Correction to Withdrawn Article[3,4] Cyclization Products of δ-Oxo-α,β-unsaturated Ketoxime During Reaction with Hydrochloric Acid in Anhydrous Diethyl Ether

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We have studied the cyclization of (4*Z*)-2,2,5,8,8-pentamethyl-4-nonene-3,7-dione (3*E*)-oxime (**2**). We have previously claimed the formation of a stable 3,5,5-trisubstituted 3-isoxazolidinol and of a bridged bicycle 4,5-dihydro-2,5-methano-1,4,3-dioxazepine in the reaction of **2** with hydrochloric acid in anhydrous diethyl ether. We report in this article that the above compounds are actually 3,3-dimethyl-1-(5′-*tert*-butyl-5′-hydroxy-3′-methylisoxazolidin-3′-yl)butan-2-one (**5**) and 1,3-di-*tert*-butyl-5-methyl-2,7-dioxa-6-azabicyclo[3.2.1]oct-3-ene (**6**). The formation of these products involves the splitting of hydroxylamine in **2** and its re-addition as an *O*-nucleophile under acidic reaction conditions. Surprisingly, **5** provided the 2-isoxazoline derivative **3** on heating or on standing in $CDCl_3$/TFA solution at room temperature.

Introduction

The reaction of pyrylium salts with hydroxylamine is known to provide pyridine 1-oxides and/or 2-isoxazolines, according to the nature of the substituents and the reaction conditions. The mechanism for the formation of these products involves the addition of hydroxylamine as an *N*-nucleophile to the α-position of the pyrylium cation, followed by (thermally allowed) electrocyclic ring opening and recyclization of the opened-chain oxime intermediate.[1]

We have isolated, in a few favorable cases, the opened-chain oxime intermediates (such as **2**)[2] and have undertaken a study of their recyclization to explain the origin of the final products. We have claimed the formation of a stable 3-isoxazolidinol in the reaction with hydrochloric acid in anhydrous diethyl ether and we explained its formation by hydration of the C=N double bond in situ. A bridged bicyclic compound obtained as a side product was assigned as a 4,5-dihydro-2,5-methano-1,4,3-dioxazepine.[3] We found, however, by subsequent studies, including X-ray analysis, that the above compounds were actually 5-isoxazolidinol (an unexpected isomer of the claimed 3-isoxazolidinol) and 4,5-dihydro-2,5-methano-1,3,4-dioxazepine (an unexpected isomer of the claimed 4,5-dihydro-2,5-methano-1,4,3-dioxazepine). We immediately withdrew the previous article.[4] It is the purpose of this paper to correct all previously mistaken assignments and to provide an account of the genuine results. To ensure this paper's comprehensibility, the main experimental data of the withdrawn article[3] has been revisited.

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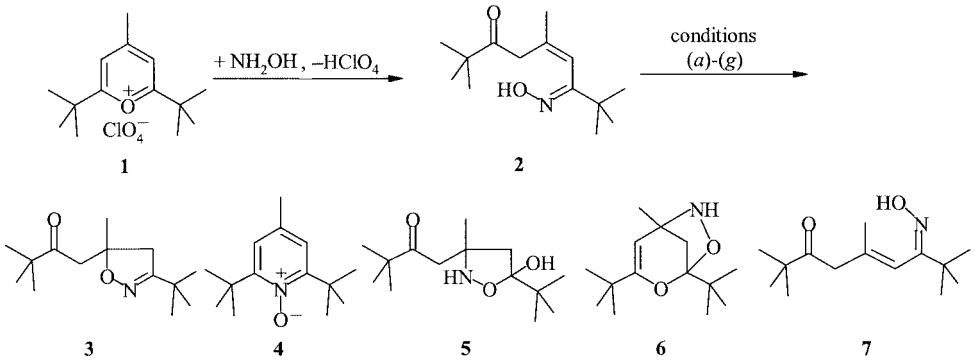
Results and Discussion

Upon treatment with hydroxylamine, 2,6-di-*tert*-butyl-4-methylpyrylium perchlorate (**1**) afforded (1*E*,2*Z*)-2-pentene-1,5-dione 1-oxime (**2**) quantitatively.[2] Recyclization of keto-oxime **2** was performed under the conditions shown in Scheme 1. The products were separated by column chromatography and their yields are displayed. The following experiments were all performed on the same scale, with identical workup procedures in order to eliminate any possible discrepancies.

Heating keto-oxime **2** with sodium methoxide in methanol (*a*), gave exclusively 2-isoxazoline **3** in 94% yield, while heating in glacial acetic acid (*b*) afforded **3** in 72% yield along with pyridine 1-oxide **4** in 18% yield. A reasonable explanation is that 2-isoxazoline **3** originated from (1*E*)-oxime **2** as a Michael-addition product, whereas formation of pyridine 1-oxide **4** required prior isomerization to the (1*Z*)-oxime and then cyclization and dehydration, promoted under acidic conditions.[2]

Should this mechanism be the case, a powerful protonating acid might accelerate both the oxime isomerization



(*a*)	94%	-	-	-	-
(*b*)	72%	18%	-	-	-
(*c*)	34%	33%	16%	traces	9%
(*d*)	34%	26%	30%	3%	-
(*e*)	34%	20%	24%	14%	-
(*f*)	32%	23%	31%	traces	4%
(*g*)	21%	10%	15%	43%	-

