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Inexpensive, multigram-scale preparation of an enantiopure cyclic nitrone via resolution at the hydroxylamine stage

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ABSTRACT

The reduction of the chiral, racemic nitrone MiPNO provides a secondary hydroxylamine. Its O-acylation with *O,O'*-dibenzoyl-L-tartaric acid anhydride gives two diastereomers, that can be easily separated by selective dissolution in orthogonal solvents. The recovery of the enantiopure nitrone is then carried out in a single step. The process allows the straightforward isolation of (*R*) and (*S*)-MiPNO in 57% and 38% yield, respectively, from *rac*-MiPNO.

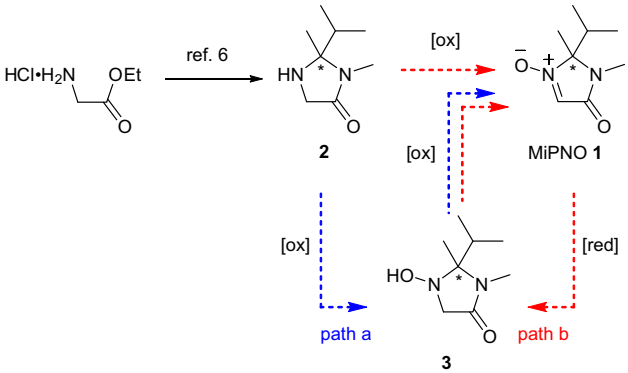
1. Introduction

Enantiopure cyclic aldonitrones are generally derived from the chiral pool, especially sugars.[1] Their preparation, with varying degrees of success, via resolution of the corresponding cyclic secondary amine,[2] or via a kinetic resolution step at the hydroxylamine[3] or the nitrone[4] stage has also been reported in the literature.[5] We are currently developing the applications of the chiral cyclic aldonitrone **1** (2-isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one, aka MiPNO,[6] Scheme 1), which exhibits a high degree of facial differentiation in cycloaddition[6] and nucleophilic addition[7] reactions. We therefore needed an efficient, multigram-scale preparation of enantiopure MiPNO. The following requirements were set: efficient recovery of both enantiomers, inexpensive reagents, no chromatographic separation, and easy handling of solid compounds. Herein, we report our investigation, which led to resolution at the hydroxylamine stage via the formation of covalent diastereomers. This case turned out to be a rare example of diastereomer separation by selective dissolution.

2. Results and discussion

2.1. Preparation of hydroxylamine 3

The preparation of racemic MiPNO **1** (Scheme 1) started from glycine ethyl ester hydrochloride. The previously described[6] pathway to the intermediate imidazolidinone **2** was slightly improved[8] upon allowing an inexpensive molar scale preparation. The secondary amine **2** was then oxidized into **1**. Considering the literature precedent on a related structure,[9] we first envisaged the resolution of amine **2** through classical diastereomeric salt formation. As we could not obtain satisfactory results, we rapidly favored the optical resolution of the corresponding hydroxylamine **3** (Scheme 1) via O-acylation with a chiral carboxylic acid. We have previously shown[10] that we were able to take advantage of the high nucleophilicity of the hydroxylamine oxygen atom[11] in such a derivatization. The enantiopure hydroxylamine is then oxidized into enantiopure MiPNO. Compound **3** can a priori be obtained either by oxidation of **2** (path a) or reduction of **1** (path b); the chemoselectivity of the reaction was crucial for preparative purposes.



Scheme 1. General scheme for the preparation of MiPNO **1** and hydroxylamine **3**.

The direct oxidation of secondary amines into hydroxylamines is generally difficult because the hydroxylamine is usually overoxidized to the nitrone. Selective oxidation into a hydroxylamine has been reported using dilute solutions of dimethyldioxirane.[12] A surface-mediated reaction with oxone over silica gel[13] and a sodium tungstate-catalysed oxidation involving urea–hydrogen peroxide complex (UHP)[14] in diethyl ether[15] have also been described.

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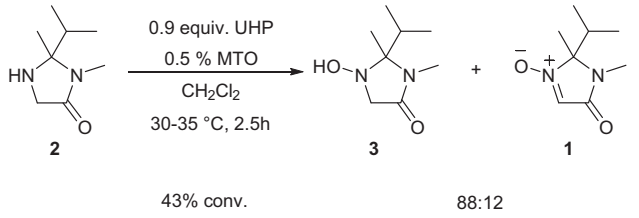
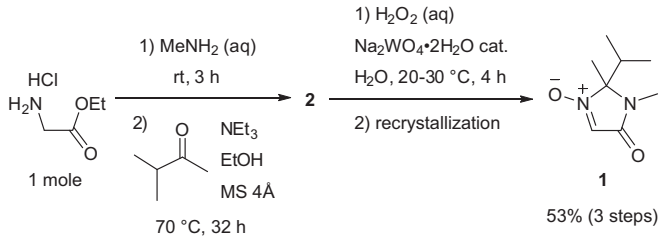
Previous work on the oxidation of related imidazolidinones in our group[16] showed that: (i) selective oxidation with 1 equiv *m*-chloro perbenzoic acid[17] was possible, but separation of the benzoic by-product was troublesome; and (ii) the use of UHP with methyltrioxorhenium (MTO) as a catalyst, in dichloromethane,[18] led to the hydroxylamines in good yields. We thus investigated the UHP/MTO system for the oxidation of amine **2** into hydroxylamine **3**. The reaction with **2** was much slower than in the case of the isomeric imidazolidinone studied previously,[16b] therefore the oxidation was performed at 30–35 °C (Scheme 2). Unfortunately, even at 43% conversion of the amine, nitrone **1** was present. Longer reaction times allowed complete conversion of the amine into a mixture of **3** and **1** but the hydroxylamine and the nitrone could not be efficiently separated on a large scale.



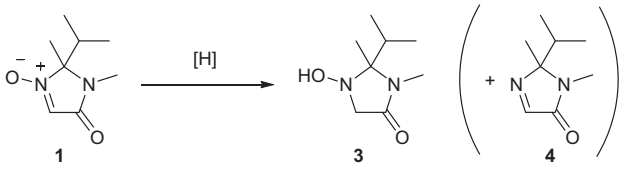
Scheme 2. Selectivity in the oxidation of imidazolidinone **2**.

