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3-Halomethylated cyclic nitronates: synthesis and nucleophilic substitution

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ABSTRACT

A method for the introduction of a halogen atom into the methyl group attached to the C-3 atom of five- and six-membered cyclic nitronates (isoxazoline *N*-oxides and oxazine *N*-oxides, respectively) has been studied. The process involves silylation of starting 3-methyl-substituted cyclic nitronates followed by halogenation of the resulting *N*-(silyloxy)enamines. While five- and six-membered cyclic enamines behave similarly toward elemental bromine and iodine, their reactions with NBS give different products, that were rationalized by stereoelectronic effects. The obtained halogenated nitronates were coupled with various nucleophiles affording new nitronates functionalized at the C-3 position.

1. Introduction

Nitronates represent an interesting class of compounds with diverse reactivity.[1] Despite the fact that nitronates are usually considered merely as derivatives of nitro compounds, their chemistry is evolving into a separate subject, given the increasing number of studies in recent years.[2]

Currently, two types of nitronates have been studied in detail, namely, silyl- and alkylnitronates (Fig. 1). The silicon derivatives **A** are moisture-sensitive and, preferably, should be generated in situ and immediately utilized in further transformations. On the other hand, the alkyl nitronate fragment is hydrolytically stable and tolerates a wide variety of functional groups. The only disadvantage of the latter, is that nitronates **B** with a conventional alkyl substituent at oxygen (e.g., Y=Me, Et) possess limited stability,[1a] and, as a consequence, much more stable cyclic nitronates **C** are mainly investigated.

Recently we communicated an approach for the synthesis of halomethyl-substituted derivatives **E** by halogenation of the methyl group in cyclic nitronates **D**, and demonstrated that the halogen can be substituted by some nucleophiles to give a wide range of nitronates **F**.[3] The latter sequence would constitute a convenient method for the preparation of functionalized cyclic nitronates, for which other strategies of synthesis may be unproductive. Herein we report the full description of these processes.

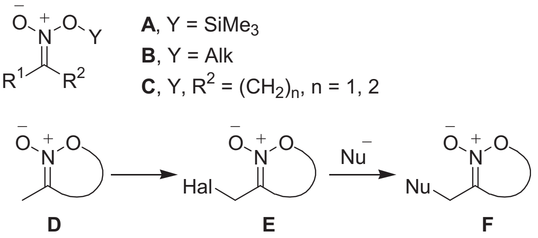

Fig. 1. Nitronates.

2. Results and discussion

Starting cyclic nitronates **1** and **2** were obtained from readily available nitro ethane according to literature procedures[4–6] (Scheme 1). Subsequent silylation of **1** or **2** was performed according to improved literature procedures[4] leading to *N*-(silyloxy)enamines **3** in high yields.[7] Compounds **3** were either used just after preparation or stored in hexane solution at −30 °C.

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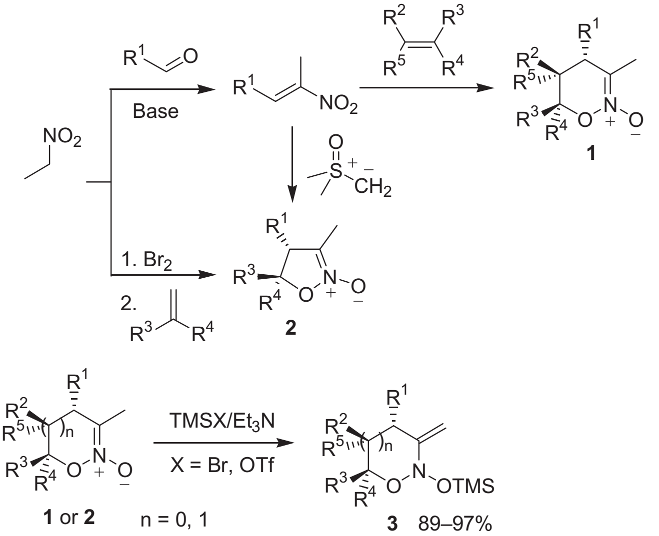
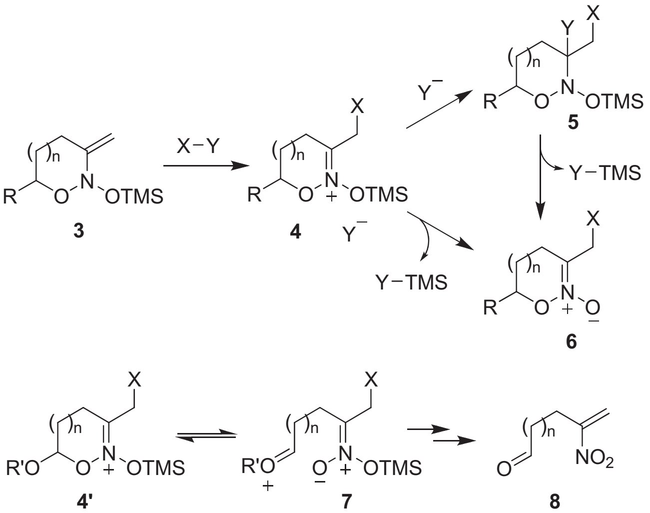


Scheme 1.

2.1. Halogenation of *N*-(silyloxy)enamines 3

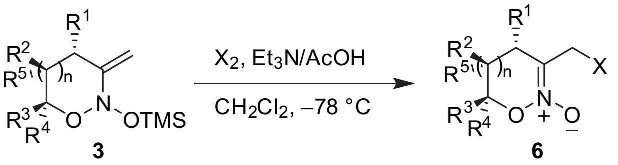
Two halogenating systems were considered—elemental halogen and *N*-halosuccinimide. The general pathway is shown in Scheme 2. After addition of halonium ion **X**$^+$ to the C=C, the intermediate iminium cation **4** may either add the counterion **Y**$^-$ to give adduct **5** or expel trimethylsilyl cation leading to nitronate **6**. The adduct **5** may also transform to **6**, although the efficiency of this step likely depends on the nature of Y.[8] When elemental bromine or iodine is used for halogenation, both pathways for the formation of **6** are indistinguishable since they are expected to proceed very fast furnishing bromo- or iodosilane as by-products. Importantly, the halosilane by-product may cause decomposition of the starting *N*-(silyloxy)enamines **3**,[9] and therefore a basic scavenger has to be present in the mixture to trap the halosilane.



Scheme 2.

If the starting *N*-(silyloxy)enamines contain the 6-alkoxy group, the intermediates **4**′ may undergo ring cleavage to generate oxocarbenium species **7**, which eventually, after stabilization and elimination of TMS–X, would afford nitro alkenes **8**.[10]

Table 1
Halogenation of enamines **3** with X_2

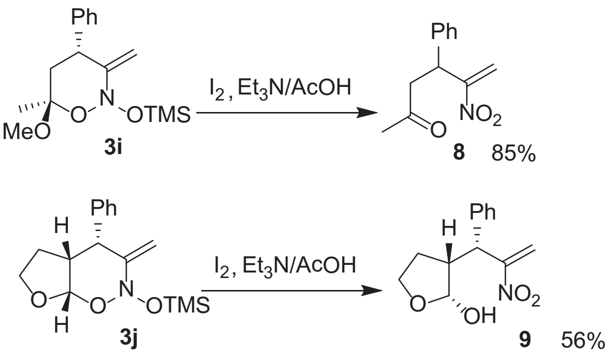


#	**3**	*n*	R^1	R^2	R^3	R^4	R^5	X_2	**6**	Yield, %[a]
1	**3a**	1	Ph	H	Me	Me	H	I_2	**6a-I**	81
2	**3b**	1	Me	H	Me	Me	H	I_2	**6b-I**	45
3	**3c**	1	OBz	H	Me	Me	H	I_2	**6c-I**	81
5	**3d**	1	Ph	$-(CH_2)_4-$		H	H	I_2	**6d-I**	86
6	**3e**	0	H	—	Ph	H	—	I_2	**6e-I**	68
7	**3e**	0	H	—	Ph	H	—	Br_2	**6e-Br**	85
8	**3f**	0	H	—	4-BrC_6H_4	H	—	Br_2	**6f-Br**	95
9	**3g**	0	H	—	CO_2Me	Me	—	Br_2	**6g-Br**	87
10	**3h**	0	Ph	—	H	H	—	Br_2	**6h-Br**	83

[a] Isolated yield.

Enamines **3** were treated with bromine or iodine in dichloromethane at −78 °C in the presence of triethylamine and acetic acid as a scavenger of the halosilane by-product (Table 1). Halogen-substituted products **6** were isolated after chromatography, in reasonable yields. Though introduction of iodine is preferable in terms of subsequent nucleophilic substitution, five-membered iodo-nitronates (and in some cases six-membered, e.g., **6b-I**) exhibited limited stability, decomposing even in their crystalline state, that decreased their yield, as well as hampered isolation and characterization. For that reason five-membered *N*-(silyloxy)enamines **3e–h** were subjected mainly to bromination, which proceeded smoothly, providing the corresponding bromo-nitronates **6e–h-Br** (entries 7–10).

Halogenation of alkoxy-substituted enamines **3i,j** led to ring-opened products, that is, the corresponding α-nitro alkenes **8** and **9**, respectively (Scheme 3).



Scheme 3.

Bromination of six-membered enamines **3a–d,i,j** with *N*-bromosuccinimide (NBS) proceeded similarly to their reactions with bromine (Table 2). Here again either bromo-nitronates **6a–d-Br** or nitro alkene **8** was produced.

