

MiPNO, a new chiral cyclic nitronne for enantioselective amino acid synthesis: the cycloaddition approach†

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The resolution of chiral nitrones *via* derivatization of hydroxylamines was applied to MiPNO, a new, stable, easily prepared chiral cyclic nitronne. 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 -amino acids.

Introduction

The regio- and diastereo-selective 1,3-dipolar cycloaddition reaction of chiral nitrones with dipolarophiles is a powerful tool for obtaining chiral nitrogenated compounds.¹ In particular, when α -alkoxycarbonyl or α -alkylaminocarbonyl nitrones are used, 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 nitronne double bond is important.³ Small-ring endocyclic chiral nitrones are thus good candidates and their more rigid cyclic skeleton compared to acyclic nitrones is another asset in obtaining high stereoselectivity. Several five-⁴ and six-⁵membered chiral cyclic nitrones of this type have been previously designed.⁶

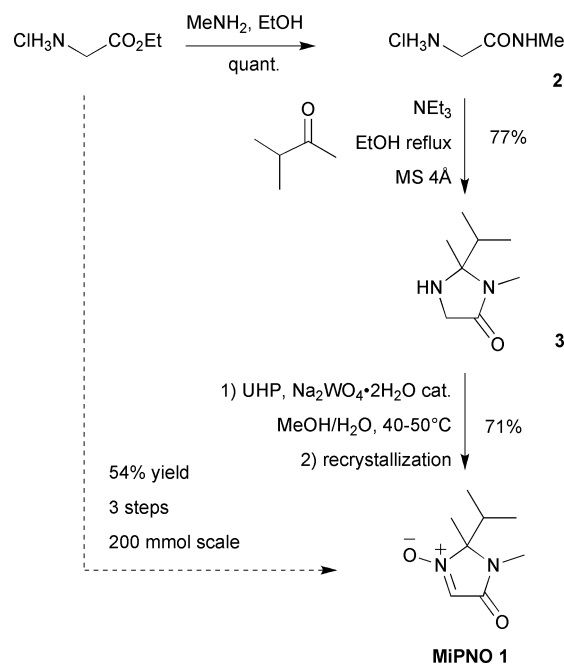
In parallel to our work in the field of *N*-hydroxy peptide synthesis and application,⁷ we sought access to *N*-hydroxy amino acids *via* the addition of functionalized organometallic reagents⁸ on to properly designed enantiopure nitrones. To this end, we designed a series of chiral nitrones^{4d,e} obtained by oxidation of imidazolidinones and based on the self-regeneration of stereocenters principle.⁹ In our continuing efforts to provide storable reagents and intermediates using inexpensive starting materials and scalable syntheses,¹⁰ we developed the new chiral nitronne **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

Nitronne **1** was conveniently prepared in three steps according to Scheme 1, starting from glycine ethyl ester hydrochloride.

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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**. CCDC reference numbers 747517 and 747518. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b918612c

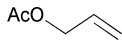
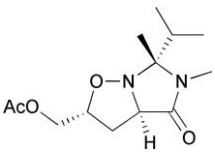
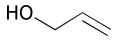
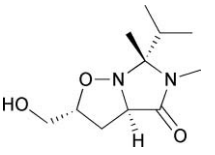
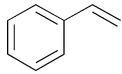
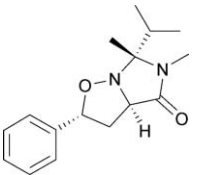
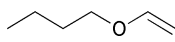
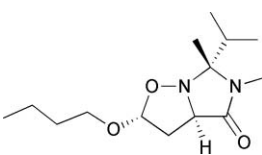
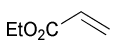
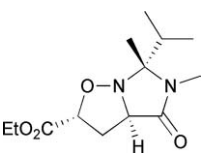
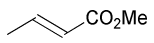
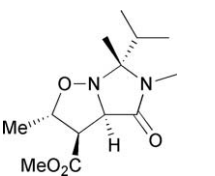

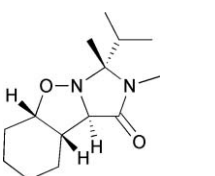

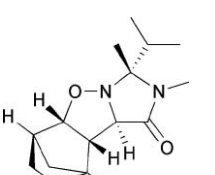
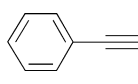
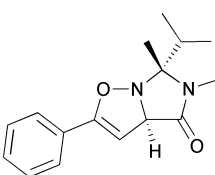


Scheme 1 Preparation of MiPNO **1**.