We then explored a two-step procedure: the preparation of racemic MiPNO **1** and its selective reduction into hydroxylamine **3** (Scheme 1). We previously performed[6] the oxidation of imidazolidinone **2** into the nitrone on a 200 mmol scale with solid UHP, using the inexpensive precatalyst $Na_2WO_4{\cdot}2H_2O$[19] in methanol. On a larger scale, the poor solubility of Na_2WO_4 in methanol made control of the exothermic reaction difficult, and whenever the reaction temperature went above 50 °C, a large amount of by-product was formed.[20] This was solved by performing the H_2O_2/Na_2WO_4 oxidation in water, as adapted from Murahashi's procedure.[21] The reaction was best run between 20 and 30 °C using 5 mol % catalyst; heat evolution was thus slow and easily controlled. The conversion of imidazolidinone **2** into the nitrone was complete within 4 h and MiPNO **1** was conveniently purified by recrystallization from ethyl acetate/cyclohexane (Scheme 3). The overall yield in recrystallized MiPNO, from glycine ethyl ester hydrochloride (three steps) is typically 53%.



Scheme 3. Improved preparation of racemic MiPNO **1**.

The reduction of nitrone **1** was next investigated using various conditions (Scheme 4 and Table 1). The reduction of nitrones into hydroxylamines is generally performed using sodium cyanoborohydride in acidic media[22] or sodium borohydride,[23] both in alcoholic solvents. In the case of nitrone **1**, reduction with sodium borohydride in methanol (MeOH) was accompanied by dehydration into imine **4** (entry 1). No reaction occurred using borane–pyridine or borane–triethylamine complexes in tetrahydrofuran (THF) at 40–50 °C (entries 2 and 3). On the other hand, the more reactive borane–dimethylsulfide complex was efficient at room temperature and hydroxylamine **3** was obtained selectively (entry 4). Although the crude product was very clean, we verified that the hydroxylamine was chromatography-stable and **3** could be recovered in 84% yield. Diethylanilineborane ($BH_3{\cdot}$DEAN), a more convenient source of borane for large scale synthesis,[24] was also efficient (entry 5) however the elimination of *N*,*N*-diethylaniline required an elevated temperature, causing degradation of hydroxylamine **3**. Finally, the reduction of **1** with sodium borohydride or lithium borohydride in THF at 20 °C cleanly afforded hydroxylamine **3** as the sole product (entries 6 and 7). We chose to continue with inexpensive sodium borohydride in THF; the reaction was performed up to a 0.3 mol scale, leading in quantitative yield to the crude hydroxylamine **3** which could be used in the following step without further purification.



Scheme 4. Reduction of MiPNO **1** into hydroxylamine **3**.

2.2. Resolution of (±)-3 via the Moc-L-Phe-OH ester

In order to rapidly obtain milligrams of MiPNO in enantiopure form, we first selected the *N*-protected L-amino acid Moc-Phe-OH (*N*-methoxycarbonyl-L-phenylalanine) as a chiral derivatizing agent providing the chromatographically separable diasteromers **5**.[6] One diastereomer **5a** led to crystals appropriate for X-ray diffraction analysis, giving access to the relative (*S*,*R*) configuration of the two stereogenic centres and, accordingly, to the (*R*) stereochemistry of the imidazolidinone moiety.[6]

For the release of the hydroxylamine (Scheme 5 and Table 2), the conditions previously used in our group,[10a] using LiOH as the nucleophile, were unsuccessful due to the acidity of the imidazolidinone ring proton (entry 1): imine **4** was formed in a large amount. We anticipated that a more suitable nucleophilicity versus basicity ratio could be met with aqueous hydrogen peroxide in the presence of sodium hydrogen carbonate.[25] Furthermore, we expected that the bicarbonate-activated peroxide[26] would oxidize the evolved hydroxylamine to the expected nitrone **1**. The conver-

Table 1
Conditions for the reduction of MiPNO **1** into hydroxylamine **3**

Entry	[H]	Equiv	Solvent	*T* (°C)	*t* (h)	Conv. (%)	**3**:**4** Ratio[a]	Isolated yield in **3**[b] (%)
1	$NaBH_4$	3.0	MeOH	0–20	1.5	100	70:30	nd[c]
2	$BH_3{\cdot}$Py	1.5	THF	50[d]	16	0	—	—
3	$BH_3{\cdot}$TEA	1.5	THF	40[d]	5	0	—	—
4	$BH_3{\cdot}$DMS	1.3	THF	20	0.3	100	100:0	Quant.
5	$BH_3{\cdot}$DEAN	1.5	THF	20	4	100	100:0	nd[c]
6	$NaBH_4$	2.0	THF	20	1.5	100	100:0	Quant.
7	$LiBH_4$	2.0	THF	20	4.5	100	100:0	83

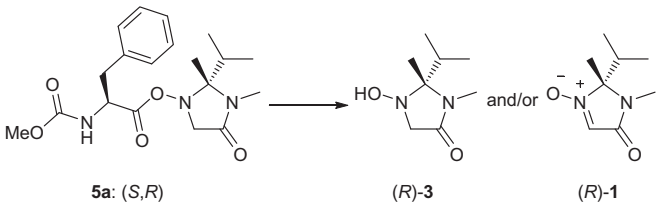
[a] Determined on the basis of the ^{1}H NMR spectrum of the crude material.
[b] Crude product.
[c] Not determined.
[d] No reaction occurred at 20 °C.