Surprisingly, the reaction of five-membered enamine **3e** with NBS did not furnish the expected halo-nitronate **6e-Br**. Instead, the product **10a** arising from the addition of NBS to the C,C-double bond was obtained as mixture of two isomers with cis-orientation of silyloxy and succinimido substituents in all cases (Table 3).[11] Similar products were formed in reactions of enamines **3e**′ and **3f**′ bearing a *tert*-butyldimethylsilyloxy group.[12] Notably, compounds **10** did not show any signs of elimination of silylsuccinimide (see Scheme 2, conversion of **5** to **6**) even after refluxing in acetonitrile for 3 h.[13]

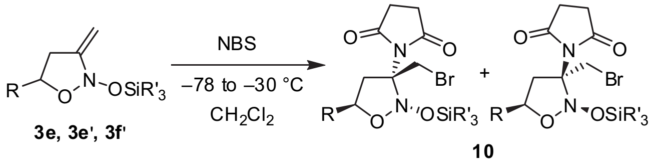
To explain the difference between reactivity of five- and six-membered enamines with NBS it is necessary to consider stereoelectronic requirements for halogenation of **3**. Thus, for effective

Table 2
Halogenation of enamines **3** ($n=1$) with NBS

No.	3	R^1	R^2	R^3	R^4	R^5	Product	Yield, %
1	**3a**	Ph	H	Me	Me	H	**6a-Br**	93
2	**3b**	Me	H	Me	Me	H	**6b-Br**	66
3	**3c**	OBz	H	Me	Me	H	**6c-Br**	80
4	**3d**	Ph	$-(CH_2)_4-$		H	H	**6d-Br**	86
5	**3i**	Ph	H	OMe	Me	H	**8**	57
6	**3j**	Ph	H	H	$-O(CH_2)_2-$		**9**	—[a]

[a] Mixture of unidentified products.

Table 3
Addition of NBS to five-membered cyclic enamines **3**



#	3	R	SiR'_3	10	Yield of **10**, %	dr[a]
1	**3e**	Ph	$SiMe_3$	**10a**	76	1.8:1
2	**3e′**	Ph	Si^tBuMe_2	**10b**	84	1.6:1
3	**3f′**	p-Br$-C_6H_4$	Si^tBuMe_2	**10c**	91	1.6:1

[a] The relative configuration was assigned by 2D-NOESY for **10b** and **10c**; the assignment of **10a** was made by analogy.

stabilization of positive charge arising upon addition of an electrophile at the C=C bond, the nitrogen lone pair should have a coplanar arrangement with the π-orbitals as shown for conformation **11** in Fig. 2. In this case, iminium ion **12** bearing planar nitrogen is formed. This is likely to be realized for six-membered *N*-(silyloxy) enamines, since according to structural data,[4] they exist in conformation **13** with an axial lone pair, which is well disposed for overlap with the C=C bond.

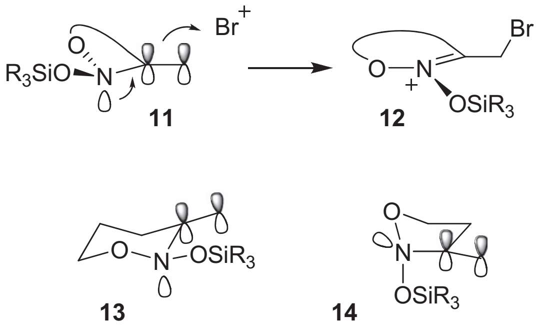


Fig. 2. Stereoelectronic effects of halogenation.

To gain some insight into the structure of five-membered enamines **3e**–**h**, compound **3f′** was studied in greater detail. In the solid state, as revealed by single crystal X-ray diffraction analysis (Fig. 3), the silyloxy group is located in a pseudo-axial orientation. Therefore, the nitrogen lone pair occupies a pseudo-equtorial position as depicted for structure **14**, that renders inefficient its overlap with the C=C bond. At the same time, as is evident from NMR spectra of **3f′**, in solution it exists as an equilibrium of two species with the ratio ca. 6:1 that may correspond either to a conformational change of the cycle or to nitrogen lone pair inversion (or a combination of both).[14] Furthermore, this equilibrium raises the questions on the relative reactivities of these species, as well as the relative rates of this stereodynamic process and bromination of **3f′**. While these questions require detailed mechanistic studies, at present we may tentatively propose that divergent behavior of five- and six-membered enamines is associated with a difference of their reactive conformations **13** versus. **14**.[15]

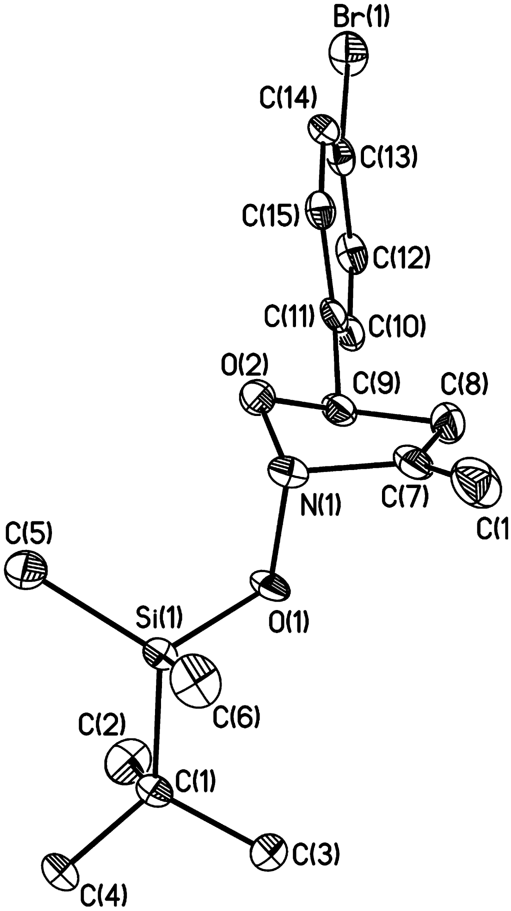


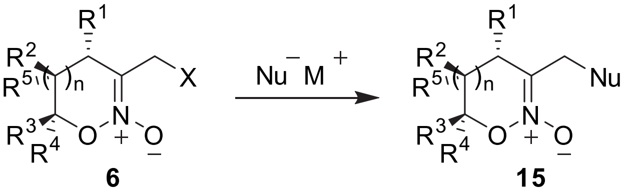
Fig. 3. The molecular structure of **3f′** Non-hydrogen atoms are presented by thermal ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

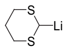
2.2. Nucleophilic substitution

Nitronates **6** were treated with various types of nucleophilic reagents to give products of substitution of halogen (Table 4). Potassium phthalimide, thiophenolate and malonate, as well as sodium benzenesulfinate, gave nitronates **15** in high yields. The reactions were typically carried out in DMF as solvent at 0 °C to room temperature, and were complete within 30 min. However, reaction of iodo-nitronate **6d-I** with malonate proceeded much cleaner when the sodium salt was used in tetrahydrofuran as solvent and mixing the reagents at −40 °C. 2-Lithio-1,3-dithiane also proved to be a suitable nucleophile affording the desired product in 92% yield (entry 5).

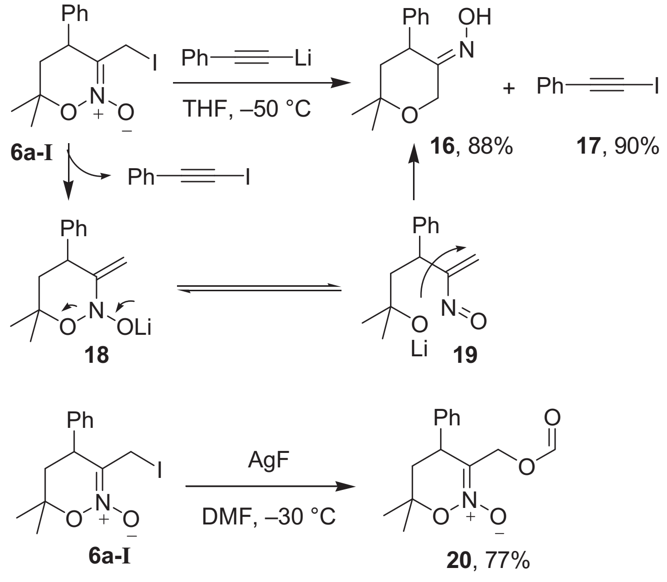
When nitronate **6a-I** was reacted with lithium phenylacetylenide in tetrahydrofuran, instead of the expected substitution product we obtained a mixture of oxime **16** and iodoacetylene **17** in good yields (Scheme 4). The mechanism of this process likely implies initial attack of the acetylenide nucleophile on the iodine[16] to generate anionic species **18**, which undergoes the cleavage of the endocyclic N–O bond followed by recyclization of nitrosoalkene **19**.[17] We also attempted to substitute the iodine by fluoride in reaction of **6a-I** with silver(I) fluoride in DMF. However, only product **20**, originating from the substitution of iodine by the molecule of DMF with subsequent hydrolysis, was observed.

