M + Na⁺, 27), 273 (M + H⁺, 16).

(rac)-(2S*,5R*)-5-[(2R*)-2-hydroxy-2-phenylethyl]-2-isopropyl-2,3-dimethylimidazolidin-4-one 8c

In a 25-mL flask, zinc dust (657 mg, 10.06 mmol) was added in one portion to a solution of **5c** (138 mg, 0.503 mmol) in acetic acid (1.7 mL). The reaction was monitored by TLC (silica gel, ethyl acetate) and was completed within 3.5 h at room temperature. The reaction mixture was filtered and the solid was rinsed with dichloromethane. After concentration of the filtrate, the crude

product was purified by column chromatography (silica gel, ethyl acetate/cyclohexane - 80:20) to yield **8c** as a colourless oil (116 mg, 0.420 mmol, 83 %) which solidified upon standing; mp 84.8-84.9 °C; $R_f = 0.32$ (ethyl acetate/cyclohexane - 80:20); v_{\max} (KBr pellet): 3345, 3066, 3033, 2970, 2873, 1677, 1451, 1405, 764 and 702; δ_H (400 MHz; CDCl₃; Me₄Si) 7.41-7.39 (m, 2H), 7.35-7.31 (m, 2H), 7.26-7.22 (m, 1H), 4.95 (dd, J 2.8 and 8.8, 1H), 3.85 (dd, J 4.4 and 7.2, 1H), 2.83 (s, 3H), 2.10-1.94 (m, 3H), 1.42 (s, 3H), 1.00 (d, J 6.8, 3H), 0.83 (d, J 6.8, 3H); δ_C (100 MHz, CDCl₃) 174.1, 144.7, 128.4, 127.3, 125.7, 81.0, 72.6, 59.4, 42.8, 35.3, 26.4, 25.7, 16.9, 16.6; MS (ES⁺): m/z 575 (2M + Na⁺, 12%), 277 (M + H⁺, 100); Anal. Found: C, 69.54; H, 8.75; N, 10.25; Calc. for C₁₆H₂₄N₂O₂: C, 69.54; H, 8.76; N, 10.14%.

(rac)-(2R*)-2-hydroxy-3-[(2S*,4R*)-1,2-dimethyl-5-oxo-2-(propan-2-yl)imidazolidin-4-yl]-propanoic acid ethyl ester 8e

In an argon-flushed 25-mL two-necked flask was introduced Pd/C 10 % (Fluka, ref 75990, 67 mg), followed by 2 mL of methanol and then a solution of **5c** (114 mg, 422 μ mol) in methanol (2 mL). Ammonium formate (532 mg, 8.43 mmol) was added in one portion and the argon inlet was removed. The reaction was monitored by TLC (silica gel, ethyl acetate) and was completed within 75 min at room temperature. The reaction mixture was filtered over Celite and the solid was rinsed with dichloromethane. The filtrate was diluted with water (2.5 mL), the aqueous layer was separated and extracted with dichloromethane (5 mL). The gathered organic layers were dried over anhydrous Na₂SO₄ and filtered. After concentration under reduced pressure, purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 80:20) yielded amino alcohol **8e** (84 mg, 308 μ mol, 73 %) as a yellow oil; $R_f = 0.26$ (ethyl acetate); v_{\max} (film): 3445, 3348, 2973, 2937, 2880, 1739, 1682, 1473 and 755; δ_H (400 MHz; CDCl₃; Me₄Si) 4.39 (t, J 4.8, 1H), 4.24 (q, J 7.2, 2H), 3.78 (t, J 6.4, 1H), 2.78 (s, 3H), 2.10-2.07 (m, 2H), 1.96 (hept, J 6.8, 1H), 1.40 (s, 3H), 1.29 (t, J 7.2, 3H), 0.99 (d, J 6.8, 3H), 0.80 (d, J 6.8, 3H); δ_C (100 MHz, CDCl₃) 174.2, 173.4, 80.9, 69.5, 61.6, 57.8, 37.1, 35.1, 26.4, 25.5, 16.8, 16.4, 14.3; MS (ES⁺): m/z 567 (2M + Na⁺, 5%), 295 (M + Na⁺, 29), 273 (M + H⁺, 100); HRMS: m/z 295.16307 (M + Na); C₁₃H₂₄N₂O₄Na requires 295.16338.