Table 2
Conditions for the removal of Moc-L-Phe-OH

Entry	Reactant	Equiv	Solvent	T (°C)	t (h)	Conv. (%)	(*R*)-**3**:(*R*)-**1** ratio[a]
1	LiOH	2	MeOH/THF	0	1	100	100:0[b]
2	H_2O_2 (aq)/$NaHCO_3$	10	THF/H_2O	20	6.5	34	100:0
3	H_2O_2 (aq)/$NaHCO_3$	10	MeOH/H_2O	20	4	100	nd[c]
4	H_2O_2 (aq)/$NaHCO_3$	10	MeOH/H_2O	20	7	100	14:86
5	H_2O_2 (aq)/$NaHCO_3$	10	MeOH/H_2O	20	24	100	0:100

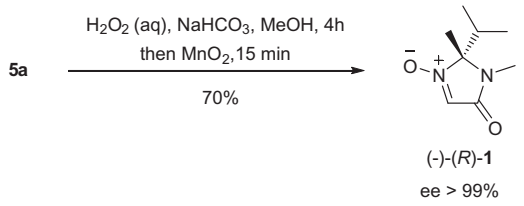
[a] Determined on the basis of the ^{1}H NMR spectrum of the crude material.
[b] A 56:44 mixture of **3** and **4**, respectively, was obtained.
[c] Not determined.

sion of **5a** was slow in THF (entry 2). In methanol no starting material remained after 4 h. The hydroxylamine obtained was slowly oxidized in situ into (−)-(*R*)-MiPNO (entries 3–5), but this reaction was too sluggish to be practically useful.



Scheme 5. Resolution via the Moc-L-Phe-OH ester: desired products from removal of the resolving agent.

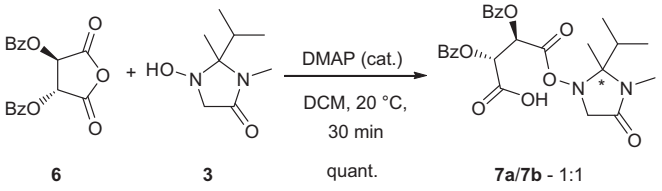
Finally, we chose to combine the rapid liberation of hydroxylamine (*R*)-**3** with basic aqueous hydrogen peroxide and the efficiency of manganese dioxide-mediated oxidation of hydroxylamines into nitrones[27] by simply adding excess MnO_2 in the reaction mixture as soon as the first step was complete (Scheme 6). The enantiomeric excess of (−)-(*R*)-MiPNO was above 99% as determined by chiral HPLC analysis.[6]



Scheme 6. Resolution via the Moc-L-Phe-OH ester: one-pot removal of the resolving agent and oxidation.

2.3. Resolution of (±)-3 via the *O,O′*-dibenzoyl-L-tartaric acid monoester

In order to perform the resolution on a larger scale, a resolving agent that would give solid diastereomers with different solubilities was sought. A screen of candidates led to the selection of *O,O′*-dibenzoyl-L-tartaric acid anhydride **6**.[28] The reaction of **6** with the racemic hydroxylamine **3** in dichloromethane (DCM) in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) gave a 1:1 mixture of diasteromers **7** in quantitative yield (Scheme 7).



Scheme 7. Resolution via the *O,O′*-dibenzoyl-L-tartaric acid monoester: diastereomer formation.

Attempts to perform fractional crystallization from different solvents came up against the relative insolubility of either diastereomer. Starting from a 1:1 mixture, a solid enriched in one diastereomer (**7a**/**7b**–ca. 9:1)[29] remained in boiling toluene or in a boiling 2:1 mixture of cyclohexane and ethyl acetate. This led us to attempt selective dissolution: we investigated the trituration of the 1:1 mixture of **7a** and **7b** in various solvents, and found an outstanding couple of orthogonal solvents. Indeed, after trituration at room temperature, solid **7a** was preferentially recovered in the case of ethyl acetate (**7a**/**7b**–ca. 9:1) and solid **7b** in the case of dichloromethane (**7a**/**7b**–ca. 1:9). Solubility measurements on isolated compounds proved that **7a** was six times more soluble than **7b** in dichloromethane, whereas **7b** was five times more soluble than **7a** in ethyl acetate.[30]

Thus, with these orthogonal solvents in hand, we developed a diastereomer separation by selective dissolution. The optimized process is illustrated in Chart 1 on a 0.3 mol scale. The amounts of solvents were adjusted to the theoretical minimum required to dissolve the more soluble diastereomer. The 1:1 mixture of diastereomers **7a**/**7b** was first triturated in dichloromethane at room temperature for 30 min, then filtered. The resulting solid **I** already presented an excellent enrichment in **7b**. After a second treatment with dichloromethane, diastereopure **7b** was isolated (solid **I′**, 30% of the initial mass). Filtrate **I** was concentrated to yield a solid that was enriched in **7a**. This solid was triturated in ethyl acetate to selectively dissolve the minor diastereomer **7b**. The remaining solid **II** (33% of the initial mass) was diastereopure **7a**. Filtrate **II** was concentrated to a solid, and another trituration in dichloromethane

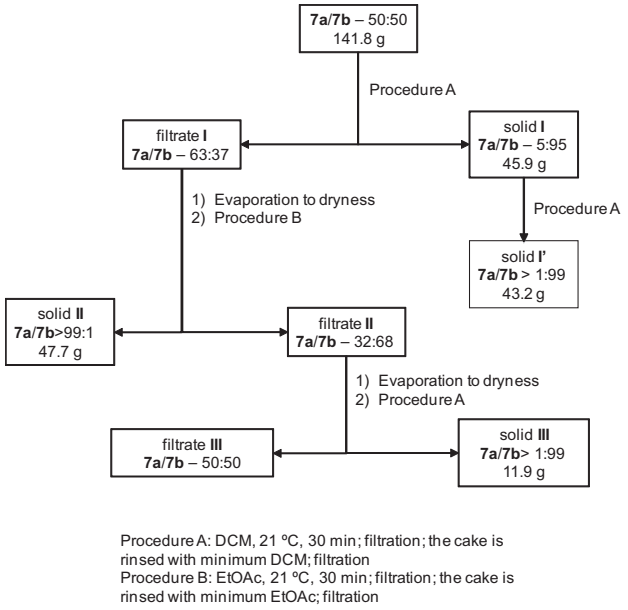


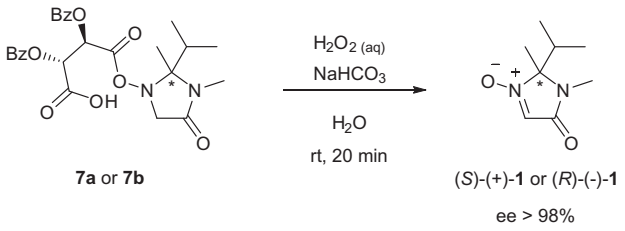
Chart 1. Resolution via the *O,O′*-dibenzoyl-L-tartaric acid monoester: flow diagram of the separation process.

led to a second batch of diastereopure **7b** (solid **III**). Filtrate **III** was concentrated, but the accumulation of protic impurities along the process hindered the crystallization of the remaining mixture of isomers, and only a small amount of **7b** was recovered by classical recrystallization from ethyl acetate.