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 mmole scale. After recrystallization the yield of **1**, over three steps, was typically 54%. Nitronne **1** could be stored at room temperature for months without noticeable degradation.

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, nitronne **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 nitronne 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 the case of the acetal **5d** (Table 1, entry 4). Nevertheless,

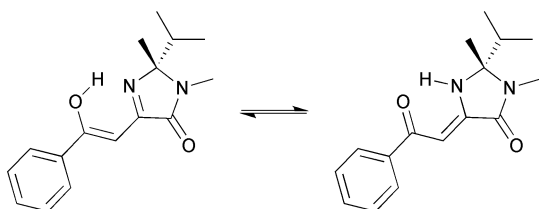
Table 1 1,3-Dipolar cycloaddition of racemic nitron 1 to alkenes **4a–h** and alkyne **6**

Entry	Dipolarophile 4 or 6	Cycloadduct ^a	Yield (%) ^b
1		4a 	5a 87 (94) ^c
2		4b 	5b 94 (86) ^c
3		4c 	5c 90
4		4d 	5d 88 ^d
5		4e 	5e 84
6		4f 	5f 80 (80) ^c
7		4g 	5g 74 ^e (65) ^{c,e}
8		4h 	5h 90 ^f
9		6 	7 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: 48 h, 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.

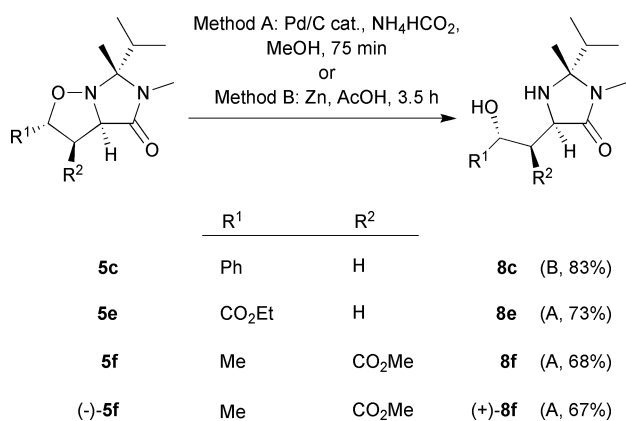
after chromatographic purification all compounds were isolated as pure cycloadducts in excellent yield.

Alkyne dipolarophiles are seldom reported in the reaction with nitrones^{1a} and the cycloadducts are prone to rearrangement.^{5c} In our hands, no reaction occurred between nitron **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).



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.

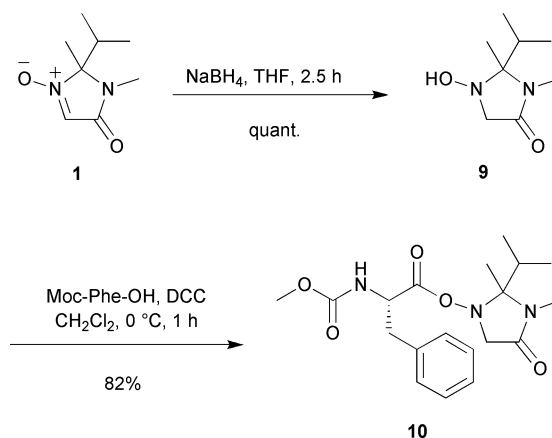


Scheme 3 Reductive cleavage of the N–O bond.

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 amounts (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.

Unfortunately, the *O*-acylated hydroxylamine proved to be very sensitive to silica gel and partially decomposed into Moc-Phe-OH



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

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** (Fig. 1),¹⁹ the stereochemistry of the imidazolidinone moiety is (*R*).