Scheme 1. (*a*) MeONa/MeOH, reflux; (*b*) AcOH (glacial), reflux; (*c*) − (*g*) HCl/Et_2O (anhydrous), room temp., 3 h. Molar concentration of **2** and molar ratio of **2**:HCl as follows: (*c*) 0.1, 1:1; (*d*) 0.2, 1:1; (*e*) 0.4, 1:1; (*f*) 0.1, 1:3; (*g*) 0.4, 1:3

and dehydration steps, and raise the yield of pyridine 1-oxide accordingly. With this purpose in mind, cyclization of **2** was performed at room temperature in anhydrous diethyl ether that had previously been saturated with dry gaseous hydrogen chloride. Under these conditions (Scheme 1, *c*−*g*), the course of the reaction proved to be more complicated as two new cyclization products were identified: 5-isoxazolidinol **5** and the bicyclic compound **6**. Proof of the structure for **5** was obtained from IR and NMR spectroscopic data and is discussed in detail below. The structure of **6** was determined by X-ray analysis and is depicted in Figure 1.

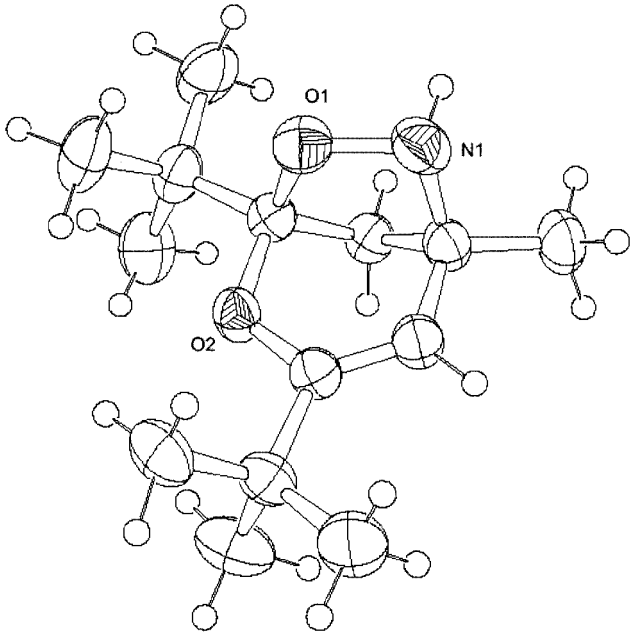


Figure 1. ORTEP representation of the bicyclic compound **6** as determined by X-ray crystallography

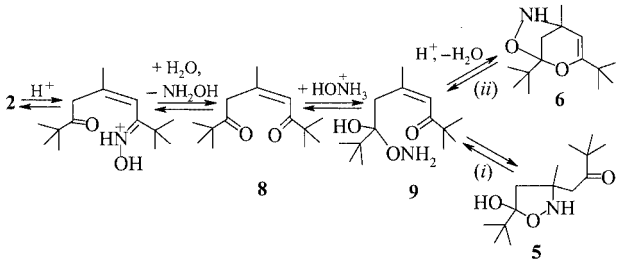
The distribution of products **3** through **6** was quite sensitive to parameters such as concentration and the amount of hydrogen chloride. On increasing the concentration of **2** (*c* vs. *d*, *e*) or the amount of HCl (*c* vs. *f*), we observed an increase in the proportions of compounds **5** and **6**, with a decrease and a small variation in the yields of **4** and **3**, respectively. Notably, in the experiments with equimolar amounts of HCl and higher dilutions (*c*, *d*), the reaction mixture was homogeneous and then a steady precipitation occurred, whereas rapid precipitation occurred when an excess of HCl was used with a concentrated solution (*g*) and the reaction remained heterogeneous throughout.

Besides the cyclic products **3**−**6**, small amounts of an acyclic compound were isolated in the runs (*c*) and (*f*). This compound was assigned as (1*E*,2*E*)-2-pentene-1,5-dione 1-oxime **7** based on IR and NMR spectroscopic data. Poor results were obtained from attempted X-ray analysis of **7**, but nevertheless it confirmed the structure and the stereochemistry of the double bonds. When the reaction in the run (*f*) was stopped at an early stage, traces of another keto-oxime were isolated, probably the 1*Z*-isomer of **7**. Therefore, our previous claim that a 3-isoxazoline derivative was formed in this reaction[3] should be withdrawn.

In compounds **5** and **6**, the hydroxylamine heteroatoms are attached through their oxygen atoms to the carbon atoms originating from the α-positions of the pyrylium ring; that is, they are in the reverse order when compared with the starting oxime **2** and its recyclization products **3** and **4**. *This assignment means that splitting of the hydroxylamine unit and its re-addition as an O-nucleophile must compete with recyclization of* **2** *to* **3** *and* **4**. *By protonating the nitrogen atom under the acidic reaction conditions, the ambident hydroxylamine was rendered an O-nucleophile instead of its usual N-nucleophilicity.*

On the other hand, formation of **5** requires a water molecule to be present, whereas the reaction had been performed under anhydrous conditions, but the water liberated in situ during pyridine 1-oxide **4** formation may account for it qualitatively and quantitatively. Indeed, **4** and **5** were obtained in comparable yields.

To explaining the origin of compounds **5** and **6**, we propose the mechanism displayed in Scheme 2.