Table 4
Nucleophilic substitution



#	6	X	*N*	R^1	R^2	R^3	R^4	R^5	Nu^-M^+	Conds.[a]	15	Yield of **15**, %
1	**6a-I**	I	1	Ph	H	Me	Me	H	PhthalNK	i	**15a**	82
2	**6a-I**	I	1	Ph	H	Me	Me	H	4-MeC_6H_4S K	ii	**15b**	87
3	**6a-I**	I	1	Ph	H	Me	Me	H	$(MeO_2C)_2CH$ K	ii	**15c**	88
4	**6a-I**	I	1	Ph	H	Me	Me	H	$PhSO_2Na$	i	**15d**	100
5	**6a-Br**	Br	1	Ph	H	Me	Me	H		iii	**15e**	92
6	**6c-I**	I	1	OBz	H	Me	Me	H	$(MeO_2C)_2CH$ K	ii	**15f**	93
7	**6d-I**	I	1	Ph	$-(CH_2)_4-$		H	H	$(MeO_2C)_2CH$ Na	iv	**15g**	97
8	**6d-I**	I	1	Ph	$-(CH_2)_4-$		H	H	$PhSO_2Na$	i	**15h**	99
9	**6e-Br**	Br	0	H	—	Ph	H	—	$(MeO_2C)_2CH$ Na	iv	**15i**	84
10	**6f-Br**	Br	0	H	—	4-BrC_6H_4	H	—	$(MeO_2C)_2CH$ Na	iv	**15j**	93
11	**6g-Br**	Br	0	H	—	CO_2Me	Me	—	$(MeO_2C)_2CH$ Na	iv	**15k**	76
12	**6h-Br**	Br	0	Ph	—	H	H	—	$(MeO_2C)_2CH$ Na	iv	**15l**	95

[a] i: PhthalNK (1.4 equiv) or $PhSO_2Na$ (1.1 equiv), DMF, 0 °C—rt, 15 min. ii: NuH (1.25 equiv), *t*BuOK (1.1 equiv), DMF, −40–0 °C, 30 min. iii: NuH (1.25 equiv), BuLi (1.05 equiv), THF, −40–0 °C, 2 h. iv: NuH (1.25 equiv), NaH (1.1 equiv), THF, −40–0 °C, 1 h.



Scheme 4.

3. Conclusions

The halogenation of five- and six-membered cyclic *N*-(silyloxy) enamines **3** has been studied. Reactions with elemental bromine or iodine provide 3-halomethylsubstituted cyclic nitronates **6**, whereas the outcome of treatment with NBS depends on the ring size. While six-membered cyclic enamines afford halogenated nitronates **6**, five-membered enamines add NBS across the C,C-double bond. The halogenated nitronates **6** undergo facile nucleophilic substitution of the halogen with a series of nucleophiles furnishing a range of 3-functionalized cyclic nitronates **15**. Given that various cyclic nitronates can be readily obtained from nitro ethane and other simple molecules, the described methodology can be considered as a base for a new strategy of assembling of cyclic nitronates bearing a functionalized substituent at the C-3 position.

4. Experimental section

4.1. General

All reactions were performed in oven-dried (150 °C) glassware under argon. The following solvents and reagents were distilled from the indicated drying agents: CH_2Cl_2, Et_3N (CaH_2); THF (Na, benzophenone ketyl); DMF (P_2O_5, under vacuum). NMR spectra were recorded on a Bruker AM-300 or AC-200 instruments and referenced to residual solvent peak. Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. The ratios of stereoisomers were derived from the relative integral intensities of the characteristic signals in the ^1H NMR spectra. IR spectra were recorded on a Bruker VECTOR 22 instrument in the range 400–4000 cm^{-1}. Elemental analyses were performed by the Analytical Laboratory of the Institute of Organic Chemistry. HRMS data were obtained on Bruker microTOFF instrument. Melting points were determined on Kofler melting point apparatus and are uncorrected.

4.2. Iodination of enamines 3

Et_3N (116 μL, 1.15 mmol) and AcOH (63 μL, 1.10 mmol) were mixed in CH_2Cl_2 (1.0 mL). The resulting solution was cooled to −78 °C (acetone/dry ice), and a solution of enamine **3** (1.00 mmol) in CH_2Cl_2 (2.0 mL) was added, followed by dropwise addition of a solution of I_2 (264 mg, 1.05 mmol) in CH_2Cl_2 (2.0 mL) over 5 min under intensive stirring. The mixture was stirred for 10 min at −78 °C and 30 min at −30 °C, poured into EtOAc (25 mL)/soln of 100 mg of $Na_2S_2O_3$ in 20 mL of H_2O. The aqueous layer was separated and back-extracted with EtOAc (2×10 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Solvents were evaporated in vacuo at 35 °C, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/5→1/3).

4.3. Bromination of enamines 3 with bromine (method A)

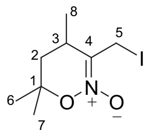
Et_3N (116 μL, 1.15 mmol) and AcOH (63 μL, 1.10 mmol) were mixed in CH_2Cl_2 (1.0 mL). The resulting solution was cooled to −78 °C (acetone/dry ice), and a solution of enamine **3** (1.00 mmol) in CH_2Cl_2 (2.0 mL) was added, followed by dropwise addition of a solution of Br_2 (51 μL, 1.05 mmol) in CH_2Cl_2 (2.0 mL) over 5 min with intensive stirring. The mixture was stirred for 10 min at −78 °C and poured into EtOAc (25 mL)/soln of 10 mg of Na_2SO_3 in 20 mL of H_2O. The aqueous layer was separated and back-extracted with EtOAc (2×10 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4. Solvents were evaporated in vacuo at 35 °C and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/5→1/3).

4.4. Bromination of enamines 3 with NBS (method B)

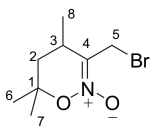
NBS (198 mg, 1.10 mmol) was added in one portion to a pre-cooled (−78 °C, acetone/dry ice) stirred solution of enamine **3** (1.00 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred for 10 min at −78 °C and for 30 min at −30 °C upon which the precipitate of NBS dissolved. The mixture was allowed to warm to room temperature. [In the case of six-membered derivatives **3**, methanol (0.5 mL) was added to hydrolize *N*-silylsuccinimide and the mixture was stirred for 10 min at room temperature.] Solvents were evaporated in vacuo at 40 °C, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/5→1/3 was used for isolation of all compounds **6** and **8**; EtOAc/hexane, 1/10→1/5 was used for isolation of nitrosoacetals **10**).

*4.4.1. 3-(Iodomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-4H-[1,2]-oxazine 2-oxide (**6a-I**).* Yield 278 mg (81%), mp=96–97 °C (Et_2O) with decomposition, R_f=0.53 (EtOAc/hexane, 1/1).[3]

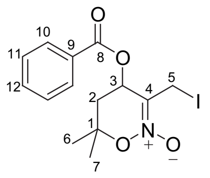
*4.4.2. 3-(Bromomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-4H-[1,2]-oxazine 2-oxide (**6a-Br**).* By method B, yield 277 mg (93%), mp=101–102 °C (Et_2O/CH_2Cl_2, 1/1) with decomposition, R_f=0.47 (EtOAc/hexane, 1/1).[3]



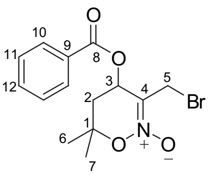
*4.4.3. 3-(Iodomethyl)-4,6,6-trimethyl-5,6-dihydro-4H-[1,2]-oxazine 2-oxide (**6b-I**).* Yield 128 mg (45%), crystalline solid but rapidly decomposes at room temperature, R_f=0.37 (EtOAc/hexane, 1/1). This compound has a short lifetime in chloroform solution. ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.27 [d, ^3J=7.0, 3H, CH_3(8)], 1.35 and 1.37 [2s, 6H, CH_3(6,7)], 1.68 [dd, ^3J=10.6, ^2J=13.6, 1H, H_{ax}C(2)], 1.99 [dd, ^3J=7.0, ^2J=13.6, 1H, H_{eq}C(2)], 2.88–3.04 [m, 1H, CH_{ax}(3)], 4.08 [d, ^2J=9.2, 1H, CH_2(5)], 4.56 [d, ^2J=9.2, 1H, CH_2(5)]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=0.1 (C-5), 18.6 (C-8), 23.8, 27.9, 28.1 (C-3, C-6, C-7), 40.4 (C-2), 82.6 (C-1), 124.9 (C-4).



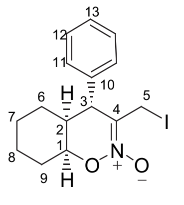
*4.4.4. 3-(Bromomethyl)-4,6,6-trimethyl-5,6-dihydro-4H-[1,2]-oxazine 2-oxide (**6b-Br**).* By method B, yield 155 mg (66%), mp=70–71 °C (Et_2O/hexane, 1/1) with decomposition, R_f=0.38 (EtOAc/hexane, 1/1). ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.26 [d, ^3J=7.0, 3H, CH_3(8)], 1.36 and 1.39 [2s, 6H, CH_3(6,7)], 1.67 [dd, ^3J=10.6, ^2J=13.6, 1H, H_{ax}C(2)], 1.98 [dd, ^3J=7.3, ^2J=13.6, 1H, H_{eq}C(2)], 2.84–298 [m, 1H, CH_{ax}(3)],4.18 [d, ^2J=10.3, 1H, CH_2(5)], 4.50 [d, ^2J=10.3, 1H, CH_2(5)]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=18.2 (C-8), 23.1, 27.8, 26.8 (C-3, C-6, C-7), 28.0 (C-5), 40.1 (C-2), 82.4 (C-1), 123.5 (C-4). Anal. Calcd for $C_8H_{14}BrNO_2$: C, 40.70; H, 5.87; N, 5.85. Found: C, 40.70; H, 5.98; N, 5.93.



