New Rearrangement of Conjugated Cyclic Ene Nitroso *O*-Trimethylsilyl Acetals: Convenient Synthesis of Dihydro-2*H*-pyran-3-one and Dihydrofuran-3-one Oximes

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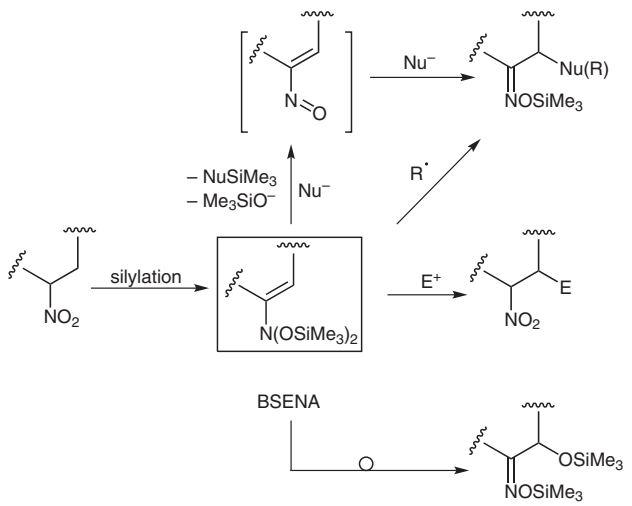
Abstract: The nucleophile-induced rearrangement of cyclic *N*-alkoxy-*N*-(silyloxy)enamines was investigated. As a result, a new strategy for the synthesis of β-pyranone and β-furanone derivatives from nitro compounds is suggested.

Key words: nitroso acetals, rearrangement, nitrogen heterocycles, 1,2-oxazines, aliphatic nitro compounds

A quarter of a century has passed since the discovery of *N*,*N*-bis(silyloxy)enamines (BSENAs) (i.e., nitro compound double silylation products).[1] Due to their availability and unique reactivity, BSENAs now play an important role among other nitro compound derivatives. Common chemical transformations of BSENAs are presented in Scheme 1. As can be seen, BSENAs are able to react with quite different types of reagents, like electrophiles, nucleophiles and radicals. Also worthy of note is the peculiar BSENA rearrangement, 1,3-N,C migration of the silyloxy group, that occurs under the action of Lewis acids, leading to the corresponding β-oximino alcohol derivatives.[2]



Scheme 1 General chemistry of BSENAs (Nu^- = nitronate anions, azoles, amines, CN^-, N_3^-, etc.; R = R′SO_2CH_2, R′O_2CCH_2; E^+ = carboxonium, iminium and episulfonium cations, diaryl carbocations, bromine)

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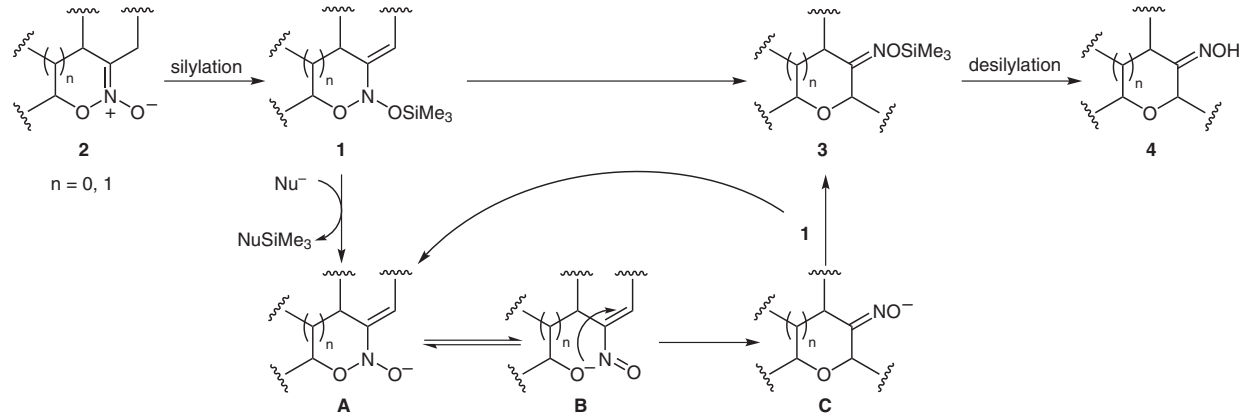
Cyclic ene nitroso acetals **1** are readily accessible as individual diastereomers by silylation[3] of the corresponding nitronates **2** (n = 0, 1) (Scheme 2).[4,5] Their reactivity is very close to BSENAs.[3] The relative configuration of ring carbon atoms in derivatives **2** should not change in their common reactions, which may allow the application of nitroso acetals **1** in stereocontrolled synthesis. At the same time, the chemistry of derivatives **1** has remarkable features compared to BSENA chemistry. This results from enamine **1** possessing different oxy groups connected to the nitrogen atom. Furthermore, cleavage of the endocyclic N–O bond does not lead to a simplification of the carbon skeleton of initial enamine **1**, because the oxygen atom remains tethered to the other part of the initial molecule. This makes the unique rearrangement **1** → **3**, depicted in Scheme 2, possible. If a nitroso acetal **1** is treated with a nucleophile Nu^- with an affinity to silicon, elimination of the trimethylsilyl moiety leads to the anion **A**, that may be in equilibrium with the open-chain anion **B**. The latter possesses a highly reactive α-nitrosoalkene fragment. In this case, ring closure leading to the oximino anion **C** is preferred. Finally, desilylation of **1** with anion **C** results in silylated oxime **3**, and anion **A**, formed from **1**, propagates the chain process. (Another possible formation of oxime **3** cannot be excluded, i.e. interaction of anion **C** with $NuSiMe_3$, leading to regeneration of the nucleophile Nu^-.)