Scheme 2

Hydrolysis of **2** occurs readily under acid catalysis, providing hydroxylamine and 2-pentene-1,5-dione **8**. Addition of hydroxylamine, that is protonated on its nitrogen atom, to the saturated carbonyl unit in **8** provides the key intermediate **9**, which may follow path (*i*) to give **5** through an internal Michael addition to the activated C=C bond. Protonation of the hydroxyl group in **9**, however, may promote another cyclization route (*ii*) leading to **6** that involves elimination of water, 1,4-Michael addition and ring closure. This path recycles water. It explains the fact that the amount of **6** is not limited by the amount of water issued from the dehydration that leads to **4**.

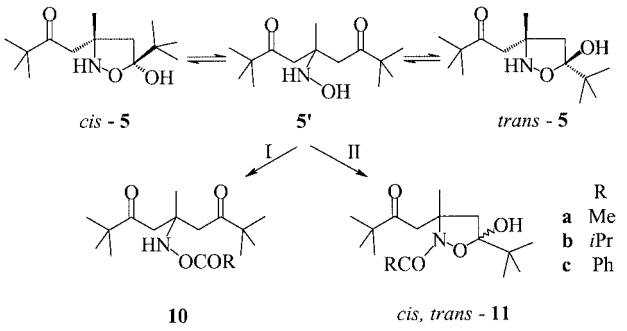
Hydrogen chloride also promotes the isomerization of the C=C double bond, as evidenced by isolation of the (1*E*,2*E*)-oxime **7** and of its evanescent 1*Z* isomer.

Ring-Chain Tautomerism of 5

As already mentioned, the structure of **5** was established from its spectroscopic data. In CCl_4 solution, the IR spectrum presents a broadened weak band at 3230 cm^{-1} (NH vibration) and two bands at 3500 (broad) and 3590 (sharp) cm^{-1} (associated and free OH vibrations, respectively).

The ^1H and ^{13}C NMR spectra of **5** in $CDCl_3$ present two sets of signals of almost equal intensities, indicating a *cis*/*trans* diastereoisomeric pair. The chemical shifts within each stereoisomer were assigned unambiguously using 2D NMR techniques (HETCOR and COLOC) and are given in the Exp. Sect. The most reliable structural proof was obtained from the ^{13}C NMR spectroscopic data of the δ values of the endocyclic atoms C-5 (ca. δ = 114 ppm, indicating an O−C−O sequence) and C-3 (ca. δ = 62 ppm, indicating a C−N sequence), in comparison to literature data on hydroxyisoxazolidines and related compounds.[5]

The diastereoisomeric *cis*/*trans*-**5** may be regarded as cyclic tautomers interconverting through the acyclic tautomer **5′** (Scheme 3), by analogy with the well-documented ring−chain tautomerism of 5(3)-hydroxyisoxazolidines.[6−8] In 5-isoxazolidinols, the tendency towards the cyclic form is very strong, with the acyclic form being only scarcely detected by NMR spectroscopy in polar solvents.[5] The spectra of **5** recorded in [D_6]DMSO and $CDCl_3$, however, exhibited only the signals of equally populated *cis* and *trans* cyclic tautomers, but on adding a trace of trifluoroacetic acid (TFA) to the $CDCl_3$ solution of **5** and recording the spectrum immediately thereafter, signals appeared that are in good agreement with the structure of the acyclic tautomer **5′**, meaning that acid catalysis favours the ring-opening process.



Scheme 3. (I) $(RCO)_2O$, reflux; (II) RCOCl, pyridine, room temp.

Notably, the signals of the tautomeric species *cis*/*trans*-**5** and **5′** in the samples of the NMR spectra above ($CDCl_3$/TFA) steadily decreased on standing at room temperature, being replaced by signals of 2-isoxazoline **3**. The transformation was complete in a few days. On the other hand, on heating **5** above its melting point (at 100−110 °C, under an inert gas), or in toluene with azeotropic distillation of water, 2-isoxazoline **3** was also obtained. *This rather surprising result can be explained only by a series of successive elimination−addition reactions that lead to the most stable isoxazoline isomer, namely 2-isoxazoline. In these reactions, hydroxylamine is formally reverted to its normal nucleophilicity at the N atom.*

No line broadening was observed, up to 100 °C, when **5** was heated in [D_8]toluene in an NMR tube. Because the interconversion of stereoisomers is slow on the NMR spectroscopic timescale, we performed a tentative resolution of the enantiomers by chiral HPLC. Single broad and distorted peaks were obtained at 25 °C upon eluting the mixtures with hexane/2-propanol on CHIRALCEL OD-H, CHIRALCEL OJ, CHIRALCEL OB-H, and CHIRALPAK AD stationary phases. On CHIRALPAK AD, a single very-broad peak was obtained at 25 °C, but splitting occurred upon cooling. Two broad peaks (each presenting a shoulder) centered at 5.8 and 7.6 min were obtained at 6 °C (hexane/2-propanol, 96:4; UV detection at 200 nm; flow rate of 1 mL·min^{-1}). The first peak gave a positive response upon polarimetric detection and the second peak a negative one.

These results are in agreement with the exchange process depicted in Scheme 3, with the open-chain achiral tautomer **5′** being a common intermediate for both *cis*/*trans* interconversion and racemization. On the other hand, the chiral chromatography indicated that neither the separation of *cis*- and *trans*-**5** nor the enantiomeric resolution of each cyclic diastereoisomer can be accomplished, since the exchange is relatively fast at room temperature.

Acyl(aroyl) Derivatives of 5

Heating **5** briefly in excess acetic anhydride at reflux (I, Scheme 3) gave **10a** in over 90% yield. The analogue **10b** also was obtained in good yield upon reaction with isobutyric anhydride. For analytical purposes, **10a** and **10b** were purified by column chromatography on silica gel.