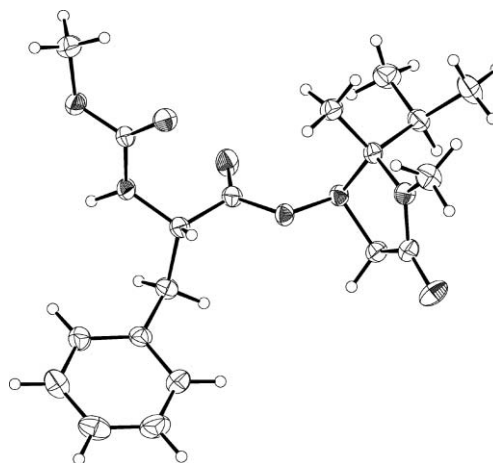
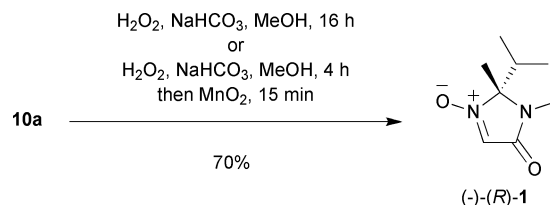


Fig. 1 ORTEP drawing of **10a**. The ellipsoids are plotted at the 25% probability level.

Treatment of **10a** with basic aqueous hydrogen peroxide overnight allowed the one-pot liberation of the hydroxylamine and its oxidation into the nitron (–)-(*R*)-**1**. More efficiently, MnO₂ may be added as soon as the first step is completed in order to accelerate the process (Scheme 5).

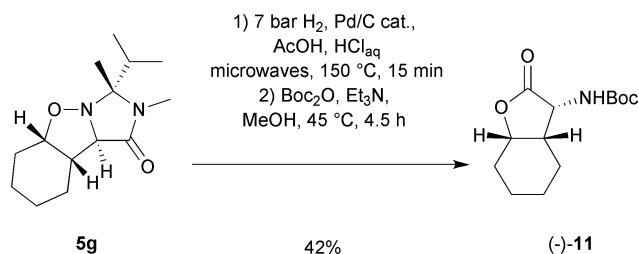


Scheme 5 Resolution of MiPNO: one-pot removal of resolving agent and oxidation.

The enantiomeric excess of (–)-**1** was above 99% as determined by chiral HPLC analysis. The nitron (–)-**1** proved to be

configurationally stable when purified by chromatography on silica gel^{4c} or when heated in toluene at 80 °C for 16 h.

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 hydrolytic 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 nitron 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, ninhydrin 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 per 100 cm³. 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 (LRMS) 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 LCOSEB, 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 magnetic 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 16 h 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 4 Å 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; Me₃Si) 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 nitron **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); *v*_{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); *v*_{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 μmol, 94%) was obtained starting from (*R*)-**1** (40 mg, 235 μmol) and allyl acetate (254 μL, 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** (≥97% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 × 100 mm, eluent water–acetonitrile 60:40, 0.5 mL min^{–1}, 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); *v*_{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 μmol, 86%) was obtained starting from (*R*)-**1** (40 mg, 235 μmol) and allyl alcohol (160 μL, 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** (≥91% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 × 100 mm, eluent water–acetonitrile 60:40, 0.5 mL min^{–1}, 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); *v*_{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); *v*_{max} (KBr pellet): 2958, 2921, 2873, 1691,

1458, 1432, 1401, 1386; δ_{H} (400 MHz; CDCl_3 ; Me_4Si) 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, CDCl_3) 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 ($2\text{M} + \text{Na}^+$, 68%), 293 ($\text{M} + \text{Na}^+$, 100), 271 ($\text{M} + \text{H}^+$, 30); Anal. Found: C, 62.36; H, 9.78; N, 10.40; Calc. for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$: C, 62.20; H, 6.70; N, 10.37%.

(rac)-(2R*,3aS*,6R*)-6-Isopropyl-5,6-dimethyl-4-oxo-hexahydroimidazo[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); v_{max} (KBr pellet): 2973, 2918, 2883, 1740, 1686, 1459, 1399, 1378, 1088, 1049 and 881; δ_{H} (400 MHz; CDCl_3 ; Me_4Si) 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, CDCl_3) 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 ($2\text{M} + \text{Na}^+$, 16%), 293 ($\text{M} + \text{Na}^+$, 100), 271 ($\text{M} + \text{H}^+$, 21); HRMS: m/z 293.14783 ($\text{M} + \text{Na}$); $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ requires 293.14718.