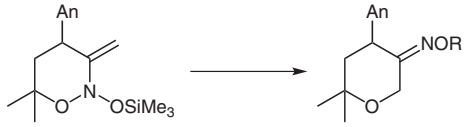
Desilylation of derivatives **3** can be considered as a simple approach to the synthesis of furanone (n = 0) or pyranone (n = 1) oximes **4**. Products of this kind possess biological activity (cytotoxic,[6a] muscarinic[6b,c] and implantation prevention in rats[6d]) and have been used in carbohydrate[7] and cyclic amino alcohol[6d,8] syntheses. A general method for the synthesis of oximes **4**, however, is lacking and these derivatives are usually obtained via oximation of the corresponding carbonyl compounds. In contrast, the strategy pointed out in Scheme 2 would allow for the assembly of oximes **4** from simple initial compounds. In this situation, oximes **4** could themselves be considered as convenient precursors in the design of target β-pyranones and β-furanones.

Recently, we tentatively mentioned two examples of the rearrangement **1** → **3**;[9] however, the target oximes **4** were obtained in rather low yields (17% and 27%) and those re-



Scheme 2 Rearrangement **1** → **3** as the key step in the general strategy for the synthesis of oximes **4** from nitronates **2**

Table 1 Optimization of the Conditions for Enamine **1a** Rearrangement



Entry	Reaction conditions[a]	Product	Yield (%)
1	TBAF[b] (0.1 equiv), CH_2Cl_2, –78 °C to r.t., then NH_4F, AcOH, MeOH[c]	**4a**	33[d]
2	TBAF·$3H_2O$ (0.1 equiv), CH_2Cl_2, –78 °C to r.t., then NH_4F, AcOH, MeOH	**4a**	25[d]
3	TBAF[b] (0.1 equiv), 3 Å MS, CH_2Cl_2, –78 °C to r.t.	**3a**	89[e]
4	TBAF[b] (0.1 equiv), 3 Å MS, CH_2Cl_2, –78 °C	**3a**	87[e]
5	TBAF[f] (0.1 equiv), CH_2Cl_2, –78 °C to r.t., then NH_4F, AcOH, MeOH	**4a**	97[d]
6	TBAF[f] (0.1 equiv), CH_2Cl_2, r.t., then NH_4F, AcOH, MeOH	**4a**	91[e]
7	**TBAF[b] (0.1 equiv), 3 Å MS, CH_2Cl_2, –78 °C to r.t., then NH_4F, AcOH, MeOH**	**4a**	**100[e]**
8	TBAF·$3H_2O$ (0.1 equiv), 3 Å MS, CH_2Cl_2, MeOH, –78 °C to r.t., then NH_4F, AcOH, MeOH	unidentified mixture of products	
9	NH_4F (2 equiv), Et_2O, MeOH, –78 to –30 °C, then NH_4F, AcOH, MeOH	unidentified mixture of products	
10	ZnF_2 (0.6 equiv), HMPA, CH_2Cl_2, r.t., 3 d	**4a**	10[e] (77[g])
11	LiF (0.6 equiv), NMP, r.t., 3 d	**4a**	21[e] (41[g])
12	*t*-BuOK (0.1 equiv), CH_2Cl_2, THF, –78 °C to r.t., then NH_4F, AcOH, MeOH	**4a**	77[e]
13	TMSONa (3 equiv), CH_2Cl_2, THF, ca. –60 °C to r.t., then AcOH	**4a**	95[e]
14	BuLi (0.87 equiv), THF, –78 °C, then AcOH, MeOH	**4a**	83[e]
15	NaOH (0.2 equiv), MeOH, r.t., then NH_4F, AcOH, MeOH	unidentified mixture of products	
16	Et_3N (0.1 equiv), CH_2Cl_2, r.t.	**3a**	41[e]
17	DMAP (0.1 equiv), CH_2Cl_2, r.t.	**3a**	87[e]