Treating **5** in diethyl ether at room temperature with acetyl (or benzoyl) chloride and pyridine in equimolar amounts (II, Scheme 3) afforded **11a** (**11c**) along with minor amounts of **10a** (**10c**) in 90−95% overall yield.

The relevant structural information of the isomeric derivatives **10** and **11** was presented by the CO frequency in their IR spectra, appearing at 1740 cm^{-1} in **10a** and 1633 cm^{-1} in **11a** (in $CHCl_3$ solutions), values that are in the frequency range used as a criterion to distinguish between *O*-acyl and *N*-acyl hydroxylamine derivatives.[9] The buffered reaction II gave the thermodynamically stable hydroxamic acid derivative **11**, whereas the unbuffered reaction I provided, under kinetic control, the *O*-acyl derivative **10**, in agreement with the ambident reactivity of hydroxylamine in monoacylation reactions.[9] This result is also chemical evidence for the tautomeric equilibrium in Scheme 3. The acyclic form, favored by acid catalysis as we have seen earlier, was completely displaced from the equilibrium under unbuffered (kinetically controlled) conditions. Similar competing *O*- or *N*-acetylation of 3,3,5-trimethyl-5-isoxazolidinol has been reported previously, in which the equilibrium is shifted towards the *O*-acetyl derivative during the workup procedure.[10]

Compounds **11a** and **11c** presented two sets of unequally populated signals in their ^1H and ^{13}C NMR spectra in $CDCl_3$, indicating the existence also of *cis* and *trans* diastereoisomers. The major stereoisomer of each compound was isolated in ≥ 95% purity by column chromatography and its chemical shifts were assigned unambiguously. The δ values of the minor stereoisomers were determined from the spectra of the mixture.

The major stereoisomer of **11c** was found to have *trans* stereochemistry by an NOEDIF experiment described in the Exp. Sect. This assignment is in agreement with the fact that the 3-Me signal in *trans*-**11c** appeared at higher field (δ = 1.50 ppm) than that in *cis*-**11c** (δ = 1.87 ppm), presumably because of through-space shielding by the OH group. The major isomer of **11a** was also assigned to have *trans* stereochemistry, with its 3-Me signal being upfield shifted by 0.4 ppm compared to that of the minor one. Based on this correlation, we made a provisional assignment of the equi-energetic pair *cis*/*trans*-**5** (see Exp. Sect.).

When adding TFA to the $CDCl_3$ solution of **10a** and *cis*/*trans*-**11a**, the ^1H NMR spectrum after 24 h at room temperature changed completely. The same simple pattern obtained in both cases corresponded to that of the pyrylium cation, which means that splitting occurred under these conditions.

The successful separation of diastereoisomers by column chromatography prompted us to investigate enantiomeric resolution by chiral HPLC. The pure stereoisomer *trans*-**11c** was baseline separated at 25 °C on CHIRALCEL OD-H (hexane/2-propanol, 99:1; 254 nm; 1mL·min^{-1}) into the corresponding pair of enantiomers, with retention times of 6.7 min for the (−) form and 9.0 min for the (+) form. On raising the temperature to 40 °C, a rather complex plateau was observed indicating an exchange between several very unequally populated forms. Under the same analytical conditions, *cis*- and *trans*-**11a** were only poorly separated at 25 °C, exhibiting a cluster of partially resolved rather-sharp peaks at ca. 13.8 and 14.2 min. Polarimetric detection, however, clearly showed four peaks (two negative then two positive), which account for the expected two pairs of enantiomers as well as for their stabilities at room temperature.

The results above make a clear-cut distinction between the diastereoisomers **5** and their *N*-substituted counterparts **11**. Indeed, only *cis*/*trans*-**5** fulfill the requirements for being labeled as tautomers, namely coexistence and relatively easy ($\Delta G^{\ddagger}$ below 25 kcal·mol^{-1}) interconversion.[8,11] As demonstrated by NMR spectroscopy, chiral HPLC analysis and the chemical transformations in Scheme 3, the interconversion occurred through the opened-chain tautomer **5′**. Conversely, diastereoisomeric separation, as well as enantiomeric resolution of each diastereomer, was achieved for compounds **11**. Under the terms defined above,[8,11] *cis*-**11** and *trans*-**11** are isomers, not tautomers.

Conclusion

Cyclization of δ-oxo-α,β-unsaturated ketoxime **2** with hydrochloric acid in anhydrous diethyl ether unexpectedly provided 3,3,5-trisubstituted 5-isoxazolidinol **5** and 4,5-dihydro-2,5-methano-1,3,4-dioxazepine derivative **6**. A mechanism that accounts for these products is proposed.

O-Acyl derivatives **10** and *N*-acyl (aroyl) derivatives **11** were prepared from 5-isoxazolidinol **5**. The ring−chain tautomerism of the parent **5** was studied by NMR spectroscopy and by chiral liquid chromatography. The *N*-substituted congeners *cis*/*trans*-**11** were found to have crossed the conventional energetic borderline for tautomers and behave as true isomers.