(rac)- and (2S,3R,3aR,6R)-6-Isopropyl-2,5,6-trimethyl-4-oxo-hexahydroimidazo[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; CDCl_3 ; Me_4Si) 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, CDCl_3) 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 ($2\text{M} + \text{Na}^+$, 26%), 293 ($\text{M} + \text{Na}^+$, 100), 271 ($\text{M} + \text{H}^+$, 16); HRMS: m/z 293.14770 ($\text{M} + \text{Na}$); $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ 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; $[\alpha]_{\text{D}}^{20}$ -96.1 (c 1.00, CHCl_3).

The enantiomeric purity of (-)-**5f** ($\geq 99\%$ ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 \times 100 mm, eluent water–acetonitrile 60 : 40, 0.5 mL min^{-1} , 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; CDCl_3 ; Me_4Si) 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, CDCl_3) 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 ($2\text{M} + \text{Na}^+$, 26%), 275 ($\text{M} + \text{Na}^+$, 42), 253 ($\text{M} + \text{H}^+$, 100); HRMS: m/z 275.17304 ($\text{M} + \text{Na}$); $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}$ 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; $[\alpha]_{\text{D}}^{20}$ +8.9 (c 1.04 in CHCl_3). The enantiomeric purity of (+)-**5g** ($\geq 99\%$ ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 \times 100 mm, eluent water–acetonitrile 68 : 32, 0.5 mL min^{-1} , 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; CDCl_3 ; Me_4Si) 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, CDCl_3) 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 ($2\text{M} + \text{Na}^+$, 42), 287 ($\text{M} + \text{Na}^+$, 20), 265 ($\text{M} + \text{H}^+$, 100). Anal. Found: C, 68.12; H, 9.25; N, 10.58; Calc. for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2$: 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; CDCl_3 ; Me_4Si) 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, CDCl_3) 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 $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2$: 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; CDCl_3 ; 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, CDCl_3) 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); ν_{max} (KBr pellet): 3345, 3066, 3033, 2970, 2873, 1677, 1451, 1405, 764 and 702; δ_{H} (400 MHz; CDCl_3 ; 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, 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, CDCl_3) 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 $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2$: 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 μmol) 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 Na_2SO_4 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 μmol , 73%) as a yellow oil; *R*_f 0.26 (ethyl acetate); ν_{max} (film): 3445, 3348, 2973, 2937, 2880, 1739, 1682, 1473 and 755; δ_{H} (400 MHz; CDCl_3 ; 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, CDCl_3) 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); $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$ 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 μmol). 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); ν_{max} (KBr pellet): 3373, 2974, 2927, 2883, 1719, 1677, 1438, 1407, 1378, 1088 and 1050; δ_{H} (400 MHz; CDCl_3 ; 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, CDCl_3) 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); $\text{C}_{13}\text{H}_{25}\text{N}_2\text{O}_4$ requires 273.18088.