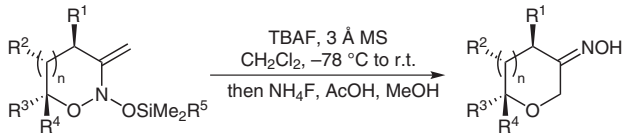
[a] Reaction times: 0.5–1.5 h at lower temperature, 0.5–1 h at higher temperature, 1 h for desilylation, unless otherwise mentioned (for details, see Supporting Information).
[b] Commercially available 1-M solution in THF.
[c] Here and in other entries: NH_4F (1.5 equiv), AcOH (2 equiv), MeOH (2 mL/1 mmol of enamine).
[d] Isolated yield after column chromatography.
[e] Based on ^1H NMR spectrum integration [ratio: signals $(CH_2O)/(CH_{Arom})$].
[f] Dried by heating under reduced pressure.[10]
[g] Approx. recovery of **1a**.

sults could not be considered as constituting a useful synthetic method for the synthesis of derivatives **4**. Here, we report a detailed investigation of the **1** → **3** rearrangement, including optimization of the conditions and elucidation of the scope of this reaction.

Optimization of the conditions was performed using model enamine **1a** (Table 1). Desilylation (step **3a** → **4a**) was not optimized separately, because nearly quantitative yields of oxime **4a** can be achieved on treatment of the reaction mixture with ammonium fluoride–acetic acid–methanol (cf. Table 1, entries 3, 4 and 5–7). As can be seen, major attention was paid to fluoride, which is known to have a high affinity to silicon. Indeed, the rearrangement with F^- in aprotic solvents already proceeds at –78 °C (Table 1, entry 4). The application of protic solvents did not lead to the desired result (Table 1, entries 8, 9). The presence of moisture also resulted in a decreased yield of oxime **4a** (cf. Table 1, entries 1, 2 and 5–7). Inorganic fluorides like zinc fluoride or lithium fluoride (Table 1, entries 10, 11) led to low yields, presumably due to extremely low solubility even in polar aprotic solvents. For best results, commercially available tetrabutylammonium fluoride trihydrate or tetrabutylammonium fluoride solution in tetrahydrofuran must be dried either by heating under reduced pressure (Table 1, entries 5, 6)[10] or with molecular sieves (entries 3, 4, 7).[11] Other nucleophiles (e.g., BuLi, *t*-BuOK or DMAP) are also applicable for realizing the rearrangement (Table 1, entries 12–14, 16, 17).