Finally, particular attention is drawn to the original and simple pathway that leads to **6**. Indeed, only a few compounds possessing the same bridged bicyclic dioxazepine skeleton have been synthesized previously through intramolecular dipolar cycloaddition of alkenyl[12] or allenyl nitrones.[13,14]

Experimental Section

Instrumentation

Melting points were determined on Boetius hot plate and are uncorrected. The IR spectra were recorded on a Carl Zeiss UR 20 instrument. The NMR spectra were recorded on a Varian Gemini 300BB instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C) or on a Bruker Avance instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C). The δ values are given in ppm from internal TMS, and the coupling constants *J* in Hz. The ^{1}H and ^{13}C NMR spectroscopic chemical shifts were determined from 1D (^{1}H, ^{13}C, DEPT) and 2D (COSY, HMQC, HMBC) experiments. The chiral HPLC experiments were performed on a screening unit composed of a Merck D-7000 system manager, a Merck−Lachrom L-7100 pump, a Merck−Lachrom L-7360 oven (which may accommodate 12 columns alimented by a Valco 12 positions valve), a Merck−Lachrom L-7400 UV-detector, and a Jasco OR-1590 polarimeter detector. Mass spectra were recorded with a Carlo−Erba QMD 1000 instrument.

CCDC-194270 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

Reagents and Solvents

Silica gel Fluka 60 was used for preparative column chromatography. The elution solvents were petroleum ether (PE; b.p. 35−45°C) and diethyl ether (EE) freshly distilled from lithium aluminum hydride. Aluminum strips (10 cm length) coated with silica gel F_{254} (Merck) were used for analytical TLC. The R_f values were measured using a PE/EE (1:1, v/v) bath.

The solvents used in chiral HPLC (hexane and 2-propanol) were HPLC grade (from SDS, Peypin, France), and were degassed and filtered through a Millipore membrane (0.45 μm) before use.

Cellulose-based chiral stationary phases, CHIRALCEL OD-H, CHIRALCEL OJ and CHIRALCEL OB-H, and amylose-based CSPs CHIRALPAK AD and CHIRALPAK AS DAICEL columns were available from Merck-Eurolab, all of them being 250 × 4.6 mm in size.

The keto-ketoxime **2** was prepared as described previously.[2] *Compound* **2** *should not be conserved since it cyclizes spontaneously on standing at room temperature giving* **3** *and* **4**. Compound **2** may be purified by chromatography on silica gel eluting with PE/EE (4:1, v/v).

Cyclization of 2: Reactions under conditions *a* and *b* in Scheme 1 were performed as described previously.[2] The reported yields are of pure compounds, isolated by column chromatography.

Reactions under Conditions *c*−*g*: Gaseous hydrogen chloride (generated from 35% hydrochloric acid and conc. sulfuric acid, and dried by bubbling through conc. sulfuric acid) was passed through anhydrous diethyl ether chilled in ice/water bath. The hydrogen chloride content (3.5 N solution was used in the runs described below) was determined by titration with sodium hydroxide using phenolphthalein as indicator. The general procedure was the following: Freshly prepared **2** (360 mg, 1.5 mmol) dissolved in anhydrous diethyl ether was treated dropwise with ethereal hydrogen chloride over 5−10 min under magnetic stirring (the amount of solvent and reagent according to the ratios in Scheme 1). Initially, a clouding of the solution was observed, followed by a steady precipitation. After stirring for 3 h at room temperature, aqueous sodium bicarbonate was added until the pH was neutral, at which point the solid dissolved. The phases were separated and the aqueous layer was extracted further with diethyl ether. The organic extract was washed with brine, dried over Na_2SO_4 and then the solvents were evaporated under vacuum. The crude mixture was separated by column chromatography on silica gel (10 g of SiO_2/g of compound). The components were collected in the following order eluting with EE/PE mixtures in the concentrations (%v) indicated in brackets: **4** (5%), **3** (10%), **7** (10%), **6** (35%), **5** (50%, then 100% EE).

1-(5′-*tert*-Butyl-5′-hydroxy-3′-methylisoxazolidin-3′-yl)-3,3-dimethylbutan-2-one (5): Colorless crystals, m.p. 77−78 °C; single spot by TLC, R_f = 0.10. $C_{14}H_{27}NO_3$ (257.4): calcd. C 65.33, H 10.58, N 5.44; found C 65.59, H 10.48, N 5.52. IR (CCl_4): 1708 (1696 sh), 3230 (br), 3500 (br), 3590 (sharp) cm^{-1}.

The NMR spectra displayed two equally populated sets of signals, assigned to a diastereoisomeric of *cis*/*trans* pair as follows:

***trans*-5:** ^{1}H NMR: δ = 1.09 (s, 9 H, ***t*Bu**C-5′), 1.18 (s, 9 H, ***t*Bu**C-2), 1.24 (s, 3 H, **Me**C-3′), 1.96 (d, J_{AB} = 13.9 Hz, 1 H, $\mathbf{H_A}$C-4′), 2.26 (d, J_{BA} = 13.9 Hz, 1 H, $\mathbf{H_B}$C-4′), 2.73 (d, J_{AB} = 18.6 Hz, 1 H, $\mathbf{H_A}$C-1), 3.03 (d, J_{BA} = 18.6 Hz, 1 H, $\mathbf{H_B}$C-1), 4.30 (1 H, br. s, D_2O-exch), 5.80 (1 H, br. s, D_2O-exch) (NH, OH) ppm. ^{13}C NMR: δ = 25.3 ($\mathbf{Me_3}$CC-5′), 26.2 ($\mathbf{Me_3}$C-3), 27.9 (**Me**C-3′), 36.5 (**C**C-5′), 42.3 (H_2**C**-1), 44.7 (C-3), 47.2 (H_2**C**-4′), 61.2 (C-3′), 113.8 (C-5′), 216.3 (C-2) ppm.