(+)-**8f** (49 mg, 180 μmol , 67%) was obtained starting from (–)-**5f** (73 mg, 270 μmol) as a colourless oil which solidified upon standing; mp 89.3–89.4 °C; $[\alpha]_{\text{D}}^{20} +47.1$ (*c* 1.06, CHCl_3). Anal. Found: C, 57.59; H, 8.90; N, 10.12; Calc. for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_4$: 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 H_2O (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 Na_2SO_4 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); ν_{max} (film): 3352, 2970, 2937, 2881, 2838, 1682, 1435 and 1405; δ_{H} (400 MHz; CDCl_3 ; 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, CDCl_3) 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); $\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2\text{Na}$ 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 diethyl ether (20 mL) and filtered off. The filtrate was stirred for 5 min with a 1 M aqueous solution of HCl (20 mL); the aqueous phase was separated and extracted twice with diethyl ether (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 diethyl ether 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, diethyl ether–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; [α]_D²⁰ +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 (1.01 g, 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 oxidation 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 nitron (*R*)-**1** as a beige solid (124 mg, 729.5 μmol, 70%); [α]_D²⁰ –28.5 (*c* 3.96 in CHCl₃). The enantiomeric purity of (–)-(*R*)-**1** (≥99% ee) was determined by chiral HPLC on a Daicel Chiralpak AD-RH column, 4.6 × 100 mm, eluent acetonitrile–water 70 : 30, 0.5 mL min⁻¹, 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 μmol), glacial acetic acid (2 mL), a 3 N 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 μmol) and methanol (1 mL), followed by di-*t*-butyl dicarbonate (147 mg, 674 μmol). 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 μmol, 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, 967 cm⁻¹; 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 μmol, 42%) was obtained starting from (+)-**5g** (62 mg, 243 μmol) as a pale yellow oil which solidified upon standing; mp 112.4–112.6 °C; [α]_D²⁰ –78.1 (*c* 1.04 in CHCl₃).

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Notes and references

- See for instance: (a) I. A. Grigor'ev, in *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, 2nd edn, ed. H. Feuer, Wiley-Interscience, 2008, pp. 129–434; (b) a recent review on asymmetric 1,3-dipolar cycloadditions: H. Pellissier, *Tetrahedron*, 2007, **63**, 3235–3285.
- Recent examples: (a) L. Manzoni, D. Arosio, L. Belvisi, A. Bracci, M. Colombo, D. Invernizzi and C. Scolastico, *J. Org. Chem.*, 2005, **70**, 4124–4132; (b) O. Tamura, T. Shiro, M. Ogasawara, A. Toyao and H. Ishibashi, *J. Org. Chem.*, 2005, **70**, 4569–4577; (c) G. Romeo, D. Iannazzo, A. Piperno, R. Romeo, A. Corsaro, A. Rescifina and U. Chiacchio, *Mini-Rev. Org. Chem.*, 2005, **2**, 59–77; (d) F. M. Cordero, S. Bonollo, F. Machetti and A. Brandi, *Eur. J. Org. Chem.*, 2006, 3235–3241; (e) K. Aouadi, E. Jeanneau, M. Msaddek and J.-P. Praly, *Tetrahedron: Asymmetry*, 2008, **19**, 1145–1152; (f) T. B. Nguyen, T. M. H. Vuong, A. Martel, R. Dhal and G. Dujardin, *Tetrahedron: Asymmetry*, 2008, **19**, 2084–2087.
- See in particular the discussion in: O. Tamura, N. Mita, Y. Imai, T. Nishimura, T. Kiyotani, M. Yamasaki, M. Shiro, N. Morita, I. Okamoto, T. Takeya, H. Ishibashi and M. Sakamoto, *Tetrahedron*, 2006, **62**, 12227–12236.
- (a) N. Katagiri, M. Okada, C. Kaneko and T. Furuya, *Tetrahedron Lett.*, 1996, **37**, 1801–1804; (b) B. Westermann, A. Walter, U. Florke and H.-J. Altenbach, *Org. Lett.*, 2001, **3**, 1375–1378; (c) S. W. Baldwin