The action of tetrabutylammonium fluoride dried with 3 Å molecular sieves (MS) in dichloromethane (see Table 1, entry 7) was chosen as the standard procedure for further investigations. These conditions were used for the rearrangement of other enamines **1b**–**n** (Table 2). The rearrangement was successfully applied to a wide variety of ene nitroso acetals **1**, regardless of ring substituents, trialkylsilyl-group character or ring size; however, some enamines **1** required an additional procedure optimization. Thus, for the bulky *tert*-butyldimethylsilyl derivative

Table 2 Synthesis of Oximes **4** via Enamine **1** Rearrangement[a]

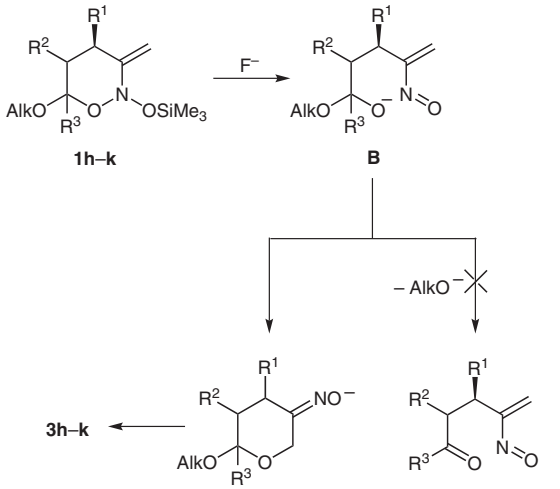


1a–n **4a–m**

Entry	1	4	n	R^1	R^2	R^3	R^4	$SiMe_2R^5$	Yield (%)
1	**a**	**a**	1	4-$MeOC_6H_4$	H	Me	Me	TMS	97
2	**b**	**b**	1	Ph	H	Me	Me	TMS	91
3	**c**	**c**	1	OBz	H	Me	Me	TMS	71
4	**d**	**d**	1	Me	H	Me	Me	TMS	80
5	**e**	**e**	1	4-$MeOC_6H_4$	H	Pr	H	TMS	95
6	**f**	**f**	1	4-$MeOC_6H_4$	H	Ph	H	TMS	76
7	**g**	**g**	1	4-$MeOC_6H_4$	$(CH_2)_4$		H	TMS	53
8	**g**	**g**	1	4-$MeOC_6H_4$	$(CH_2)_4$		H	TMS	61[b]
9	**h**	**h**	1	4-$MeOC_6H_4$[c]	$(CH_2)_2O$		H	TMS	53
10	**i**	**i**	1	4-$MeOC_6H_4$	H	OMe	Me	TMS	83[d]
11	**j**	**j**	1	4-$MeOC_6H_4$	H	OEt	H	TMS	76[d]
12	**k**	**k**	1	4-$MeOC_6H_4$	H	H	OEt	TMS	90[d]
13	**l**	**l**	0	H	–	Ph	H	TMS	83
14	**m**	**m**	0	H	–	CO_2Me	Me	TMS	60
15	**n**	**a**	1	4-$MeOC_6H_4$	H	Me	Me	TBS	77[e]

[a] General reaction conditions: enamine **1** (0.5 M), TBAF (0.1 equiv, 0.05 M), 3 Å MS, CH_2Cl_2, –78 °C for 1.6 h, r.t. for 1 h, then NH_4F, AcOH, MeOH.
[b] Reaction conditions: enamine **1g** (0.1 M), TBAF (0.1 equiv, 0.01 M), 3 Å MS, CH_2Cl_2, –78 °C to r.t., then NH_4F, AcOH, MeOH.
[c] dr ~4:1. The relative configuration of R^1 in the major diastereomer was opposite to that shown above.
[d] For desilylation, NH_4F, MeOH was used instead of NH_4F, AcOH, MeOH.
[e] Reaction conditions: enamine **1n** (0.33 M), TBAF (0.3 equiv, 0.05 M), 3 Å MS, CH_2Cl_2, –78 °C for 0.5 h, r.t. for 1 h, then TFA (3 equiv), MeOH.

1n, an increase in the tetrabutylammonium fluoride amount and the use of trifluoroacetic acid for desilylation were necessary. For bicyclic enamine **1g**, some improvement was achieved by decreasing the concentration of the reagents (cf. Table 2, entries 7, 8). It is remarkable that enamines **1h–k** bearing an alkoxy substituent at C-6 (R^3 or R^4 = OAlk) can be successfully involved in the rearrangement. Evidently, the rate of intramolecular cyclization of anion **B** (see Scheme 2) is greater than the rate of RO^- elimination from C-6 (Scheme 3).