(rac)- and (2S,3R)-3-Hydroxy-2-((2S,4R)-2-isopropyl-1,2-dimethyl-5-oxo-imidazolidin-4-yl)-butyric acid methyl ester 8f and (+)-8f

8f was prepared as described for **8e** using **5f** (83 mg, 307 μ mol). Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 80:20 to 100:0) yielded amino alcohol **8f** (57 mg, 0.209 mmol, 68%) as a colourless oil which solidified upon standing; mp 72.3-72.4 °C; $R_f = 0.21$ (ethyl acetate/cyclohexane - 80:20); v_{\max} (KBr pellet): 3373, 2974, 2927, 2883, 1719, 1677, 1438, 1407, 1378, 1088 and 1050; δ_H (400 MHz; CDCl₃; Me₄Si) 4.24 (quint, J 6.4, 1H), 4.04 (d, J 6.4, 1H), 3.70 (s, 3H), 2.82-2.76 (m, 1H), 2.80 (s, 3H), 1.97 (hept, J 6.8, 1H), 1.34 (s, 3H), 1.23 (d, J 6.4, 3H), 0.96 (d, J 6.8, 3H), 0.81 (d, J 6.8, 3H); δ_C (100 MHz, CDCl₃) 172.9, 172.7, 80.9, 67.2, 59.3, 56.2, 51.7, 35.2, 26.2, 25.5, 21.3, 16.8, 16.4; MS (ES⁺): m/z 567 (2M + Na⁺, 5%), 295 (M + Na⁺, 10), 273 (M + H⁺, 100); HRMS: m/z 273.18081 (M + H); C₁₃H₂₅N₂O₄ requires 273.18088.

(+)-**8f** (49 mg, 180 μ mol, 67%) was obtained starting from (-)-**5f** (73 mg, 270 μ mol) as a colourless oil which solidified on standing; mp 89.3-89.4 °C; $[\alpha]_D^{20} +47.1$ (c 1.06, CHCl₃); Anal. Found: C, 57.59; H, 8.90; N, 10.12; Calc. for C₁₃H₂₄N₂O₄: C, 57.33; H, 8.88; N, 10.29%.

(rac)-1-Hydroxy-2-isopropyl-2,3-dimethyl-imidazolidin-4-one 9

In a 100-mL flask under an argon atmosphere, nitron **1** (3.40 g, 20.00 mmol) was dissolved in anhydrous THF (40 mL). Sodium borohydride (1.51 g, 40.00 mmol) was added in one portion. The reaction mixture was stirred for 2.5 h at room temperature and was then treated with H₂O (2.9 mL, 160.00 mmol). The reaction mixture was stirred until the end of dihydrogen evolution (15 min) and then the solvent was removed under reduced pressure. The crude product was taken up in ethyl acetate (50 mL), the organic layer was separated from the aqueous one, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum to yield pure **9** (3.44 g, 20.00 mmol, quantitative yield) as a pale yellow oil; $R_f = 0.32$ (ethyl acetate); v_{\max} (film): 3352, 2970, 2937, 2881, 2838, 1682, 1435 and 1405; δ_H (400 MHz; CDCl₃; Me₄Si) 5.78 (s, 1H), 3.79 (d, J 16.0, 1H), 3.57 (d, J 16.0, 1H), 2.77 (s, 3H), 1.86 (hept, J 6.8, 1H), 1.38 (s, 3H), 1.01 (d, J 6.8, 3H), 0.84 (d, J 6.8, 3H); δ_C (100 MHz, CDCl₃) 170.1, 88.3, 59.8, 35.3, 26.1, 17.5, 17.2, 15.8; MS (ES⁺): m/z 367 (2M + Na⁺, 58%), 195 (M + Na⁺, 100), 173 (M + H⁺, 37); HRMS: m/z 195.11024 (M + Na); C₈H₁₆N₂O₂Na requires 195.11040.

(S)-2-Methoxycarbonylamino-3-phenyl-propionic acid (R)-2-isopropyl-2,3-dimethyl-4-oxo-imidazolidin-1-yl-ester 10a

Moc-Phe-OH (11.41 g, 51.11 mmol, 87%) was prepared from L-phenylalanine (9.69 g, 58.66 mmol) according to ref. 23.