*4.4.5. 4-Benzoyloxy-3-(iodomethyl)-6,6-dimethyl-5,6-dihidro-4H-[1,2]-oxazine 2-oxide (**6c-I**).* Yield 315 mg (81%), mp=78–80 °C (Et_2O/hexane, 2/1) with decomposition, R_f=0.62 (EtOAc/hexane, 1/1). ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.47 and 1.56 [2s, 6H, CH_3(6,7)], 2.16 [dd, ^3J=4.4, ^2J=14.7, 1H, H_{eq}C(2)], 2.43 [dd, ^3J=7.0, ^2J=14.7, 1H, H_{ax}C(2)], 4.14 [d, ^2J=9.5, 1H, CH_2(5)], 4.29 [d, ^2J=9.5, 1H, CH_2(5)], 6.04 [dd, ^3J=4.4, 7.0, 1H, CH_{eq}(3)], 7.48 [t, ^3J=7.7, 2H, CH(11)], 7.62 [t, ^3J=7.7, 1H, CH(12)], 8.06 [d, ^3J=7.7, 2H, CH(10)]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=−1.4 (C-5), 25.4 and 26.3 (C-6 and C-7), 37.7 (C-2), 64.7 (C-3), 82.7 (C-1), 119.2 (C-4), 128.7 and 129.9 (C-10 and C-11), 129.0 (C-9), 133.9 (C-12), 165.6 (C-8). IR (KBr, cm^{-1}): 1722 (ν, C=O), 1594 (ν, C=N), 1267, 1250, 1109, 710. Anal. Calcd for $C_{14}H_{16}INO_4$: C, 43.21; H, 4.14; N, 3.60. Found: C, 43.71; H, 4.43; N, 3.42.

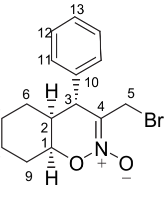


*4.4.6. 4-Benzoyloxy-3-(bromomethyl)-6,6-dimethyl-5,6-dihidro-4H-[1,2]-oxazine 2-oxide (**6c-Br**).* By method B, Yield 272 mg (80%), mp=91–92 °C (Et_2O/hexane, 2/1), R_f=0.61 (EtOAc/hexane, 1/1). ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.48 and 1.57 [2s, 6H, CH_3(6 or 7)], 2.18 [dd, ^3J=4.4, ^2J=14.7, 1H, H_{eq}C(2)], 2.45 [dd, ^3J=7.0, ^2J=14.7, 1H, H_{ax}C(2)], 4.32 [d, ^2J=10.3, 1H, CH_2(5)], 4.43 [d, ^2J=10.3, 1H, CH_2(5)], 6.02 [dd, ^3J=4.4, 7.0, 1H, CH_{eq} (3)], 7.48 [t, ^3J=7.7, 2H, CH(11)], 7.62 [t, ^3J=7.7, 1H, CH(12)], 8.05 [d, ^3J=7.7, 2H, CH(10)]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=25.2 and 26.2 (C-6 and C-7), 26.1 (C-5), 37.6 (C-2), 64.8 (C-3), 82.8 (C-1), 118.1 (C-4), 128.8 and 129.9 (C-10 and C-11), 129.0 (C-9), 133.9 (C-12), 165.6 (C-8). IR (KBr, cm^{-1}): 1716 (ν, C=O), 1590 (ν, C=N), 1321, 1264, 1105, 1096, 1027, 879, 711. Anal. Calcd for $C_{14}H_{16}BrNO_4$: C, 49.14; H, 4.71; N, 4.09. Found: C, 49.30; H, 4.90; N, 4.01.



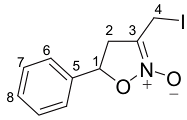
*4.4.7. rel-(4R,4aS,8aS)-3-(Iodomethyl)-4-phenyl-4a,5,6,7,8,8a-hexahydro-4H-benzo[e]-[1,2]-oxazine 2-oxide (**6d-I**).* Yield 318 mg (86%), mp=131–132 °C (EtOAc/hexane, 5/1) with decomposition,

R_f=0.62 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=1.31–1.91 [m, 8H, CH$_2$(6), CH$_2$(7), CH$_2$(8) and CH$_2$(9)], 2.04 [dd, ^{3}J=3.3, 14.7, 1H, CH(2)], 3.54 [d, ^{2}J=9.2, 1H, CH$_2$(5)], 3.77 [br s, 1H, CH(3)], 4.51 [d, ^{2}J=9.2, 1H, CH$_2$(5)], 4.66 [br s, 1H, CH(1)], 7.17 [d, ^{3}J=7.0, 2H, CH (11)], 7.27–7.42 [m, 3H, CH(12) and CH(13)]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=3.2 (C-5), 19.9, 24.3, 26.9 and 28.7 (C-6, C-7, C-8 and C-9), 39.3 and 46.7 (C-2 and C-3), 76.7 (C-1), 120.5 (C-4), 127.8 and 129.3 (C-11 and C-12), 127.9 (C-13), 141.2 (C-10). Anal. Calcd for C$_{15}$H$_{18}$INO$_2$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.32; H, 4.97; N, 3.76.

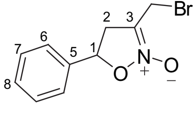


*4.4.8. rel-(4R,4aS,8aS)-3-(Bromomethyl)-4-phenyl-4a,5,6,7,8,8a-hexahydro-4H-benzo[e]-[1,2]-oxazine 2-oxide (**6d-Br**).* By method B, yield 279 mg (86%), mp=118–120 °C (Et$_2$O), R_f=0.64 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=1.29–1.93 [m, 8H, CH$_2$(6), CH$_2$(7), CH$_2$(8) and CH$_2$(9)], 2.05 [dd, ^{3}J=3.3, 15.0, 1H, CH(2)], 3.62 [d, ^{2}J=9.9, 1H, CH$_2$(5)], 3.72 [br s, 1H, CH(3)], 4.64 [d, ^{2}J=9.9, 1H, CH$_2$(5)], 4.66 [br s, 1H, CH(1)], 7.18 [d, ^{3}J=6.9, 2H, CH(11)], 7.28–7.42 [m, 3H, CH(12) and CH(13)].

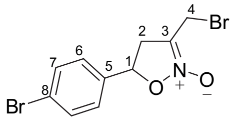
^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=19.9, 24.3, 27.0, and 28.6 (C-6, C-7, C-8, and C-9), 29.1 (C-5), 39.3 and 46.7 (C-2 and C-3), 76.8 (C-1), 119.2 (C-4), 127.8 and 129.3 (C-11 and C-12), 127.9 (C-13), 140.8 (C-10). Anal. Calcd for C$_{15}$H$_{18}$ BrNO$_2$: C, 55.57; H, 5.60; N, 4.32. Found: C, 55.81; H, 5.81; N, 4.32.



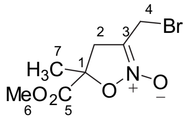
*4.4.9. 3-Iodomethyl-4-phenylisoxazoline 2-oxide (**6e-I**).* Prepared according to a slightly modified iodination procedure: Et$_2$O was used for extraction instead of EtOAc, and the product was crystallized from Et$_2$O after evaporation. Yield 206 mg (68%), mp=48–49 °C (Et$_2$O/hexane, 1/1) with decomposition, R_f=0.50 (EtOAc/hexane, 1/1). ^{1}H NMR (200.13 MHz, 300 K, CDCl$_3$): δ=3.29 [dd, ^{3}J=7.7, ^{2}J=16.5, 1H, CH$_2$(2)], 3.67 [dd, ^{3}J=9.5, ^{2}J=16.5, 1H, CH$_2$(2)], 4.09 [d, ^{2}J=7.0, 1H, CH$_2$(4)], 4.14 [d, ^{2}J=7.0, 1H, CH$_2$(4)], 5.63 [dd, ^{3}J=7.7, 9.5, 1H, CH(1)], 7.29–7.52 [m, 5H, Ph]. ^{13}C NMR (50.32 MHz, 300 K, CDCl$_3$): δ=−5.7 (C-4), 38.7 (C-2), 76.9 (C-1), 113.3 (C-3), 125.7 and 128.9 (C-6, C-7, and C-8), 138.0 (C-5).



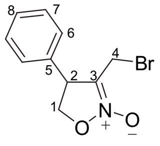
*4.4.10. 3-Bromomethyl-5-phenylisoxazoline 2-oxide (**6e-Br**).* By method A, yield 218 mg (85%), mp=51–52 °C (EtOAc), R_f=0.58 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=3.26 [dd, ^{3}J=7.3, ^{2}J=16.5, 1H, CH$_2$(2)], 3.64 [dd, ^{3}J=9.5, ^{2}J=16.5, 1H, CH$_2$(2)], 4.27 [s, 2H, CH$_2$(4)], 5.67 [ddd, ^{3}J=7.3, 9.5, J=0.4, 1H, CH(1)], 7.35–7.47 [m, 5H, Ph]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=22.7 (C-2), 38.8 (C-4), 76.4 (C-1), 111.8 (C-3), 125.8 and 129.1 (C-6 and C-7), 129.2 (C-8), 138.2 (C-5). IR (KBr, cm^{-1}): 1634 (ν, C=N), 1315, 1281, 1241, 896, 832, 708, 627. Anal. Calcd for C$_{10}$H$_{10}$BrNO$_2$: C, 46.90; H, 3.94; N, 5.47. Found: C, 46.89; H, 4.12; N, 5.42.



*4.4.11. 3-Bromomethyl-5-(4-bromophenyl)isoxazoline 2-oxide (**6f-Br**).* By method A, yield 319 mg (95%), mp=117–118 °C (hexane) with decomposition, R_f=0.41 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=3.20 [dd, ^{3}J=7.3, ^{2}J=16.9, 1H, CH$_2$(2)], 3.65 [dd, ^{3}J=9.6, ^{2}J=16.9, 1H, CH$_2$(2)], 4.26 [s, 2H, CH$_2$(4)], 5.63 [dd, ^{3}J=7.3, 9.6, 1H, CH(1)], 7.29 [d, ^{3}J=8.7, 2H, CH(6)], 7.56 [d, ^{3}J=8.7, 2H, CH(7)]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=22.5 (C-2), 38.8 (C-4), 76.6 (C-1), 111.6 (C-3), 123.2 (CBr), 127.4 and 132.3 (C-6 and C-7), 137.3 (C-5). Anal. Calcd for C$_{10}$H$_9$Br$_2$NO$_2$: C, 35.85; H, 2.71; N, 4.18. Found: C, 35.99; H, 2.61; N, 3.86.