These four triturations are sufficient to recover diastereopure **7a** in 67% yield and diastereopure **7b** in 77% yield.

To the best of our knowledge, separation of diastereomers by selective dissolution has rarely been reported.[31] Remarkably, the reversal of solubilities observed in the case of **7a**/**7b** allows the isolation of almost equal, large amounts of each diastereopure compound from a single[32] and inexpensive resolving agent.

Another advantage of esters **7a**, **b** compared to the Moc-L-Phe-OH derivative is their solubility in basic water caused by the free carboxylic acid. Thus, when **7a**, **b** was added to an equimolar mixture of H_2O_2 and $NaHCO_3$ in water (10-fold excess), dissolution was followed by a fast and clean liberation of the hydroxylamine. Moreover, under these conditions the hydroxylamine is also rapidly oxidized into nitrone MiPNO **1**. After catalytic decomposition of the excess peroxide by addition of the minimum amount of MnO_2, and repeated extractions in ethyl acetate, enantiopure MiPNO **1** was recovered in 57–74% yield (Scheme 8). The recycling of the resolving agent **6** was also possible.[30]



Scheme 8. Resolution via the *O*,*O*′-dibenzoyl-L-tartaric acid monoester: removal of the resolving agent.

Diastereomer **7a** led to (+)-MiPNO and **7b** to (−)-MiPNO. The absolute configurations of each enantiomer were first assigned on the basis of our previous results with **5a** leading to (*R*)-(−)-MiPNO. In the case of **7b**, crystals suitable for X-ray diffraction analysis could be obtained. The relative configuration of **7b** was thus established and confirmed the (*R*) stereochemistry for the imidazolidinone moiety in **7b**. On the other hand, all crystals obtained from compound **7a** led to low-quality X-ray diffraction patterns, preventing unit cell determination and structure elucidation.

Thus, the resolution via the *O*,*O*′-dibenzoyl-L-tartaric acid monoester led to (*R*)- and (*S*)-MiPNO in 57% and 38% yield, respectively, starting from (*rac*)-MiPNO.

2.4. Crystal structures of racemic and enantiopure MiPNO 1

We noticed strong discrepancies between enantiopure MiPNO and its racemic counterpart with regards to their physical properties. The melting point of (*R*)- or (*S*)-**1** is 47 °C lower than that of *rac*-**1** (67 vs 114 °C). Compound *rac*-**1** is much less soluble in diethyl ether and THF. It is even possible to recover enantiopure **1** from a 90% ee sample by simple dissolution.[33]

To gain insight into these differences, a crystallographic analysis of (*R*)-MiPNO was conducted and the results obtained for the racemate[34] were re-examined, especially regarding the hydrogen-bonding network in the crystal. The crystal packings proved to be different. Thus, in the case of (*R*)-**1**, four distinct orientations of the molecules can be found in the cell unit, each being either donor or acceptor in a C–H···O interaction (Fig. 1).[35] The hydrogen-bond donor is an aldonitrone CH group and the acceptor a nitrone oxygen atom (d(D–H) 0.95 Å, d(H···A) 2.27 Å, d(D···A) 3.20 Å; angle (DHA) 162.1°). On the other hand, the crystal structure of *rac*-**1** is composed of heterochiral dimers, with two hydrogen bonds between the (*R*)- and (*S*)-enantiomers, both linking the aldonitrone hydrogen of one enantiomer with the nitrone oxygen of its antipode (Fig. 2,[35] d(D–H) 0.95 Å, d(H···A) 2.37 Å, d(D···A) 3.27 Å; angle (DHA) 158.2°).

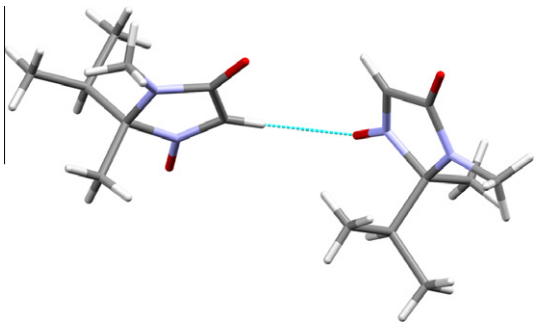


Figure 1. Crystal structure of (*R*)-**1**. The dashed line represents the hydrogen bonds.

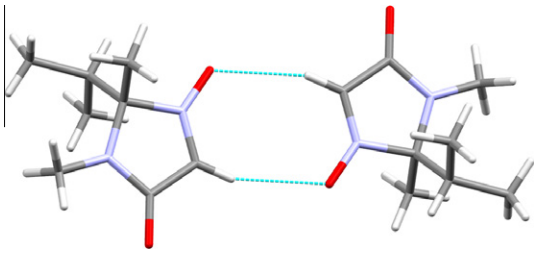


Figure 2. Crystal structure of (*rac*)-MiPNO. The dashed lines represent the hydrogen bonds.