***cis*-5:** ^{1}H NMR: δ = 1.04 (s, 9 H, ***t*Bu**C-5′), 1.15 (s, 9 H, ***t*Bu**C-2), 1.39 (s, 3 H, **Me**C-3′), 1.96 (d, J_{AB} = 13.6 Hz, 1 H, $\mathbf{H_A}$C-4′), 2.41 (d, J_{BA} = 13.6 Hz, 1 H, $\mathbf{H_B}$C-4′), 2.81 (d, J_{AB} = 18.4 Hz, 1 H, $\mathbf{H_A}$C-1), 2.97 (d, J_{BA} = 18.4 Hz, 1 H, $\mathbf{H_B}$C-1), 4.30 (br. s, 1 H, D_2O-exch), 5.80 (br. s, 1 H, D_2O-exch) (NH, OH) ppm. ^{13}C NMR: δ = 25.1 ($\mathbf{Me_3}$CC-5′), 26.4 ($\mathbf{Me_3}$C-3), 22.7 (**Me**C-3′), 36.6 (**C**C-5′), 46.2 (H_2**C**-1), 44.4 (C-3), 47.2 (H_2**C**-4′), 62.5 (C-3′), 113.7 (C-5′), 215.5 (C-2) ppm.

5-Hydroxyamino-2,2,5,8,8-pentamethylnonane-3,7-dione (5′): ^{1}H NMR ($CDCl_3$/trace of TFA): 1.15 (s, 18 H, ***t*Bu**C-3, ***t*Bu**C-7), 1.45 (s, 3 H, **Me**C-5), 3.08 (d, J_{AB} = 18.4 Hz, 2 H, $\mathbf{H_A}$C-4, $\mathbf{H_A}$C-6), 3.17 (d, J_{BA} = 18.4 Hz, 2 H, $\mathbf{H_B}$C-4, $\mathbf{H_B}$C-6) ppm.

1,3-Di-*tert*-butyl-5-methyl-2,7-dioxa-6-aza-bicyclo[3.2.1]oct-3-ene (6): Colorless crystals, m.p. 117−119°C; R_f = 0.15. MS (rel. int.): *m*/*z* = 240 [M + 1] (0.2), 239 [M] (0.6), 224 (12.3), 207 [M − NHOH] (78.9), 140 [M − *t*BuCOCH$_2$] (77.6), 57 (100.0). ^{1}H NMR: δ = 1.07 (s, 9 H, ***t*Bu**C-3), 1.08 (s, 9 H, ***t*Bu**C-1), 1.32 (s, 3 H, **Me**C-5), 1.95 (d, J_{AB} = 10.8 Hz, 1 H, $\mathbf{H_A}$C-8), 2.09 (d, J_{AB} = 10.8 Hz, 1 H, $\mathbf{H_B}$C-8), 4.70 (s, 1 H, **H**C-4), 5.40 (1 H, br. s, N**H**) ppm. ^{13}C NMR: δ = 18.6 (**Me**C-5), 25.3 ($\mathbf{Me_3}$CC-1), 27.8 ($\mathbf{Me_3}$CC-3), 34.4 (**C**C-3), 36.2(**C**C-1), 42.3 (H_2**C**-8), 58.1 (C-5), 99.0 (H**C**-4), 112.7 (C-1), 162.2 (C-3) ppm.

(3-*E*, 4-*E*)-2,2,5,8,8-Pentamethylnon-4-ene-3,7-dione 3-oxime (7): Colorless crystals, m.p. 146−147°C; R_f = 0.45. IR (KBr): $\tilde{\nu}$ = 3320 (br., OH), (CCl_4) 1705, 3260 (br), 3590 (sharp) cm^{-1}. MS (rel. int.) *m*/*z* = 239 [M$^+$] (0.1), 224 (2.7), 140 (62.2), 57 (100.0). ^{1}H NMR: δ = 1.13 (s, 9 H, ***t*Bu**C-3), 1.15 (s, 9 H, ***t*Bu**C-7), 1.56 (s, 3 H, **Me**C-5), 3.34 (s, 2 H, $\mathbf{H_2}$C-6), 5.48 (s, 1 H, **H**C-4), 7.50 (1 H, br., **H**O) ppm. ^{13}C NMR: δ = 19.8 (**Me**C-5), 26.3 ($\mathbf{Me_3}$C-8), 27.8 ($\mathbf{Me_3}$C-2), 37.6 (C-2), 44.6 (C-8), 46.4 (C-6), 118.5 (H**C**-4), 138.7 (C-5), 163.0 (C-3), 213.0 (C-7) ppm.

Reaction of 5 with Anhydrides (Method I): 5 (514 mg, 2 mmol) in acetic anhydride (2 mL) was heated at 100−110°C (oil bath) for 15 min. After cooling, water (25 mL) was added and several extractions with diethyl ether were made. The ethereal phases were carefully neutralized with sodium hydrogen carbonate solution, washed with brine and then the solvents were evaporated, giving **10a** (570 mg, 95% yield). An analytical sample was obtained by column chromatography on silica gel, eluting with PE/EE (4:1, v/v). In a similar manner, reaction with isobutyric anhydride gave **10b** in 87% yield.