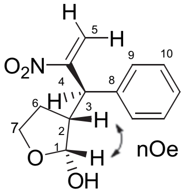


*4.4.12. 3-Bromomethyl-5-methyl-5-methoxycarbonylisoxazoline 2-oxide (**6g-Br**).* By method A, yield 219 mg (87%), mp=44–45 °C (Et$_2$O), R_f=0.39 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=1.71 [s, 3H, CH$_3$(7)], 3.15 [d, ^{2}J=17.1, 1H, CH$_2$(2)], 3.58 [d, ^{2}J=17.1, 1H, CH$_2$(2)], 3.83 [s, 3H, CH$_3$(6)], 4.15 [d, ^{2}J=11.2, 1H, CH$_2$(4)], 4.23 [d, ^{2}J=11.2, 1H, CH$_2$(4)]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=22.5 (C-4), 23.0 (C-7), 40.7 (C-2), 55.4 (C-6), 77.4 (C-1), 111.8 (C-3), 171.0 (C-5). Anal. Calcd for C$_7$H$_{10}$BrNO$_4$: C, 33.35; H, 4.00; N, 5.56. Found: C, 33.42; H, 4.20; N, 5.52.



*4.4.13. 3-Bromomethyl-4-phenylisoxazoline 2-oxide (**6h-Br**).* By method A, yield 213 mg (83%), mp=49 °C (Et$_2$O), R_f=0.53 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=3.74 [dd, ^{2}J=11.0, J=0.7, 1H, CH$_2$(4)], 4.36 [d, ^{2}J=11.0, 1H, CH$_2$(4)], 4.40 [t, $^{3}J\approx{}^{2}J$=7.3, 1H, CH$_2$(1)] 4.70 [dd, ^{3}J=7.0, 9.9, 1H, CH(2)], 4.87 [dd, ^{2}J=7.7, ^{3}J=9.9, 1H, CH$_2$(1)], 7.25–7.34 [m, 2H] and 7.37–7.47 [m, 3H] (Ph). ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=21.6 (C-4), 49.5 (C-2), 71.5 (C-1), 114.9 (C-3), 127.8 and 129.7 (C-6 and C-7), 128.9 (C-8), 137.1 (C-5). Anal. Calcd for C$_{10}$H$_{10}$BrNO$_2$: C, 46.90; H, 3.94; N, 5.47. Found: C, 47.27; H, 4.34; N, 5.36.

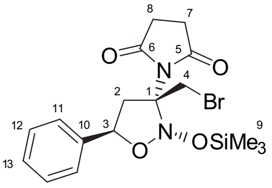
*4.4.14. 5-Nitro-4-phenylhex-5-ene-2-one (**8**).* Yield 186 mg (85%), colorless liquid, R_f=0.44 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=2.11 [s, 3H, CH$_3$], 3.04 [d, ^{3}J=7.3, 2H, CH$_2$], 4.78 [td, ^{4}J=2.2, ^{3}J=7.3, 1H, CHPh], 5.59 [br s, 1H] and 6.54 [br d, ^{4}J=2.2, 1H] (CH$_2$=), 7.20–7.35 [m, 5H, Ph]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=30.3 (CH$_3$), 40.7 (CHPh), 47.9 (CH$_2$), 117.5 (CH$_2$=), 127.6 (CH$_{p\text{-Ph}}$), 127.7 and 129.0 (both CH$_{\text{Ph}}$), 138.9 (C$_{i\text{-Ph}}$), 160.2 (CNO$_2$), 204.7 (CO). IR (thin layer from CHCl$_3$, cm^{-1}): 1718 (ν, C=O), 1525 (ν_{as}, NO$_2$), 1495, 1454, 1421, 1342 (ν_s, NO_2), 1167, 949, 756, 701. HRMS (ESI): calcd for $C_{12}H_{13}NO_3$ (M+Na) 242.0788. Found 242.0786.



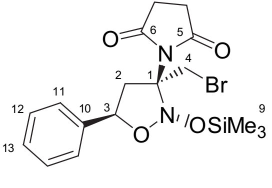
*4.4.15. rel-(2R,3R)-3-((R)-2-Nitro-1-phenylallyl)tetrahydrofuran-2-ol (**9**).* Yield 134 mg (56%), mp=142–143 °C (EtOAc/Et_2O, 1/2), R_f=0.34 (EtOAc/hexane, 1/1). ^1H NMR (300.13 MHz, 300 K, DMSO-d_6, COSY, NOESY): δ=1.63–1.83 [m, 1H, CH_2(6)], 1.96–2.10 [m, 1H, CH_2 (6)], 2.67–2.85 [m, 1H, CH (2)], 3.77 [dd, ^3J=8.2, ^2J=16.0, 1H, CH_2(7)], 3.95 [tdd, ^3J=2.8, 9.6, ^2J=16.0, 1H, CH_2(7)], 4.26 [d, ^3J=11.4, 1H, CH(3)], 4.68 [t, ^3J=4.1, 1H, CH(1)], 6.07 [d, ^3J=4.1, 1H, OH], 6.30 [br s, 1H, CH_2(5)], 6.57 [br s, 1H, CH_2(5)], 7.20–7.37 [m, 5H, Ph]. ^{13}C NMR (75.47 MHz, 300 K, DMSO-d_6, HSQC): δ=27.4 (C-6), 45.5 (C-3), 47.0 (C-2), 65.7 (C-7), 95.9 (C-1), 119.0 (C-5), 127.0 (C-11), 128.3 (C-9 and C-10), 139.7 (C-8), 160.2 (C-4). IR (KBr, cm^{-1}): 3360 (ν, OH), 1532 (ν_{as}, NO_2), 1408, 1340 (ν_s, NO_2), 1264, 1088, 1072, 988, 956, 896, 772, 712. HRMS (ESI): calcd for $C_{13}H_{15}NO_4$ (M+Na) 272.0893. Found 272.0895.

Nitrosoacetals **10a–c** were obtained according to method B. They were isolated as mixtures of diastereoisomers, and their relative configurations were determined by 2D-NOESY measurements (see Supplementary data).

Compound **10a** (mixture of **10a**-α and **10a**-β, dr 1.8:1). Yield 325 mg (76%), colorless oil, rapidly decomposes at room temperature, R_f=0.62 (EtOAc/hexane, 1/1). IR (for mixture of isomers, thin layer from $CHCl_3$, cm^{-1}): 1784 (ν, C=O), 1724 (ν, C=O), 1433, 1356, 1251, 1165, 1132, 877, 845, 756, 700.

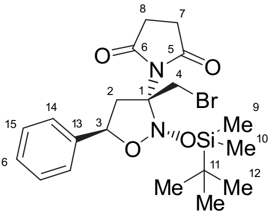


*4.4.16. 1-{rel-(2S,3S,5R)-3-Bromomethyl-5-phenyl-2-(trimethylsilyloxy)isoxazolidine-3-yl}-pyrrolidine-2,5-dione (**10a**-α).* ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=0.20 [s, 9H, $3CH_3$(9)], 2.62 [dd, ^3J=5.5, ^2J=13.6, 1H, CH_2(2)], 2.67–2.85 [m, 4H, CH_2(7) and CH_2(8)], 3.30 [d, ^2J=10.6, 1H, CH_2(4)], 4.17 [ddd, ^4J=1.8, ^3J=9.5, ^2J=13.6, 1H, CH_2(2)], 4.64 [dd, ^4J=1.8, ^2J=10.6, 1H, CH_2(4)], 5.64 [dd, ^3J=5.5, 9.5, 1H, CH(3)], 7.28–7.48 [m, 5H, Ph]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=−0.2 (C-9), 27.7 and 28.8 (br, C-7 and C-8), 35.9 and 36.6 (C-2 and C-4), 80.1 (C-1), 91.3 (C-3), 126.3 (C-13), 128.2 and 128.6 (C-11 and C-12), 138.6 (C-10), 175.7 and 176.6 (br, C-5 and C-6).

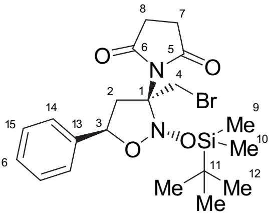


*4.4.17. 1-{rel-(2S,3S,5S)-3-Bromomethyl-5-phenyl-2-(trimethylsilyloxy)isoxazolidine-3-yl}-pyrrolidine-2,5-dione (**10a**-β).* ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=0.15 [s, 9H, $3CH_3$(9)], 2.67–2.85 [m, 4H, CH_2(7) and CH_2(8)], 3.40 [dd, ^3J=7.0, ^2J=13.6, 1H, CH_2(2)], 3.51 [d, ^2J=11.0, 1H, CH_2(4)], 3.59 [dd, ^4J=2.2, ^3J=10.3, ^2J=13.6, 1H, CH_2(2)], 4.55 [dd, ^4J=2.2,^2J=11.0, 1H, CH_2(4)], 5.20 [dd, ^3J=7.0, 10.3, 1H, CH(3)], 7.28–7.48 [m, 5H, Ph]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=−0.1 (C-9), 27.7 and 28.8 (br, C-7 and C-8), 32.0 and 37.7 (C-2 and C-4), 84.1 (C-1), 90.5 (C-3), 126.3 and 128.3 (C-11 and C-12), 127.9 (C-13), 139.8 (C-10), 175.7 and 176.6 (C-5 and C-6).