Scheme 3 Proposed mechanism for the rearrangement of 6-alkoxy-substituted enamines **1h–k**

The structures of oximes **4** were confirmed by ^1H and ^{13}C NMR spectroscopy and elemental analysis (or HRMS) data. In addition, an X-ray crystallographic analysis of oxime **4a** was performed (Figure 1).[12] In most cases, de-

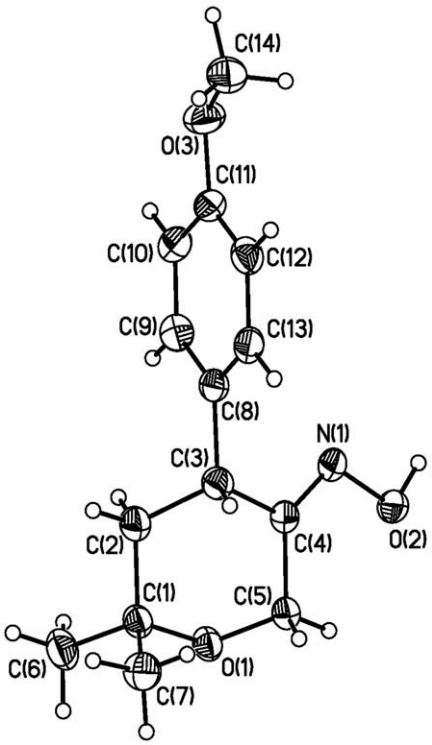
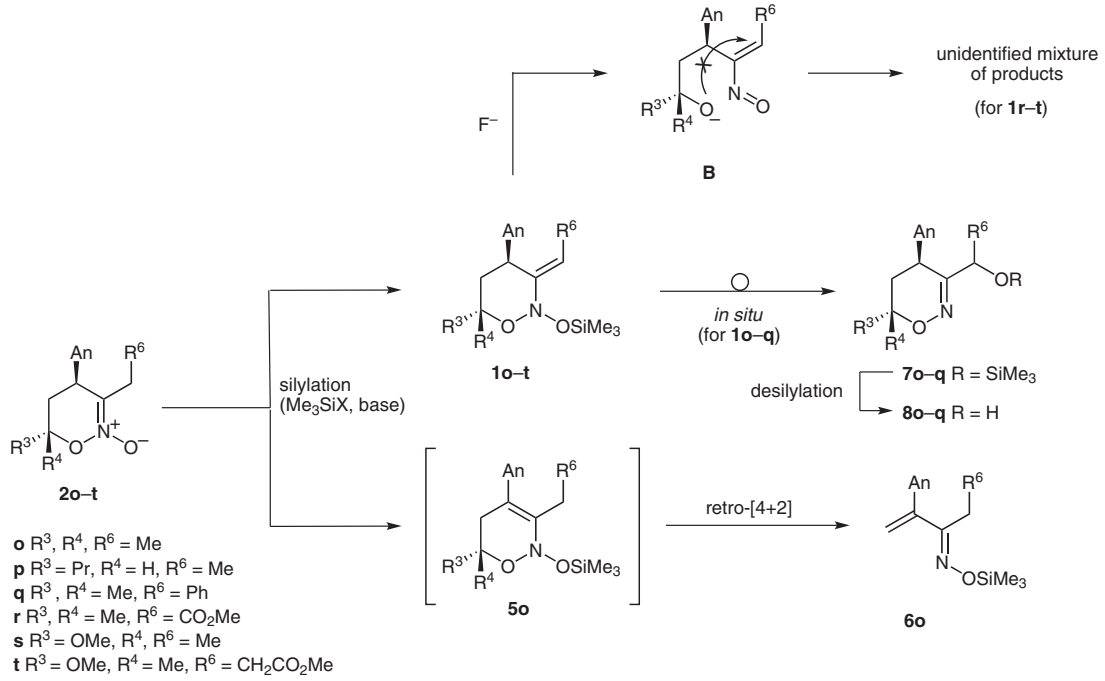


Figure 1 X-ray data of compound **4a** (ORTEP drawing)

rivatives **4** were obtained as a mixture of *E*/*Z*-isomers (for assignment and further details, see experimental section).