We previously encountered such a double, head-to-tail H-bonding arrangement, in the crystals of the closely related nitrone 4-methyl-3-oxo-1,4-diazaspiro[4.5]dec-1-ene 1-oxide **8** (Fig. 3).[36] The same pattern was also reported in a nitronyl-nitroxide.[37] Interrogation of the CSD database produced seven other occurrences.[38] If the N^+–O^- motif is known to be a powerful hydrogen-bond acceptor[39] and the nitrones have been used as hydrogen-bonding templates for supramolecular assembly,[40] the hydrogen-bond donor ability of the aldonitrone C–H motif has rarely been documented. An analogy with aromatic amine *N*-oxides can however be proposed, as their self association in dimers or networks via C–H···O interactions has been described.[41,42]

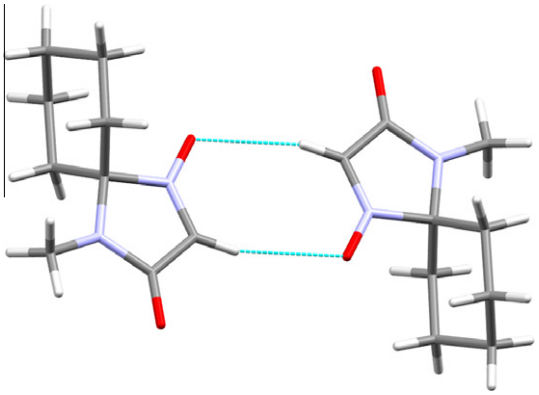


Figure 3. Crystal structure of 4-methyl-3-oxo-1,4-diazaspiro[4.5]dec-1-ene 1-oxide. The dashed lines represent the hydrogen bonds.

3. Conclusion

We have shown here that the acylation of a secondary hydroxylamine with a chiral carboxylic acid provides a straightforward access to the enantiopure nitrone MiPNO **1**. The hydroxylamine is best prepared by the reduction of the racemic nitrone; recovery of the enantiopure nitrone from the *O*,*O*′-dibenzoyl-L-tartaric acid monoester is effected in a single step. Therefore, both enantiomers of MiPNO, a new chiral glycine synthon, are easily available in enantiopure form on a multigram-scale, from a single, inexpensive resolving agent. Furthermore, the examination of the crystal structures of (*R*)- and (*rac*)-**1** led us to point out interesting properties of cyclic aldonitrones as hydrogen-bond donors and acceptors.

4. Experimental

4.1. General

Non-aqueous reactions were performed under a positive pressure of dry nitrogen in oven-dried glassware equipped with a magnetic stirrer bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Tetrahydrofuran was distilled over sodium benzophenone ketyl. Technical grade ethanol, methanol, dichloromethane (stabilized with amylene) and ethyl acetate were purchased from Carlo Erba reagents and used without further purification. All reagent-grade chemicals were purchased from either Acros or Aldrich chemical companies and used without purification unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminium-backed silica gel plates (Merck, Kieselgel 60 F_{254}). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with an appropriate staining solution ($KMnO_4$, basic TTC (2,3,5-triphenyltetrazolium chloride) for hydroxylamines). Product purification by filtration over silica gel was performed using Macherey Nagel Silica Gel 60 M (230–400 mesh). Melting points (mp) were determined in capillary tubes with a Büchi B-540 apparatus (heating rate 5 °C/min) and are given uncorrected. Optical rotations [α] were measured on a Perkin Elmer 341 polarimeter, the corresponding concentration is given in g per 100 cm.[3] Infrared spectra (IR) were recorded on a Nicolet 'Magna 550' spectrometer using ATR (Attenuated Total Reflexion) or a Nicolet Impact-400 Fourier transform infrared spectrometer from a thin film; data are reported in reciprocal centimetres (cm^{-1}). 1D and 2D NMR spectra were recorded on either a Bruker Advance 300 or Advance 400 spectrometer. Chemical shifts (δ) are given in ppm using internal references or TMS as external reference for $CDCl_3$. Multiplicities are declared as follows: s (singlet), d (doublet), hept (heptuplet), m (multiplet), qq (quadruplet of quadruplet). Coupling constants (*J*) are given in Hertz. Low Resolution Mass Spectra (LRMS) were recorded on a Bruker Daltonics Esquire 3000 Plus ion-trap spectrometer (ESI) or a Thermo Fischer Scientific Polaris Q spectrometer, using ammonia/isobutene–63:37 for chemical ionization. High Resolution Mass Spectra (HRMS) were recorded on a Thermoquest Orbitrap spectrometer at the LCOSB, UMR 7613, Université Pierre et Marie Curie, Paris. Experimental errors for HRMS data are estimated between 1 and 2 ppm. Elemental analysis were performed at the Service d'Analyse Elémentaire du Département de Chimie Moléculaire, Grenoble.

Compounds **1**, **2**, **3**, **5a** were previously described in the literature.[6]

4.2. Preparation of *rac*-2-isopropyl-2,3-dimethyl-1-oxy-2, 3-dihydro-imidazol-4-one (MiPNO, 1) on a 75 g scale

In a 1-L flask under magnetic stirring, methylamine (40% in water, 300 mL, 3.5 mol) was added to solid glycine ethyl ester hydrochloride (200.7 g, 1.438 mol). Endothermic dissolution was followed by a gentle exothermic reaction. The solution was kept at room temperature for 3 h, then concentrated under reduced pressure at 40 °C. Ethanol (200 mL) was added and evaporation resumed; this step was repeated four times, leaving the amino amide hydrochloride as a syrup (230 g, theo. 179 g). To this crude material were added ethanol (120 mL), 3-methyl-2-butanone (230 mL, 2.16 mol), triethylamine (201 mL, 1.44 mol) and activated 4 Å molecular sieves (beads, 380 g). The flask was fitted with a reflux condenser and heated at 70 °C for 32 h without stirring, The sieves were separated by filtration of the hot mixture. The filtrate was concentrated under reduced pressure, and precipitation took place. The crude white slurry was taken up in ethyl acetate (800 mL), the solid triethylamine hydrochloride was filtered off and the filtrate concentrated under reduced pressure to yield 177.7 g (theo. 154.7 g) of crude **2** as an orange oil.