5-Acetooxyamino-2,2,5,8,8-pentamethylnonane-3,7-dione (10a): Oil. $C_{16}H_{29}NO_4$ (299.4): calcd. N 4.68; found N 4.63. R_f = 0.30. IR ($CHCl_3$): 1475 (1462 sh), 1703, 1740, 3240 cm^{-1}. ^1H NMR: δ = 1.11 (s, 18 H, ***t*Bu**C-3, ***t*Bu**C-7), 1.21 (s, 3 H, **Me**C-5), 2.08 (s, 3 H, **Me**-CO), 2.95 (d, J_{AB} = 18.3 Hz, 2 H, $\mathbf{H_A}$C-4, $\mathbf{H_A}$C-6), 3.04 (d, J_{BA} = 18.3 Hz, 2 H, $\mathbf{H_B}$C-4, $\mathbf{H_B}$C-6), 8.00 (1 H, br. s, NH) ppm. ^{13}C NMR: δ = 19.2 (**Me**-CO), 22.4 (**Me**C-5), 26.3 ($\mathbf{Me_3}$C-2, $\mathbf{Me_3}$C-8), 41.0 (H_2**C**-4, H_2**C**-6), 44.8 (C-2, C-8), 58.5 (C-5), 169.9 (O**C**O), 215.5 (C-3, C-7) ppm.

5-Isobutyrooxyamino-2,2,5,8,8-pentamethylnonane-3,7-dione (10b): R_f = 0.50. ^1H NMR: δ = 1.11 (s, 18 H, ***t*Bu**C-3, ***t*Bu**C-7), 1.20 (d, *J* = 7 Hz, 6 H, $\mathbf{Me_2}$CH), 1.22 (s, 3 H, **Me**C-5), 2.61 (sep, 1 H, *J* = 7, Me_2**CH**), 2.95 (d, J_{AB} = 18.3 Hz, 2 H, $\mathbf{H_A}$C-4, $\mathbf{H_A}$C-6), 3.04 (d, J_{BA} = 18.3 Hz, 2 H, $\mathbf{H_B}$C-4, $\mathbf{H_B}$C-6), 8.13 (br. s, 1 H, N**H**) ppm. ^{13}C NMR: δ = 19.0 ($\mathbf{Me_2}$CH), 22.4 (**Me**C-5), 26.3 ($\mathbf{Me_3}$C-2, $\mathbf{Me_3}$C-8), 33.0 (**C**HMe_2), 40.9 (H_2**C**-4, H_2**C**-6), 44.7 (C-2, C-8), 58.6 (C-5), 175.8 (O**C**O), 215.4 (C-3, C-7) ppm.

Reaction of 5 with Acetyl or Benzoyl Chloride (Method II): A solution of **5** (514 mg, 2 mmol) and pyridine (160 mg, 2 mmol) in diethyl ether (5 mL) stirring at room temperature was treated dropwise over 15 min with freshly distilled acetyl chloride (160 mg, 2 mmol) dissolved in diethyl ether (5 mL). After an additional 45 min of stirring, the pyridinium chloride precipitate was filtered off and washed with diethyl ether. The ethereal filtrate was washed with brine, dried over sodium sulfate and then the solvents were evaporated under vacuum to give the acetylation product (535 mg, 89% yield). The crude product (determined by ^1H NMR spectroscopy) was composed of **11a** and **10a** (97:3). The cyclic derivative **11a** consisted, in turn, of two diastereoisomers in a 3:1 ratio. Column chromatography with EE/PE (1:2.3, v/v) gave the major stereoisomer, *trans*-**11a**, in ≥ 95% purity (295 mg, 50% yield). The reaction of **5** with benzoyl chloride, performed in a similar manner, gave a mixture consisting of **11c** and **10c** in an 87:13 molar ratio. The diastereoisomeric ratio in **11c** was 6:1. Column chromatography afforded **10c** (9%) and the major stereoisomer *trans*-**11c** (54%) in ≥ 95% purity.

5-Benzoyloxyamino-2,2,5,8,8-pentamethylnonane-3,7-dione (10c): R_f = 0.50. ^1H NMR: δ = 1.12 (s, 18 H, ***t*Bu**C-3, ***t*Bu**C-7), 1.33 (s, 3 H, **Me**C-5), 3.06 (d, J_{AB} = 18.2 Hz, 2 H, $\mathbf{H_A}$C-4, $\mathbf{H_A}$C-6), 3.14 (d, J_{BA} = 18.2 Hz, 2 H, $\mathbf{H_B}$C-4, $\mathbf{H_B}$C-6), 7.46 (t, *J* = 7.6, *meta*-2 H), 7.59 (t, *J* = 7.9, *para*-1 H), 7.98 (d, *J* = 7.9, *ortho*-2 H), 8.50 (1 H, br. s, N**H**) ppm.