Compound **10b** (mixture of **10b**-α and **10b**-β, dr 1.6:1). Yield 395 mg (84%), colorless oil, gradually decomposes at room temperature, R_f=0.67 (EtOAc/hexane, 1/1).

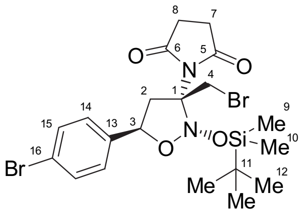


*4.4.18. 1-{rel-(2S,3S,5R)-3-Bromomethyl-2-(tert-butyldimethylsilyloxy)-5-phenylisoxazolidine-3-yl}-pyrrolidine-2,5-dione (**10b**-α).* ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=0.14 and 0.26 [2s, 6H, $2CH_3$(9,10)], 0.89 [s, 9H, $3CH_3$(12)], 2.60 [dd, ^3J=5.5, ^2J=13.6, 1H, CH_2(2)], 2.66–2.81 [m, 4H, CH_2(7) and CH_2(8)], 3.29 [d, ^2J=11.0, 1H, CH_2(4)], 4.23 [ddd, ^4J=1.8, ^3J=9.5, ^2J=13.6, 1H, CH_2(2)], 4.67 [dd, ^4J=1.8, ^2J=11.0, 1H, CH_2(4)], 5.65 [dd, ^3J=5.5, 9.5, 1H, CH(3)], 7.26–7.50 [m, 5H, Ph]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=−5.2 and −4.7 (C-9 and C-10), 17.8 (C-11), 25.8 (3C-12), 27.8 and 28.8 (br, C-7 and C-8), 35.8 and 36.3 (C-2 and C-4), 80.2 (C-1), 91.5 (C-3), 126.3 (C-16), 128.2 and 128.8 (C-14 and C-15), 138.7 (C-13), 175.8 and 176.8 (br, C-5 and C-6). ^{29}Si (59.63 MHz, 300 K, $CDCl_3$): δ=28.6.

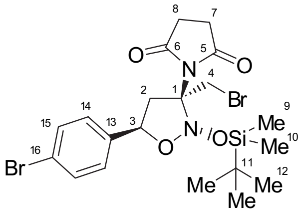


*4.4.19. 1-{rel-(2S,3S,5S)-3-Bromomethyl-2-(tert-butyldimethylsilyloxy)-5-phenylisoxazolidine-3-yl}-pyrrolidine-2,5-dione (**10b**-β).* ^1H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=0.11 and 0.13 [2s, 6H, $2CH_3$(9,10)], 0.80 [s, 9H, $3CH_3$(12)], 2.67–2.85 [m, 4H, CH_2(7) and CH_2(8)], 3.36 [dd, ^3J=6.6, ^2J=13.2, 1H, CH_2(2)], 3.51 [d, ^2J=11.0, 1H, CH_2(4)], 3.77 [dd, ^4J=2.2, ^3J=10.3, ^2J=13.2, 1H, CH_2(2)], 4.63 [dd, ^4J=2.2,^2J=11.0, 1H, CH_2(4)], 5.22 [dd, ^3J=6.6, 10.3, 1H, CH(3)], 7.26–7.50 [m, 5H, Ph]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=−5.1 and −4.0 (C-9 and C-10), 17.6 (C-11), 25.8 (3C-12), 27.8 and 28.7 (br, C-7 and C-8), 31.8 and 36.7 (C-2 and C-4), 83.8 (C-1), 90.9 (C-3), 126.3 and 128.3 (C-14 and C-15), 127.8 (C-16), 139.6 (C-13), 175.8 and 176.9 (C-5 and C-6). ^{29}Si (59.63 MHz, 300 K, $CDCl_3$): δ=27.9.

Compound **10c** (mixture of **10c**-α and **10c**-β, dr 1.6:1). Yield 499 mg (91%), mp=107–110 °C (hexane, for 1.26:1 mixture of **10c**-α and **10c**-β). R_f=0.72 (EtOAc/hexane, 1/1). Anal. Calcd for $C_{20}H_{28}Br_2N_2O_4Si$: C, 43.85; H, 5.15; Br, 29.14; N, 5.11; Si, 5.12. Found: C, 44.19; H, 5.32; Br, 29.15; N, 5.12; Si, 5.12.



*4.4.20. 1-{rel-(2S,3S,5R)-3-Bromomethyl-5-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)-isoxazolidine-3-yl}-pyrrolidine-2,5-dione (**10c**-α).* ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=0.13 and 0.24 [2s, 6H, 2CH$_3$(9,10)], 0.88 [s, 9H, 3CH$_3$(12)], 2.66 [dd, ^3J=5.0, ^2J=11.4, 1H, CH$_2$(2)], 2.60–2.81 [m, 4H, CH$_2$(7) and CH$_2$(8)], 3.19 [d, ^2J=11.0, 1H, CH$_2$(4)], 4.23 [ddd, ^4J=1.8, ^3J=9.6, ^2J=11.4, 1H, CH$_2$(2)], 4.66 [dd, ^4J=1.8, ^2J=11.0, 1H, CH$_2$(4)], 5.58 [dd, ^3J=5.0, 9.6, 1H, CH(3)], 7.24 [d, ^2J=8.2, 2H, CH(14)], 7.52 [d, ^2J=8.2, 2H, CH(15)]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=−5.2 and −4.7 (C-9 and C-10), 17.8 (C-11), 25.7 (C-12), 27.8 and 28.8 (br, C-7 and C-8), 35.6 and 36.4 (C-2 and C-4), 79.5 (C-1), 91.4 (C-3), 122.2 (C-16), 127.9 and 132.0 (C-14 and C-15), 137.8 (C-13), 176.4 and 177.8 (br, C-5 and C-6). ^{29}Si NMR (59.63 MHz, 300 K, CDCl$_3$): δ=28.9.



*4.4.21. 1-{rel-(2S,3S,5R)-3-Bromomethyl-5-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)-isoxazolidine-3-yl}-pyrrolidine-2,5-dione (**10c**-β).* ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=0.11 and 0.12 [2s, 6H, 2CH$_3$(9,10)], 0.80 [s, 9H, 3CH$_3$(12)], 2.55–2.82 [m, 4H, CH$_2$(7) and CH$_2$(8)], 3.36 [dd, ^3J=6.4, ^2J=13.8, 1H, CH$_2$(2)], 3.47 [d, ^2J=11.0, 1H, CH$_2$(4)], 3.73 [dd, ^4J=1.8, ^3J=9.6, ^2J=13.8, 1H, CH$_2$(2)], 4.62 [dd, ^4J=1.8,^2J=11.0, 1H, CH$_2$(4)], 5.17 [dd, ^3J=6.4, 9.6, 1H, CH(3)], 7.34 [d, ^2J=8.2, 2H, CH(14)], 7.46 [d, ^2J=8.2, 2H, CH(15)]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=−5.1 and −4.0 (C-9 and C-10), 17.6 (C-11), 25.7 (C-12), 27.8 and 28.9 (br, C-7 and C-8), 31.7 and 36.7 (C-2 and C-4), 83.1 (C-1), 90.9 (C-3), 122.2 (C-16), 129.5 and 131.5 (C-14 and C-15), 138.8 (C-13), 176.4 and 176.9 (C-5 and C-6). ^{29}Si NMR (59.63 MHz, 300 K, CDCl$_3$): δ=28.3.

4.5. Reaction of halomethylnitronates with PhSO$_2$Na (Table 4, typical procedure i)

Nitronate **6a-I** (207 mg, 0.60 mmol) was added to the stirred suspension of sodium benzenesulfinate (118 mg, 0.72 mmol) in DMF (1.5 mL) at 0 °C. The temperature was allowed to rise to room temperature and the reaction mixture was stirred for 15 min until all the precipitate was dissolved. Then the reaction mixture was poured into Et$_2$O (15 mL)/water (20 mL). The aqueous layer was separated and back-extracted with Et$_2$O (2×6 mL). The combined organic phase was washed with water (20 mL), brine (20 mL), and dried over Na$_2$SO$_4$. The solvents were evaporated in vacuo at 40 °C, and the residue dried under high vacuum (0.03 Torr) to give pure white crystalline nitronate **15d** (215 mg, 100%).

4.6. Reaction of halomethylnitronates with dimethylmalonate in DMF (Table 4, typical procedure ii)

Dimethylmalonate (72 μL, 0.63 mmol) was added to the stirred solution of *t*-BuOK (52 mg, 0.56 mmol) in DMF (1.3 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, cooled to −40 °C, and nitronate **6a-I** (175 mg, 0.51 mmol) was added. The reaction mixture was stirred for 15 min at −40 °C, and the temperature was allowed to rise to 0 °C over 15 min. The reaction mixture was poured into Et$_2$O (20 mL)/water (20 mL), the aqueous layer was separated and washed with Et$_2$O (2×10 mL). The combined organic phases were dried over Na$_2$SO$_4$. The solvents were evaporated in vacuo at 40 °C and residue was subjected to column chromatography on silica (EtOAc/hexane, 1/3) to give nitronate **15b** as colorless flakes (156 mg, 88%).

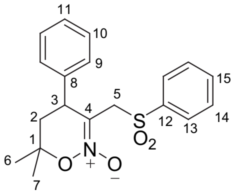
4.7. Reaction of nitronate 6a-Br with 2-lithio-2,3-dithiane (Table 4, procedure iii)

n-BuLi (287 μL, 2.5 M solution in hexanes) was added to a stirred solution of 1,3-dithiane (93 mg, 0.77 mmol) in THF (2.5 mL) at −20 °C. The reaction mixture was stirred for 10 min, cooled to −60 °C, and nitronate **6a-Br** (200 mg, 0.67 mmol) was added. The reaction mixture was kept for 1 h at −60 °C, then was allowed to warm up to room temperature and poured into Et$_2$O (15 mL)/water (15 mL). The aqueous layer was separated and extracted with Et$_2$O (2×5 mL). The combined organic phases were washed with water (10 mL), brine (15 mL) and dried over Na$_2$SO$_4$. The solvents were evaporated in vacuo at 40 °C, and the residue was subjected to column chromatography on silica gel (EtOAc/hexane, 1/3) to give nitronate **15e** as colorless flakes (208 mg, 92%).