In a 1-L flask fitted with a reflux condenser, a thermometer and a 250-mL dropping funnel, were introduced 99.5 g of crude **2**. A solution of $Na_2WO_4{\cdot}2H_2O$ (10.23 g, 31 mmol) in 20 mL water was added; the temperature rose from 18 to 24 °C. The flask was placed in an ice-salt bath, and H_2O_2 (217 g of 30% solution in water, 1.9 mol) was added dropwise over 45 min, so that the pot temperature was kept below 30 °C. At the end of the addition, the ice bath was replaced by a water bath (18 °C) and stirring was continued. The reaction was moderately exothermic for the first 3 h and a precipitate formed. After 5 h, filtration of the reaction mixture produced 82.8 g of crude nitrone **1**. The water phase was placed in a 1-L Erlenmeyer flask with magnetic stirring, cooled with an ice bath and treated with MnO_2 (3.5 g) to decompose the excess H_2O_2. After the end of the intense frothing, the water phase was filtered on paper, and then extracted with 5 × 200 mL ethyl acetate. The solid nitrone was dissolved in the gathered organic phases, and the solution was washed with brine (50 mL), dried over $MgSO_4$, and concentrated to a pale yellow solid (78.6 g). Recrystallization in ethyl acetate (75 mL)/cyclohexane (200 mL) yielded pure **1** (pale yellow crystals, 72.51 g, 0.427 mol) in 53% yield from glycine ethyl ester hydrochloride**.**

4.3. Preparation of *rac*-1-hydroxy-2-isopropyl-2,3-dimethyl-imidazolidin-4-one 3 by the reduction of MiPNO with $BH_3{\cdot}DMS$

In a 25-mL flask under a nitrogen atmosphere, nitrone *rac*-**1** (317 mg, 1.86 mmol) was dissolved in anhydrous THF (5 mL). A commercial solution of borane dimethylsulfide complex in THF (2 M, 1.21 mL, 2.42 mmol) was slowly added and the mixture was stirred for 20 min at room temperature (20 °C). The reaction mixture was stirred with methanol (10 mL) until the end of dihydrogen evolution and concentrated under reduced pressure. This operation was repeated three times to give pure **3** (320 mg, 1.86 mmol, quantitative yield) as a pale yellow oil. Further purification by flash chromatography (cyclohexane/ethyl acetate–30:70) yielded a colourless oil (269 mg, 1.56 mmol, 84% yield).

4.4. Characterization data for *rac*-2-isopropyl-2,3-dimethyl-2,3-dihydro-imidazol-4-one 4

Yellow oil; R_f 0.29 (ethyl acetate); IR (thin film): 2972, 2929, 2881, 1697, 1599, 1428; δ_H (400 MHz; $CDCl_3$) 7.80 (1H, s), 2.84 (3H, s), 2.05 (1H, qq, *J* = 6.8, 7.2 Hz), 1.40 (3H, s), 1.11 (3H, d, *J* = 6.8 Hz), 0.48 (3H, d, *J* = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 163.1, 159.7, 91.9, 33.8, 25.6, 22.1, 17.6, 15.3; LRMS (DCI) *m*/*z*: 155.3 (100, $(M+H)^+$), 183.4 (28, $(M+C_2H_5)^+$), 195.3 (8, $(M+C_3H_5)^+$); HRMS (ESI^+) *m*/*z*: found, 177.09945 (M+Na); $C_8H_{14}N_2ONa$ requires 177.09983.

4.5. Resolution via the *O*,*O*′-dibenzoyl-L-tartaric acid monoester

4.5.1. Synthesis of O,O′-dibenzoyl-L-tartaric anhydride 6[43]

A mixture of L-tartaric acid (150.09 g, 1.00 mol) and benzoyl chloride (405 mL, 3.49 mol) was heated for 2 h at 125 °C in the presence of a catalytic amount of DMAP (100 mg) (Caution! The apparatus should be equipped with a hydrogen chloride trap). The solid residue was triturated two times in diethyl ether at room temperature, and then dried under vacuum over P_2O_5 to give *O*,*O*′-dibenzoyl-L-tartaric anhydride **6** as a white solid (282 g, 829 mmol, 83%). Mp: 191.1–191.2 °C; $[\alpha]_D^{25} = +147$ (*c* 1.07, acetone). Lit.[44] mp: 188–189 °C; $[\alpha]_D^{25} = +153$ (*c* 1.07, acetone).

4.5.2. Derivatization of hydroxylamine 3: synthesis of (2*R*,3*R*)-2,3-bis-benzoyloxy-succinic acid mono-((*S*)-2-isopropyl-2,3-dimethyl-4-oxo-imidazolidin-1-yl) ester 7a and (2*R*,3*R*)-2,3-bis-benzoyloxy-succinic acid mono-((*R*)-2-isopropyl-2,3-dimethyl-4-oxo-imidazolidin-1-yl) ester 7b

In a 1-L round-bottomed flask under vigourous magnetic stirring, crude hydroxylamine **3** (47.74 g, 277 mmol) was dissolved in dichloromethane (380 mL). Next, DMAP (130 mg, 1.16 mmol) was added, followed by anhydride **6** (94.32 g, 277 mmol). The reaction was almost athermic, the anhydride dissolved and precipitation took place. After 30 min, the reaction mixture was concentrated.

4.5.3. Separation of diastereomers 7a and 7b

The solid was transferred to a 2-L Erlenmeyer flask, suspended in 1.5 L dichloromethane and stirred at 21 °C (room temperature) for 30 min. The remaining solid was filtered and the cake was rinsed with 100 mL dichloromethane. Filtration yielded 45.9 g of a white solid (solid **I**, **7a**/**7b**–5:95 as determined by ^{1}H NMR), and filtrate **I**. Solid **I** (entire quantity) was stirred in dichloromethane (47 mL) for 30 min and filtration yielded diastereopure **7b** as a white solid (solid **I**′, 43.2 g, **7a**/**7b** > 1:99). The filtrate was added to filtrate **I**.

Filtrate **I** (entire quantity) was concentrated under reduced pressure to yield 98.1 g of a 63:37 mixture of diastereomers **7a**/**7b** which was triturated in ethyl acetate (1 L) for 30 min at 21 °C. The remaining solid was filtered and the cake was rinsed with 50 mL ethyl acetate. Filtration yielded 47.7 g of diastereopure **7a** as a white solid (solid **II**, **7a**/**7b** > 99:1), and filtrate **II**.