In a 100-mL flask, *N*-(methoxycarbonyl)-L-phenylalanine (1.34 g, 6.00 mmol) was dissolved in dichloromethane (10 mL) and solid 1,3-dicyclohexylcarbodiimide (1.24 g, 6.00 mmol) was added. A solution of hydroxylamine **9** (861 mg, 5.00 mmol) in dichloromethane (10 mL) was added rapidly at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, then the urea was precipitated by addition of diethylether (20 mL) and filtered off. The filtrate was stirred for 5 minutes with a 1M aqueous solution of HCl (20 mL); the aqueous phase was separated and extracted twice with diethylether (50 mL). The gathered organic layers were washed with a saturated aqueous solution of NaHCO₃ (100 mL), then with brine (100 mL), dried over anhydrous Na₂SO₄ and filtered. After removal of the solvents under reduced pressure, more urea was precipitated in diethylether and filtered off. Concentration of the filtrate under vacuum yielded the 1:1 mixture of diastereoisomers **10** as a white foam (1.55 g, 4.10 mmol). Separation by medium pressure liquid chromatography (silica gel, diethylether/dichloromethane - 10:90 to 100:0 in 15 min, 15 mL.min⁻¹) yielded the diastereoisomer **10a** (300 mg, 0.795 mmol, 32%) as a white solid; mp 121.3-121.4 °C; $[\alpha]_D^{20} +21.2$ (c 0.98

in CHCl₃); R_f = 0.38 (dichloromethane/*t*-butyl methyl ether - 70:30); v_{\max} (KBr pellet): 3326, 3020, 2963, 2933, 2920, 1776, 1701, 1686, 1540, 1125, 751 and 710; δ_H (400 MHz; CDCl₃; Me₄Si) 7.32-7.27 (m, 3H), 7.17 (d, J 6.4, 2H), 5.22 (br d, J 6.4, 1H), 4.52-4.47 (m, 1H), 3.82 (d, J 17.2, 1H), 3.67 (s, 3H), 3.07 (dd, J 6.8 and 13.6, 1H), 3.01 (d, J 17.2, 1H), 2.98 (dd, J 8.0 and 13.6, 1H), 2.79 (s, 3H), 1.85 (hept, J 6.8, 1H), 1.30 (s, 3H), 0.99 (d, J 6.8, 3H), 0.91 (d, J 6.8, 3H); δ_C (100 MHz, CDCl₃) 170.4, 169.5, 156.3, 135.3, 129.4, 129.0, 127.6, 89.5, 58.7, 54.1, 52.6, 38.7, 36.1, 26.6, 17.5, 17.2, 16.4; MS (ES⁺): m/z 777 (2M + Na⁺, 14%), 400 (M + Na⁺, 100), 378 (M + H⁺, 11), 177 (M + Na - Moc-Phe-OH⁺, 39), 155 (M + H - Moc-Phe-OH⁺, 84); Anal. Found: C, 60.67; H, 7.12; N, 11.15; Calc. for C₁₉H₂₇N₃O₅: C, 60.47; H, 7.21; N, 11.14%.

The relative configuration of **10a** was determined by X-ray crystallography of an analytical sample recrystallized in ethanol.

(*R*)-2-Isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one (*R*)-1

In a 50-mL flask, **10a** (394 mg, 1.04 mmol) was dissolved in methanol (15 mL). NaHCO₃ (877 mg, 10.44 mmol) was added, followed by a 35% aqueous solution of hydrogen peroxide (1.01g, 10.44 mmol). The reaction was monitored by TLC (ethyl acetate); hydrolysis of the ester bond was completed within 4 h at room temperature. MnO₂ (Fluka, ref 63548, 600 mg) was then added portionwise, both to destroy the excess of hydrogen peroxide and complete the oxydation of the intermediate hydroxylamine. The reaction mixture was stirred for 15 min at room temperature and was then filtered over Celite. The solid was rinsed with ethyl acetate and the solvents were removed under vacuum. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane - 70:30), followed by recrystallization from ethyl acetate/cyclohexane (1.0 mL/0.7 mL) yielded the nitrone (*R*)-**1** as a beige solid (124 mg, 729.5 μ mol, 70%); $[\alpha]_D^{20}$ -28.5 (c 3.96 in CHCl₃). The enantiomeric purity of (-)-(*R*)-**1** (\geq 99% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 x 100 mm, eluent acetonitrile/water - 70:30, 0.5 mL/min, retention time for (*R*)-**1** 6.96 min and for (*S*)-**1** 5.94 min.