4.8. Reaction of halomethylnitronates with dimethylmalonate in DMF (Table 4, typical procedure iv)

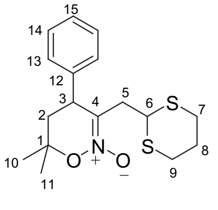
NaH (37 mg, 60% suspension in mineral oil, 0.93 mmol) was added to a stirred solution of dimethylmalonate (115 μL, 1.01 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C, cooled to −40 °C, and nitronate **6d-I** (300 mg, 0.81 mmol) was added. The reaction mixture was stirred for 30 min at −40 °C, and the temperature was allowed to rise to 0 °C over 15 min. The reaction mixture was poured into Et$_2$O (20 mL)/water (20 mL), the aqueous layer was separated and washed with Et$_2$O (2×10 mL). The combined organic phases were dried over Na$_2$SO$_4$. The solvents were evaporated in vacuo at 40 °C and residue was subjected to the column chromatography (EtOAc/hexane, 1/3) to give nitronate **15g** as colorless prisms (295 mg, 97%).

Nitronates **15a** (yield 82%), **15b** (yield 87%), and **15c** (yield 88%) have been described.[3]

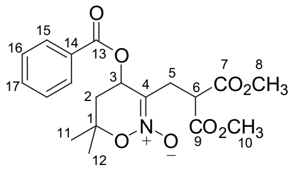


*4.8.1. 6,6-Dimethyl-4-phenyl-3-[(phenylsulfonyl)methyl]-5,6-dihydro-4H-[1,2]-oxazine 2-oxide (**15d**).* Yield 215 mg (100%), mp=119–121 °C (Et$_2$O), R_f=0.33 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=1.40 and 1.52 [2 s, 6H, CH$_3$(6,7)], 2.02 [t, $^3J\approx{}^2J$=14.7, 1H, H$_{ax}$C(2)], 2.22 [dd, ^3J=7.8, ^2J=13.7, 1H, H$_{eq}$C(2)], 3.51 [d, ^2J=14.2, 1H, CH$_2$(5)], 4.24 [dd, ^3J=7.8, 11.0, 1H,

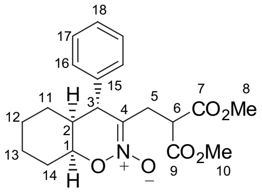
$CH_{ax}(3)$], 4.79 [d, ^2J=14.2, 1H, $CH_2(5)$], 7.22 [d, ^3J=7.7, 2H, CH (9)], 7.26–7.41 [m, 3H, CH(10) and CH(11)], 7.54 [t, ^3J=7.3, 2H, CH(14)], 7.65 [t, ^3J=7.3, 1H, CH(15)], 7.94 [d, ^3J=7.3, 2H, CH(13)]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=22.2 and 27.8 (C-6 and C-7), 40.9 and 41.7 (C-2 and C-5), 83.1 (C-1), 115.4 (C-4), 128.3 (C-11), 128.0, 128.1, 129.2, 129.5 (all CH_{Ph}), 134.2 (C-15), 139.4 and 140.4 (C-8 and C-12). IR (KBr, cm^{-1}): 1598 (ν, C=N), 1317, 1295, 1281, 1162, 1152, 705, 525. Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.45; H, 6.04; N, 4.04.



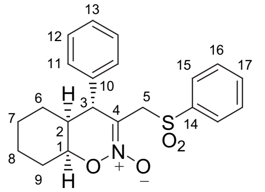
*4.8.2. 6,6-Dimethyl-3-((1,3-dithian-2-yl)methyl)-4-phenyl-5,6-dihydro-4H-[1,2]-oxazine 2-oxide (**15e**).* Yield 208 mg (92%), mp=155–157 °C (Et_2O), R_f=0.37 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.42 and 1.57 [2s, 6H, CH_3(10, 11)], 1.80–2.18 [m, 4H, $CH_2(2)$ and $CH_2(8)$], 2.27 [dd, ^3J=11.0, ^2J=14.2, 1H, $CH_2(5)$], 2.78–2.88 [br m, 4H, $CH_2(7)$ and $CH_2(9)$], 3.08 [dd, ^3J=5.0, ^2J=14.2, 1H, $CH_2(5)$], 3.91 [dd, ^3J=8.2, 10.5, 1H, $CH_{ax}(3)$], 4.68 [dd, ^3J=5.0, 11.0, 1H, CH(6)], 7.19 [d, ^3J=6.9, 2H, $CH_{o\text{-}Ph}$], 7.29–7.41 [m, 3H, CH_{Ph}]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=22.6 and 27.9 (C-10 and C-11), 25.6 (C-8), 29.0 and 29.1 (C-7 and C-9), 36.0 and 41.8 (C-2 and C-5), 40.9 and 43.9 (C-3 and C-6), 82.0 (C-1), 122.2 (C-4), 127.8 (C-15), 128.1 and 129.4 (C-13 and C-14), 140.0 (C-12). Anal. Calcd for $C_{17}H_{23}NO_2S_2$: C, 60.50; H, 6.87; N, 4.15; S, 19.00. Found: C, 60.47; H, 7.20; N, 3.93; S, 18.99.



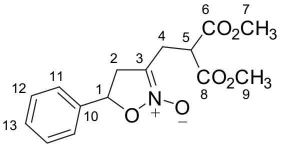
*4.8.3. Dimethyl [2-(4-benzoyloxy-6,6-dimethyl-2-oxo-5,6-dihydro-4H-[1,2]-oxazin-3-yl)-methyl]malonate (**15f**).* Obtained similar to **15b** according to the procedure ii from 215 mg, 0.55 mmol of **6c-I**. Yield 201 mg (93%), colorless needles, mp=91–92 °C (Et_2O/hexane, 3/1), R_f=0.29 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.43 and 1.53 [2s, 6H, CH_3(11, 12)], 2.10 [dd, ^3J=4.4, ^2J=14.7, 1H, $H_{eq}C(2)$], 2.38 [dd, ^3J=6.6, ^2J=14.7, 1H, $H_{ax}C(2)$], 2.91 [dd, ^3J=9.9, ^2J=14.3, 1H, $CH_2(5)$], 3.04 [dd, ^3J=5.1, ^2J=14.3, 1H, $CH_2(5)$], 3.68 and 3.73 [2s, 6H, CH_3(8,10)], 4.29 [dd, ^3J=5.1, 9.9, 1H, CH(6)], 5.94 [dd, ^3J=4.4, 6.6, 1H, $CH_{eq}(3)$], 7.46 [t, ^3J=7.7, 2H, CH(16)], 7.60 [t, ^3J=7.7, 1H, CH(17)], 8.01 [d, ^3J=7.7, 2H, CH(15)]; ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=25.3 and 25.7 (C-11 and C-12), 28.6 and 37.5 (C-2 and C-5), 45.9 (C-6), 52.8 and 52.9 (C-8 and C-10), 66.6 (C-3), 81.7 (C-1), 118.5 (C-4), 128.7 and 129.8 (C-15 and C-16), 129.2 (C-14), 133.7 (C-17), 165.5 (C-13), 168.9 and 169.3 (C-7 and C-9). IR (KBr, cm^{-1}): 1750 (ν, C=O), 1733 (ν, C=O), 1717 (ν, C=O), 1613 (ν, C=N), 1323, 1289, 1260, 1225, 1108, 715. Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 58.10; H, 5.85; N, 3.68.



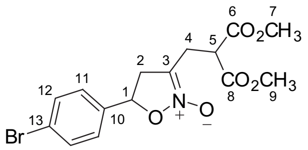
*4.8.4. Dimethyl {2-[rel-(4R,4aS,8aS)-4-phenyl-2-oxo-4a,5,6,7,8,8a-hexahydro-4H-benzo[e]-[1,2]-oxazin-3-yl]methyl}malonate (**15g**).* Obtained according to the procedure iv. Yield 285 mg (97%), mp=127–128 °C (EtOAc/hexane, 1/3), R_f=0.43 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.19–1.87 [m, 8H, $(CH_2)_4$,], 1.93–2.05 [m, 1H, CH(2)], 2.44 [t, $^3J \approx {}^2J$=11.9, 1H, $CH_2(5)$], 3.01 [dd, ^3J=3.2, ^2J=13.7, 1H, $CH_2(5)$], 3.64 [br s, 1H, CH(3)], 3.69 and 3.76 [2s, 6H, CH_3(8,10)], 4.41 [dd, ^3J=3.2, 10.5, 1H, CH(6)], 4.62 [br s, 1H, CH(1)], 7.15 [d, ^3J=6.4, 2H, CH(16)], 7.25–7.42 [m, 3H, CH(17) и CH(18)]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=20.0, 24.7, 27.3 and 28.7 (C-11, C-12, C-13 and C-14), 31.7 (C-5), 39.6 and 45.9 (C-2 and C-3), 49.7 (C-6), 52.6 and 52.8 (C-8 and C-10), 75.8 (C-1), 120.1 (C-4), 127.7 (C-18), 127.8 and 129.3 (C-16 and C-17), 141.2 (C-15), 169.0 and 169.5 (C-7 and C-9). HRMS (ESI): calcd for $C_{20}H_{25}NO_6$ (M+H) 376.1755. Found 376.1745.