- and A. Long, *Org. Lett.*, 2004, **6**, 1653–1656; (d) F. Cantagrel, S. Pinet, Y. Gimbert and P. Y. Chavant, *Eur. J. Org. Chem.*, 2005, 2694–2701; (e) A. Pernet-Poil-Chevrier, F. Cantagrel, K. Le Jeune, C. Philouze and P. Y. Chavant, *Tetrahedron: Asymmetry*, 2006, **17**, 1969–1974.
- 5 (a) O. Tamura, K. Gotanda, R. Terashima, M. Kikuchi, T. Miyawaki and M. Sakamoto, *Chem. Commun.*, 1996, 1861–1862; (b) S. W. Baldwin, B. G. Young and A. T. McPhail, *Tetrahedron Lett.*, 1998, **39**, 6819–6822; (c) F. Heaney, J. Fenlon, O. M. C. P. McArdle and D. Cunningham, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3382–3392; (d) P.-F. Wang, P. Gao and P.-F. Xu, *Synlett*, 2006, 1095–1099.
- 6 For other enantiopure cyclic nitrones see the review: J. Revuelta, S. Cicchi, A. Goti and A. Brandi, *Synthesis*, 2007, 485–504.
- 7 (a) P. Maire, V. Blandin, M. Lopez and Y. Vallée, *Synlett*, 2003, 671–674; (b) J. Lawrence, L. Cointeaux, P. Maire, Y. Vallée and V. Blandin, *Org. Biomol. Chem.*, 2006, **4**, 3125–3141; (c) J. Lawrence, M. Jourdan, Y. Vallée and V. Blandin, *Org. Biomol. Chem.*, 2008, **6**, 4575–4581.
- 8 (a) S. U. Pandya, C. Garcon, P. Y. Chavant, S. Py and Y. Vallée, *Chem. Commun.*, 2001, 1806–1807; (b) S. Pinet, S. U. Pandya, P. Y. Chavant, A. Ayling and Y. Vallée, *Org. Lett.*, 2002, **4**, 1463–1466; (c) S. U. Pandya, S. Pinet, P. Y. Chavant and Y. Vallée, *Eur. J. Org. Chem.*, 2003, 3621–3627.
- 9 See for instance the review: D. Seebach, A. R. Sting and M. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2708–2748.
- 10 (a) N. PraveenGanesh, S. d'Hondt and P. Y. Chavant, *J. Org. Chem.*, 2007, **72**, 4510–4514; (b) N. PraveenGanesh and P. Y. Chavant, *Eur. J. Org. Chem.*, 2008, 4690–4696.
- 11 E. Marcantoni, M. Petrini and O. Polimanti, *Tetrahedron Lett.*, 1995, **36**, 3561–3562.
- 12 Crystal data for **1** (C₈H₁₄N₂O₂, racemic sample). *M*: 170.21 g mol⁻¹; crystal system: triclinic; unit-cell dimensions and volume: *a* = 6.900(2) Å, *b* = 7.365(2) Å, *c* = 11.610(3) Å, α = 83.78(2)°, β = 86.06(2)°, γ = 84.78(2)°, *V* = 442.9(5) Å³, temperature of measurement: 293.0 K; space group symbol: *P* $\bar{1}$; no. of formula units in the unit cell *Z* = 2; no. of measured and independent reflections: 9127 and 2392, *R*_{int}: 0.09; refinement vs. *F*; final *R* values (observed data): *R* = 0.0533, *wR* = 0.0867. For the ORTEP drawing of **1**, see ESI†.
- 13 The reaction between MiPNO and cyclohexene, sluggish in toluene, was also performed in a polar solvent, NMP, without any improvement: 48 h, 64% conversion.
- 14 The stereochemistry of the cycloadducts was assigned on the basis of their NOESY spectra.
- 15 Such a ring opening was previously reported: A. Padwa, M. Meske and Z. Ni, *Tetrahedron Lett.*, 1993, **34**, 5047–5050.
- 16 Attempted NOESY experiments were not conclusive enough to allow determination of the relative configuration of the minor isomer.
- 17 O. N. Burchak, C. Philouze, P. Y. Chavant and S. Py, *Org. Lett.*, 2008, **10**, 3021–3023.
- 18 Moc-Phe-OH (*N*-methoxycarbonyl-L-phenylalanine): (*S*)-2-methoxycarbonylamino-3-phenylpropanoic acid.
- 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.
- 20 Note that this step produces only volatile side products (3-methylbutanone and methylamine).
- 21 For related compounds, see: (a) B. Merla, H.-J. Grumbach and N. Risch, *Synthesis*, 1998, 1609–1614; (b) W. Notz, S.-i. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka and C. F. Barbas III, *Adv. Synth. Catal.*, 2004, **346**, 1131–1140.
- 22 R. Fitzzi and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 345–346.
- 23 M. W. Liladhar, J. J. McKenna, A. Bach, M. Prashad, O. Repic and T. J. Blacklock, *Synth. Commun.*, 2007, **37**, 1445–1454.