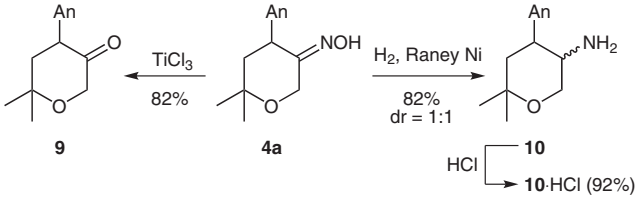
The only limitation of the rearrangement is that it requires the absence of an R^6 substituent in the starting enamines **1**, i.e. the C–C double bond should be terminal. If this was not the case, other processes occurred (Scheme 4). Unfortunately, all our attempts to overcome these problems



Scheme 4 Side processes in the preparation and rearrangement of internal enamines **1o–t**

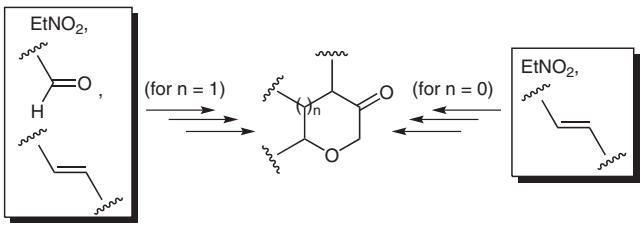
failed. One problem related to internal nitroso acetals **1** is connected with complications in their preparation. In particular, the synthesis of enamine **1o** is accompanied by formation of enoxime **6o** which is the product of [4+2] cycloreversion of endocyclic enamine **5o**.[9] Moreover, bulky Hünig's base turned out to be too weak to afford enamine **1o** with trimethylsilyl bromide. Switching from trimethylsilyl bromide to the more powerful trimethylsilyl trifluoromethanesulfonate led to some rearrangement to **7o** in the reaction mixture.[9] Increasing the steric hindrance in the initial nitronate was also unsuccessful. Thus, only oxazine **7p** was observed on silylation of nitronate **2p**. This might be due to the rearrangement of **1p**[9] under the silylation conditions or during workup. Increasing the acidity of the exocyclic hydrogen by using an electron-withdrawing group as R^6 favored exocyclic hydrogen abstraction, but enamine **1q** (R^6 = Ph) rearranged to **7q**, just as described for **1p**. The methoxycarbonyl-containing enamine **1r** was stable, but failed to undergo rearrangement **1** → **3** and led to a complex mixture of products. Enamines **1s**,**t**,[9] although stable, also led to a complex mixture of products upon treatment with tetrabutylammonium fluoride. Presumably, this results from shielding of the nitrosoalkene moiety in anion **B** due to R^6 bulkiness.

To demonstrate the synthetic utility of oximes **4**, we have performed the deoximation of **4a** to ketone **9** and the reduction of **4a** to amine **10**. The latter was characterized as its hydrochloride, **10**·HCl (Scheme 5).



Scheme 5 Deoximation and reduction of oxime **4a**

In conclusion, the rearrangement of cyclic *N*,*N*-bis(oxy)enamines **1**, prepared by the silylation of cyclic nitronates **2**, was investigated. As a result, a new strategy for the assembly of dihydro-2*H*-pyran-3-ones and dihydrofuran-3-ones from nitroethane and other simple molecules has been suggested (Scheme 6).



Scheme 6 Assembly of pyranones and furanones from nitroethane and other readily available precursors

All reactions were performed in oven-dried (150 °C) glassware. Melting points were determined on a Koffler melting-point apparatus and are uncorrected. Chromatographic separations were performed on silica gel (Acros, 40–60 μm, 60 Å) with analytical grade solvents, driven by air pressure. Analytical thin-layer chromatography was performed on Fluka silica gel plates with fluorescent indicator (254 nm). Visualization was accomplished with UV light and/or anisaldehyde and/or ninhydrin. 1D and 2D NMR spectra were recorded on a Bruker AV-300 NMR spectrometer (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz, ^{29}Si: 59.63 MHz) for $CDCl_3$ solutions at 298 K (unless otherwise mentioned) with residual solvent peak as an internal standard.[13] The INEPT pulse sequence was used for observation of the ^{29}Si signals. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Atom numering is shown in Figure 2. Coupling constants, *J*, are reported in hertz. Determination of the C=N bond configuration (*E* or *Z*) was made based on the chemical shifts in the ^{13}C NMR spectra: the carbon atom in *syn* arrangement to the OR group (R = H, $SiMe_3$) is shifted to higher field compared to the signal from the same carbon in the opposite isomer.[14] Elemental analyses were performed by the Analytical Centre of the N.D. Zelinsky Institute of Organic Chemistry. IR spectra were recorded as thin layers on a Bruker Vector 22 spectrometer. HRMS were recorded on a Bruker microTOF mass spectrometer.