(*rac*)- and (3*R*,3*aS*,7*aS*)-(2-Oxo-octahydro-benzofuran-3-yl)-carbamic acid *tert*-butyl ester **11** and (-)-**11**

In a 10-mL microwave vial were introduced isoxazolidine **5g** (85 mg, 337 μ mol), glacial acetic acid (2 mL), a 3N aqueous solution of HCl (2 mL) and Pd/C 10% (Fluka, ref 15990, 20 mg). The vial was brought into the microwave reactor, evacuated, filled up with H₂ and the reaction mixture was stirred under H₂ pressure (7 bar) for 15 min at 150 °C. After filtration through Celite, the solids were rinsed with acetic acid and concentration under vacuum yielded the acetate salt of the lactone.

The crude salt was dissolved in methanol (3 mL) and added to a mixture of triethylamine (0.12 mL, 842 μ mol) and methanol (1 mL), followed by di-*t*-butyldicarbonate (147 mg, 674 μ mol). The reaction mixture was stirred for 4.5 h at 45 °C, then concentrated under reduced pressure. Purification by column chromatography (silica gel, dichloromethane/*t*-butyl methyl ether - 98:2) yielded *N*-Boc lactone **11** (35 mg, 137 μ mol, 42%) as a colourless oil which solidified upon standing; mp 95.6-95.7 °C; R_f = 0.26 (dichloromethane/*t*-butyl methyl ether - 97:3); v_{\max} (KBr pellet): 3328, 2994, 2975, 2937, 2663, 1787, 1684, 1527, 1164 and 967; δ_H (400 MHz; CDCl₃; Me₄Si) 5.00 (br s, 1H), 4.54-4.50 (m, 2H), 2.73-2.68 (m, 1H), 2.26-2.23 (m, 1H), 1.76-1.54 (m, 4H), 1.45 (s, 9H), 1.41-1.29 (m, 1H), 1.19 (qt, J 2.8 and 13.2, 1H), 0.91 (dq, J 3.2 and 13.2, 1H); δ_C (100 MHz, CDCl₃) 175.8, 155.6, 80.4, 76.8, 57.3, 39.4, 28.4, 27.4, 22.8, 22.0, 19.7; MS (ES⁺): m/z 533 (2M + Na⁺, 47%), 278 (M + Na⁺, 100); Anal. Found: C, 60.94; H, 8.47; N, 5.21; Calc. for C₁₃H₂₁NO₄: C, 61.16; H, 8.29; N, 5.49%.

(-)-**11** (26 mg, 102 μ mol, 42%) was obtained starting from (+)-**5g** (62 mg, 243 μ mol) as a pale yellow oil which solidified upon standing; mp 112.4-112.6 °C; $[\alpha]_D^{20}$ -78.1 (c 1.04 in CHCl₃).

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Notes and references

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† Electronic Supplementary Information (ESI) available: copies of ¹H and ¹³C NMR spectra for all new compounds, NOESY spectra for **5f** and **5h**, description of the microwave irradiation parameters, ORTEP drawings of **1** and **10a**. See DOI: 10.1039/b000000x/

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- 19 Crystal data for **10a** (C₁₉H₂₇N₃O₅, enantiopure sample). *M*: 377.44 g.mol⁻¹; crystal system: monoclinic; unit-cell dimensions and volume: a = 10.080(3) Å, b = 9.129(4) Å, c = 11.610(3) Å, β = 112.49(3)°, V = 987.2(6) Å³, temperature of measurement: 293.0 K; space group symbol: P 2₁; No. of formula units in the unit cell Z = 2; No. of measured and independent reflections: 2273 and 2174, *R*_{int}: 0.07; refinement vs. F; final *R* values (observed data): *R* = 0.0531, *wR* = 0.0921. The relative stereochemistry (*R*) at C5 was attributed knowing the (*S*) configuration at C11 from the starting material Moc-Phe-OH.
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