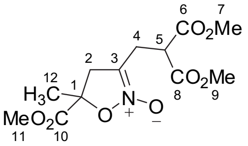
*4.8.5. rel-(4R,4aS,8aS)-3-(phenylsulfonyl)methyl-4-ahenyl-4a,5,6,7,8,8a-hexahydro-4H-benzo[e]-[1,2]-oxazine 2-oxide (**15h**).* Obtained similar to **15d** according to the procedure i from 300 mg, 0.81 mmol of **6d-I**. Yield 309 mg (99%), white flakes, mp=174–175 °C (Et_2O/pentane, 3/1) with decomposition, R_f=0.37 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=1.25–2.07 [m, 9H, $CH_2(6)$, $CH_2(7)$, $CH_2(8)$, $CH_2(9)$ and CH(2)], 3.56 [d, ^2J=14.2, 1H, $CH_2(5)$], 4.00 [br s, 1H, CH(3)], 4.62 [br s, 1H, CH(1)], 4.82 [d, ^2J=14.2, 1H, $CH_2(5)$], 7.14 [d, ^3J=7.7, 2H, CH (11)], 7.30–7.41 [m, 3H, CH(12) and CH(13)], 7.57 [t, ^3J=7.3, 2H, CH(16)], 7.68 [t, ^3J=7.3, 1H, CH(17)], 7.97 [d, ^3J=7.3, 2H, CH(15)]. ^{13}C NMR (75.47 MHz, 300 K, $CDCl_3$): δ=20.0, 24.3, 27.4, and 28.4 (C-6, C-7, C-8 and C-9), 39.7 and 47.7 (C-2 and C-3), 57.4 (C-5), 76.9 (C-1), 113.1 (C-4), 127.9 (C-13), 128.0, 128.2, 129.2, 129.4 (all CH_{Ph}), 134.3 (C-17), 139.9 and 140.6 (C-10 and C-14). Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found: C, 65.39; H, 6.07; N, 3.75.



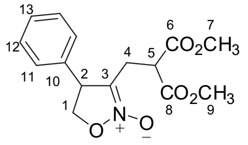
*4.8.6. Dimethyl 2-(2-oxido-5-phenylisoxazolin-3-ylmethyl)malonate (**15i**).* Obtained similar to **15g** according to the procedure *iv* from 330 mg, 1.29 mmol of **6e-Br**. Yield 331 mg (84%), white flakes, mp=40–41 °C ($Et_2O/CHCl_3$, 2/1), R_f=0.37 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, $CDCl_3$): δ=2.94 [d, ^3J=7.3, 2H, $CH_2(4)$], 3.14 [dd, ^3J=7.8, ^2J=17.0, 1H CH$_2$(2)], 3.55 [dd, ^3J=9.2, ^2J=17.0, 1H CH$_2$(2)], 3.69 and 3.76 [2s, 6H; CH$_3$(7,9)], 4.00 [t, ^3J=7.3, 1H, CH(5)], 5.60 [dd, ^3J=7.8, ^3J=9.2, CH(1)], 7.38 [br s, 5H, Ph]; ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=25.4 (C-4), 41.5 (C-2), 46.7 (C-5), 52.9, and 53.0 (C-7 and C-9), 76.2 (C-1), 112.6 (C-3), 125.6 and 128.9 (C-11 and C-12), 128.8 (C-13), 138.7 (C-10), 168.6 (C-6 and C-8). IR (KBr, cm^{-1}): 1754 (ν, C=O), 1738 (ν, C=O), 1648 (ν, C=N), 1438, 1309, 1275, 1141, 869, 703. Anal. Calcd for C$_{15}$H$_{17}$NO$_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.29; H, 5.46; N, 4.52.



*4.8.7. Dimethyl 2-(2-oxido-5-phenylisoxazolinyl-3-ylmethyl)malonate (**15j**).* Obtained similar to **15g** according to the procedure *iv* from 150 mg, 0.45 mmol of **6f**-**Br**. Yield 161 mg (93%), white solid, mp=27 °C (Et$_2$O), R_f=0.39 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=2.91 [d, ^3J=7.3, 2H, CH$_2$(4)], 3.08 [dd, ^3J=7.3, ^2J=17.4, CH$_2$(2)], 3.55 [dd, ^3J=9.6, ^2J=17.4, CH$_2$(2)], 3.69 and 3.75 [2s, 6H; CH$_3$(7,9)], 3.97 [t, ^3J=7.3, 1H, CH(5)], 5.54 [t, $^3J\approx{}^3J$=8.7, CH(1)], 7.25 [d, ^3J=8.3, 2H, CH(11)], 7.52 [d, ^3J=8.3, 2H, CH(12)]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=25.4 (C-4), 41.5 (C-2), 46.7 (C-5), 53.0 and 53.1 (C-7 and C-9), 75.5 (C-1), 112.3 (C-3), 122.8 (C-13), 127.4 and 132.2 (C-11 and C-12), 137.9 (C-10), 168.6 (C-6 and C-8). Anal. Calcd for C$_{15}$H$_{16}$BrNO$_6$: C, 46.65; H, 4.18; N, 3.63; Found: C, 46.69; H, 4.45; N, 3.48.



*4.8.8. Dimethyl 2-(2-oxido-5-methyl-5-methoxycarbonylisoxazoline-3-ylmethyl)malonate (**15k**).* Obtained similar to **15g** according to the procedure *iv* from 214 mg, 0.85 mmol of **6g**-**Br**. Yield 195 mg (76%), colorless oil, R_f=0.41 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=1.57 [s, 3H, CH$_3$(12)], 2.79 [d, ^3J=7.3, 2H, CH$_2$(4)], 3.00 [d, ^2J=17.4, 1H, CH$_2$(2)], 3.42 [d, ^2J=17.4, 1H, CH$_2$(2)], 3.67 [s, 6H, CH$_3$(7,9)], 3.72 [s, 3H, CH$_3$(11)], 3.85 [t, ^3J=7.3, 1H, CH(5)]. ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=22.8 (C-12), 25.1 (C-4), 43.0 (C-2), 46.5 (C-5), 52.8 (C-7 and C-9), 53.0 (C-11), 79.0 (1), 112.3 (3), 168.3 (C-6 and C-8), 171.3 (C-10). HRMS (ESI): calcd for C$_{12}$H$_{17}$NO$_8$ (M+Na) 326.0846. Found 326.0846.



*4.8.9. Dimethyl 2-(2-oxido-4-phenylisoxazolin-3-ylmethyl)malonate (**15l**).* Obtained similar to **15g** according to the procedure *iv* from 204 mg, 0.77 mmol of **6h**-**Br**. Yield 232 mg (95%), colorless oil, R_f=0.40 (EtOAc/hexane, 1/1). ^{1}H NMR (300.13 MHz, 300 K, CDCl$_3$): δ=2.62 [dd, ^3J=9.6, ^2J=15.1, 1H, CH$_2$(4)], 2.84 [ddd, J=1.3, ^3J=5.5, ^2J=15.1, 1H, CH$_2$(4)], 3.69 and 3.74 [both s, 6H, CH$_3$(7 and 9)], 3.96 [dd, ^3J=5.5, 9.6, 1H, CH(5)], 4.33 [dd, ^3J=6.4, ^2J=7.3, 1H, CH$_2$(1)], 4.55 [t, $^3J\approx{}^2J$=6.4, 1H, CH(2)], 4.76 [dd, ^2J=7.3, ^3J=9.6, 1H, CH$_2$(1)], 7.23–7.30 [m, 2H, CH(11)], 7.35–7.43 [m, 3H, CH(12) and CH(13)]; ^{13}C NMR (75.47 MHz, 300 K, CDCl$_3$): δ=24.4 (C-4), 46.5 and 51.9 (C-2 and C-5), 52.9 and 53.0 (C-7 and C-9), 71.5 (C-1), 115.5 (C-3), 127.7 and 129.5 (C-11 and C-12), 128.6 (C-13), 137.8 (C-10), 168.5 and 168.8 (C-6 and C-8). HRMS (ESI): calcd for C$_{15}$H$_{17}$NO$_6$ (M+Na) 330.0948. Found 330.0950.

CCDC-812034 (for **3f′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Synthesis of starting compounds, characterization data for compounds **16**, and **20**, copies of 2D-NOESY spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.078.

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7. The use of TMSOTf was found to be advantageous for the silylation of nitronates, which do not contain alkoxy substituent (R^3 or R^4), see Supplementary data for details.
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13. The addition of NBS to enamines **3** can give products **10** with N–C(imide)–CH_2–Br fragment or alternative regioisomers with N–C(Br)–CH_2-imide fragment. The assignment for structure **10** follows from: (a) The alternative regioisomer would contain R_3Si–O–N–C–Br fragment which could readily eliminate R_3SiBr to give five-membered nitronates, see Ref. 5a; (b) The observed ^{13}C chemical shifts of exocyclic CH_2-group correspond to CH_2Br (ca. 36 ppm), rather than to CH_2-imido (ca. 55 ppm, based on ACD/Labs prediction).
14. For studies of stereodynamic processes of six-membered *N*-(silyloxy)enamines, see Khomutova, Y. A.; Smirnov, V. O.; Mayr, H.; Ioffe, S. L. *J. Org. Chem.* **2007**, *72*, 9134–9140.
15. Concerning the reaction of five-membered enamines with NBS, the intermediate generation of the bromonium ion can be proposed. In this case, the exclusive formation of products **10** with cis-arrangement of succinimido and silyloxy groups may be explained by generation of the bromonium ion on the face anti to the pseudoaxial silyloxy substituent followed by S_N2 ring-opening with succinimide.
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