Filtrate **II** (entire quantity) was concentrated under reduced pressure to yield 51.1 g of a 32:68 mixture of diastereomers **7a**/**7b** which was triturated in dichloromethane (340 mL) for 30 min at 21 °C. The remaining solid was filtered and the cake was rinsed with 20 mL dichloromethane. Filtration yielded 11.9 g of diastereopure **7b** as a white solid (solid **III**, **7a**/**7b** > 1:99), and filtrate **III**.

Filtrate **III** (entire quantity) was concentrated under reduced pressure to yield 39.07 g of a 50:50 mixture of diastereomers **7a**/**7b**. The addition of ethyl acetate (25 mL), overnight standing at room temperature, and filtration yielded only 3.38 g of a 88:12 mixture of **7a**/**7b**, which was not processed further. After concentration, the filtrate did not crystallize.

Global yield of diastereopure **7a**: 67% (white solid, 47.7 g).

Global yield of diastereopure **7b**: 77% (white solid, 55.1 g).

Compound **7a**: mp: 146–150 °C (dec); $[\alpha]_D^{20} = -52.0$ (*c* 1.26, $CHCl_3$); R_f 0.55 (ethyl acetate/ethanol–50:50); IR (ATR): 3085, 2977, 2942, 2885, 1796, 1721, 1646, 1623, 1243, 1093, 726; δ_H (400 MHz; $(CD_3)_2SO$) 8.04-8.02 (4H, m), 7.76–7.73 (2H, m), 7.63–7.59 (4H, m), 6.01 (1H, d, *J* = 2.8 Hz), 5.97 (1H, d, *J* = 2.8 Hz), 3.93 (1H, d, *J* = 17.2 Hz), 3.32 (1H, d, *J* = 17.2 Hz), 2.69 (3H, s), 1.91 (1H, hept, *J* = 6.8 Hz), 1.35 (3H, s), 0.89 (3H, d, *J* = 6.8 Hz), 0.77 (3H, d, *J* = 6.8 Hz); δ_C (100 MHz; $(CD_3)_2SO$) 168.3, 166.9, 164.1, 164.5, 134.4, 134.2, 129.5, 129.4, 129.2, 129.1, 128.3, 128.0, 88.9, 71.0, 70.7, 57.9, 34.8, 26.1, 17.2, 16.8, 15.5; LRMS (ESI$^+$) *m*/*z*: 513 (21, $(M+H)^+$), 535 (100, $(M+Na)^+$), 1025 (6, $(2\,M+H)^+$), 1047 (12, $(2\,M+Na)^+$); Anal.: found, C61.26; H5.50; N5.73; $C_{26}H_{28}N_2O_9$ requires C60.94; H5.51; N5.47.

Compound **7b** mp: 140 °C (dec); $[\alpha]_D^{20} = -54.0$ (*c* 1.08, EtOH); R_f 0.55 (ethyl acetate/ethanol–50:50); IR (ATR): 3672, 3562, 3069, 3031, 2965, 2952, 2882, 1787, 1781, 1723, 1646, 1448, 1245, 1095, 712; δ_H (400 MHz; $(CD_3)_2SO$) 8.03–8.02 (4H, m), 7.74–7.73 (2H, m), 7.62–7.59 (4H, m), 6.11 (1H, d, *J* = 2.8 Hz), 5.88 (1H, d, *J* = 2.8 Hz), 4.02 (1H, d, *J* = 17.2 Hz), 3.61 (1H, d, *J* = 17.2 Hz), 2.64 (3H, s), 1.83 (1H, hept, *J* = 6.8 Hz), 1.16 (3H, s), 0.73 (3H, d, *J* = 6.8 Hz), 0.68 (3H, d, *J* = 6.8 Hz); δ_C (100 MHz; $(CD_3)_2SO$) 168.4, 166.7, 164.1, 164.6, 134.4, 134.2, 129.5, 129.4, 129.2, 129.1, 128.3, 128.1, 88.6, 71.2, 70.8, 58.4, 34.8, 26.0, 17.0, 16.5, 16.0; LRMS (ESI$^+$) *m*/*z*: 513 (21, $(M+H)^+$), 535 (100, $(M+Na)^+$), 1025 (6, $(2M+H)^+$), 1047 (12, $(2M+Na)^+$); Anal.: found, C60.60; H5.27; N5.53. $C_{26}H_{28}N_2O_9$ requires C60.94; H5.51; N5.47.

4.5.4. Solubility measurements

A saturated solution of **7a** (or **7b**) in the solvent at 18 °C (internal temperature; glassware placed in a thermostated water bath) was prepared and a precise volume of the supernatant was sampled and concentrated.

Solubility of **7a** in EtOAc: 7 mg/mL; in DCM: 41–48 mg/mL.

Solubility of **7b** in EtOAc: 32–33 mg/mL; in DCM: 8 mg/mL.

4.5.5. (*S*)-2-Isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one (*S*)-1 [(*S*)-MiPNO]

In a 250-mL Erlenmeyer flask were introduced $NaHCO_3$ (14.0 g, 165 mmol), water (35 mL) and a 30% aqueous solution of hydrogen peroxide (18.7 g, 165 mmol). Under vigourous stirring, solid **7a** (8.52 g, 16.5 mmol) was added in one portion. Frothing and dissolution then took place. After 20 min stirring, MnO_2 (0.3 g) was added portion-wise (brisk frothing). After 5 min the water phase was extracted six times with 50 mL ethyl acetate. The gathered organic layers were dried over Na_2SO_4 and concentrated to yield (*S*)-**1** (1.65 g), that crystallized upon standing. The solid was stirred in 25 mL diethyl ether. The solution was filtered and concentrated to yield 1.61 g of (*S*)-**1** (>98% ee, 57% yield). An analytical sample of (*S*)-**1** was obtained by recrystallization from ethanol: mp: 67.0–67.1 °C; $[\alpha]_D^{25} = +16.5$ (*c* 2.0, EtOH).