***trans*-1-(2′-Acetyl-5′-*tert*-butyl-5′-hydroxy-3′-methylisoxazolidin-3′-yl)-3,3-dimethylbutan-2-one (11a):** Colourless crystals, m.p. 68−71 °C. $C_{16}H_{29}NO_4$ (299.4): calcd. N 4.68; found N 4.59. R_f = 0.20. IR ($CHCl_3$): 1633 (1608 sh), 1698, 3365 (br) cm^{-1}. ^1H NMR: δ = 1.02 (s, 9 H, ***t*Bu**C-5′), 1.11 (s, 9 H, ***t*Bu**C-2), 1.32 (s, 3 H, **Me**C-3′), 1.94 (s, 3 H, **Me**CO), 2.20 (d, J_{AB} = 13.3 Hz, 1 H, $\mathbf{H_A}$C-4′), 2.33 (d, J_{BA} = 13.3 Hz, 1 H, $\mathbf{H_B}$C-4′), 2.77 (d, J_{AB} = 19.1 Hz, 1 H, $\mathbf{H_A}$C-1), 4.01 (d, J_{BA} = 19.1 Hz, 1 H, $\mathbf{H_B}$C-1), 7.10 (s, 1 H, OH) ppm. ^{13}C NMR: δ = 21.9 (**Me**CO), 25.0 ($\mathbf{Me_3}$CC-5′), 26.8 ($\mathbf{Me_3}$C-3), 27.0 (**Me**C-3′), 36.2 (**C**C-5′), 43.2 (H_2**C**-1), 44.5 (C-3), 48.9 (H_2**C**-4′), 61.0 (C-3′), 109.0 (C-5′), 167.4 (N**C**O), 216.5 (C-2) ppm.

***cis*-11a:** ^1H NMR: δ = 1.04 (s, 9 H, ***t*Bu**C-5′), 1.12 (s, 9 H, ***t*Bu**C-2), 1.73 (s, 3 H, **Me**C-3′), 2.02 (s, 3 H, **Me**CO), 2.33 (d, J_{AB} = 13.2 Hz, 1 H, $\mathbf{H_A}$C-4′), 2.54 (d, J_{BA} = 13.2 Hz, 1 H, $\mathbf{H_B}$C-4′), 2.76 (d, J_{AB} = 18.0 Hz, 1 H, $\mathbf{H_A}$C-1), 3.66 (d, J_{BA} = 18.0 Hz, 1 H, $\mathbf{H_B}$C-1), 7.40 (1 H, br. s, OH) ppm. ^{13}C NMR: δ = 22.1 (**Me**CO), 23.9 (**Me**C-3′), 25.0 ($\mathbf{Me_3}$CC-5′), 26.2 ($\mathbf{Me_3}$C-3), 36.8 (**C**C-5′), 44.5 (C-3), 44.6 (H_2**C**-1), 47.9 (H_2**C**-4′), 63.5 (C-3′), 108.2 (C-5′), 166.0 (N**C**O), 214.1 (C-2) ppm.

***trans*-1-(2′-Benzoyl-5′-*tert*-butyl-5′-hydroxy-3′-methylisoxazolidin-3′-yl)-3,3-dimethylbutan-2-one (11c):** Colourless crystals, m.p. 109−110°C. $C_{21}H_{31}NO_4$ (361.5): calcd. N 3.87; found N 3.90. R_f = 0.30. IR ($CHCl_3$): $\tilde{\nu}$ = 1578, 1618, 1694, 3370 (br) cm^{-1}. ^1H NMR: δ = 1.06 (s, 9 H, ***t*Bu**C-5′), 1.17 (s, 9 H, ***t*Bu**C-2), 1.50 (s, 3 H, **Me**C-3′), 2.35 (d, J_{AB} = 13.2 Hz, 1 H, $\mathbf{H_A}$C-4′), 2.45 (d, J_{BA} = 13.2 Hz, 1 H, $\mathbf{H_B}$C-4′), 2.87 (d, J_{AB} = 19.2 Hz, 1 H, $\mathbf{H_A}$C-1), 4.29 (d, J_{BA} = 19.2 Hz, 1 H, $\mathbf{H_B}$C-1), 7.34 (t, *J* = 7.2, *meta*-2 H), 7.39 (t, *J* = 7.2, *para*-1 H), 7.53 (s, 1 H, OH), 7.87 (d, *J* = 6.8, *ortho*-2 H) ppm. ^{13}C NMR: δ = 25.0 ($\mathbf{Me_3}$CC-5′), 26.3 (**Me**C-3′), 26.9 ($\mathbf{Me_3}$C-3), 36.2 (**C**C-5′), 43.3 (H_2**C**-1), 44.8 (C-3), 48.8 (H_2**C**-4′), 61.6 (C-3′), 109.3 (C-5′), 127.5 (*meta*-2**C**H), 129.4 (*ortho*-2**C**H), 130.6 (*para*-**C**H), 134.3 (Cq in C_6H_5), 165.0 (N**C**O), 216.8 (C-2) ppm.

The stereochemical assignment of *trans*-**11c** was based on the following NOEDIF experiment: Irradiation of the proton H_B at C-1 (δ = 4.29 ppm) gave positive signal for the *t*Bu group at C-5′ (δ = 1.06 ppm), meaning that substituents 5′-*t*Bu and CH_AH_B (linked to C-3′) are on the same side of the heterocyclic ring.

***cis*-11c:** ^1H NMR: δ = 1.02 (s, 9 H, ***t*Bu**C-5′), 1.16 (s, 9 H, ***t*Bu**C-2), 1.87 (s, 3 H, **Me**C-3′), 2.38 (d, J_{AB} = 13.5 Hz, 1 H, $\mathbf{H_A}$C-4′), 2.65 (d, J_{BA} = 13.5 Hz, 1 H, $\mathbf{H_B}$C-4′), 2.93 (d, J_{AB} = 18.0 Hz, 1 H, $\mathbf{H_A}$C-1), 3.83 (d, J_{BA} = 18.0 Hz, 1 H, $\mathbf{H_B}$C-1), 7.30−7.40 (m, 3 H, 1 × *para*-H, 2 × *meta*-H), 7.76 (d, *J* = 6.8 Hz, 2 H, *ortho*-H) ppm.

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