4.5.6. Recovery of resolving agent 6

The water layers from the liberation of (*S*)-**1** were acidified to pH 1 and extracted with 2 × 100 mL ethyl acetate; the gathered organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield *O*,*O*′-dibenzoyl-L-tartaric acid (6.45 g) as a thick oil. To a suspension of crude *O*,*O*′-dibenzoyl-L-tartaric acid (6.45 g, 18 mmol) in cyclohexane (100 mL) was added acetyl chloride (6.28 g, 80 mmol). The reaction mixture was stirred for 9 h at 50 °C and concentrated. The residue was taken up in Et_2O (40 mL) and the white solid was filtered off to yield *O*,*O*′-dibenzoyl-L-tartaric anhydride **6** (3.98 g, 11.7 mmol, 65%). The specific rotation was identical to that of the sample used for the resolution of MiPNO.

4.5.7. (*R*)-2-Isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one (*R*)-1 [(*R*)-MiPNO]

Compound (*R*)-**1** was prepared as described for (*S*)-**1** starting from **7b** (8.47 g). Yield: 74% (2.07 g, >98% ee). An analytical sample of (*R*)-**1** was obtained by recrystallization from ethanol: mp: 66.6–66.7 °C; $[\alpha]_D^{25} = -16.2$ (*c* 2.0, EtOH).

4.5.8. HPLC determination of the ee

The enantiomeric purity of **1** 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, retention time 5.9 min for (*S*)-MiPNO and 6.9 min for (*R*)-MiPNO.

4.6. X-Ray crystal structure determination

4.6.1. Diastereomer 7b: (2*R*,3*R*)-2,3-bis-benzoyloxy-succinic acid mono-((*R*)-2-isopropyl-2,3-dimethyl-4-oxo-imidazolidin-1-yl) ester

Data for the crystal structure of compound **7b** (recrystallized from ethanol) were collected on a Bruker AXS-Enraf-Nonius Kappa-CCD diffractometer working at the Mo-Kα wavelength (0.71073 Å) using the program Collect.[45] The temperature was maintained at 200 K using a 700 series Cryostream cooling device. The unit cells determinations were performed using Dirax[46] and the data were integrated with EvalCCD.[47] $C_{26}H_{28}N_2O_9$, M = 512.50 g mol^{-1}, trigonal, $P3_2$, a = 12.439(1), b = 12.439(1), c = 14.846(4) Å, V = 1989.3(3) Å^3, Z = 3, Z' = 1, Dx = 1.283 g cm^{-3}. A total of 12690 reflections were measured and 2746 unique (R_{int} = 0.0718) were used in all calculations. The final R values were: R_1 = 0.0368 and wR_2 = 0.0768 for $I > 2\sigma$ (I) and R_1 = 0.0505 and wR_2 = 0.0847 for all data. The structure was solved with one molecule in the asymmetric unit by the charge flipping algorithm implemented in the program Superflip[48] and refined by full-matrix least square methods using SHELXL[49] through Olex2 GUI software.[50] A twinning was discovered, with two twin domains in a 1:1 ratio, and taken into account after structure determination for subsequent refinement. The twin law was determined as the matrix (0 1 0/1 0 0/ 0 0 −1) and the twin scale factor was refined to a final value of 0.442. The space group discrimination between P31 and P32 was achieved according to the prior knowledge of compound configuration. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were positioned with idealized geometry using the riding model proposed in Shelx97 with C–H = 0.93 Å or 0.96 Å, and N–H = 0.86 Å, and with U_{iso}(H) = 1.2U_{eq}(C-aromatic) and 1.5U_{eq}(*C*-methyl). The data have been deposited at the Cambridge Crystallographic Data Centre (Reference No. CCDC 819651).

4.6.2. (*R*)-MiPNO 1

Data for the crystal structure of compound (*R*)-**1** (recrystallized from ethanol) were collected on a Bruker AXS-Enraf-Nonius MACH3 diffractometer working at the Cu-Kα wavelength (1.54178 Å) and at 296 K. $C_8H_{14}N_2O_2$, M = 170.21 g mol^{-1}, monoclinic, $P2_1$, a = 6.803(2), b = 11.399(4), c = 12.260(3) Å, β = 92.48(2)°, V = 949.8(5) Å^3, Z = 4, Dx = 1.191 g cm^{-3}. A total of 2042 reflections were collected; 2011 independent reflections (R_{int} = 0.0454). The structure was solved by direct methods with SIR92[51] and refined against F by least square method implemented by TeXsan.[52] C, N, and O atoms were refined anisotropically by the full matrix least-squares method. H atoms were set geometrically and recalculated before the last refinement cycle. There are two independent molecules in the asymetric unit. The final R values obtained for 1767 reflections with $I > 2\sigma$ (I) and 217 parameters are R_1 = 0.0615, wR_2 = 0.0844 and for all 2011 unique reflections R_1 = 0.0653, wR_2 = 0.0858. The data have been deposited at the Cambridge Crystallographic Data Centre (Reference No. CCDC 819649).

4.6.3. 4-Methyl-3-oxo-1,4-diazaspiro[4.5]dec-1-ene 1-oxide 8

Data for the crystal structure of compound **8** were collected on a Bruker AXS-Enraf-Nonius CAD4 diffractometer working at the Cu-Kα wavelength (1.54178 Å) and at 296 K. $C_9H_{14}N_2O_2$, M = 182.22, monoclinic, $P2_1/a$, a = 11.213(2), b = 9.824(3), c = 8.631(3) Å, β = 98.11(2)°, V = 941.3(4) Å^3, Z = 4, Dx = 1.286 g cm^{-3}. A total of 2195 reflections were collected; 1927 independent reflections (R_{int} = 0.0227). The structure was solved by direct methods with SIR92[51] and refined against F by least square method implemented by TeXsan.[52] C, N, and O atoms were refined anisotropically by the full matrix least-squares method. H atoms were set geometrically and recalculated before the last refinement cycle. The final R values obtained for 1373 reflections with $I > 2\sigma$ (I) and 119 parameters are R_1 = 0.0425, wR_2 = 0.0857 and for all 1927 unique reflections R_1 = 0.0763, wR_2 = 0.1365. The data have been deposited at the Cambridge Crystallographic Data Centre (Reference No. CCDC 823684).

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