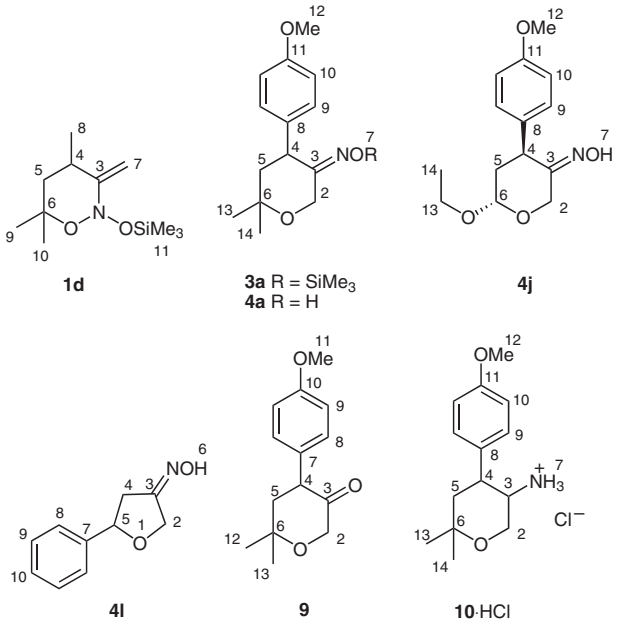


Figure 2 Atom-numbering in selected compounds

The following compounds were prepared according to literature procedures: nitronates **2a**,**d**,[15] **2e**,[16] and enamines **1a**,**l**,**m**,[17] **1b**,**g**,**i**–**k**,[3] **1c**,**f**,**s**,[18] **1t**.[9] Previously unknown nitronates **2h**,**p**–**r** were prepared by procedures similar to those known[3] (for details, see Supporting Information). For oxazines **8p**,**q**, also see Supporting Information.

4,6,6-Trimethyl-3-methylene-2-(trimethylsilyloxy)-1,2-oxazinane (1d); Typical Procedure

Et_3N (0.24 g, 0.33 mL, 2.4 mmol, 1.2 equiv) and TMSBr (0.34 g, 0.29 mL, 2.2 mmol, 1.1 equiv) were successively added to a stirred soln of nitronate **2d** (0.32 g, 2 mmol) in CH_2Cl_2 (4 mL) at –78 °C under argon atmosphere. The mixture was maintained at –78 °C for 1 d, then the cooling bath was removed. The mixture was diluted with hexane (10 mL) and transferred to a mixture of hexane (40 mL) and H_2O (20 mL). The organic layer was washed with a soln of

$NaHSO_4$ (60 mg/mmol of **2**) in H_2O (20 mL), and brine (2 × 20 mL), then treated with activated charcoal, filtered and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give target enamine **1d** as a colorless oil, that was sufficiently pure (NMR analysis) and used without additional purification; yield: 0.29 g (63%).

^{1}H NMR: δ = 0.19 (s, 9 H, 11-CH_3), 1.11 (d, *J* = 6.6 Hz, 3 H, 8-CH_3), 1.20 (s, 3 H, 9-CH_3), 1.32 (dd, *J* = 14.0, 12.5 Hz, 1 H, H_{ax}5), 1.43 (s, 3 H, 10-CH_3), 1.60 (dd, *J* = 12.5, 5.1 Hz, 1 H, H_{eq}5), 2.53–2.68 (m, 1 H, H4), 4.40 (s, 1 H, H_a7), 4.99 (s, 1 H, H_b7).

^{13}C NMR: δ = –0.8 (C11), 17.7, 24.1 (br), 28.9 and 30.1 (C4, C8, C9 and C10), 45.7 (br, C5), 76.8 (C6), 93.3 (C7), 159.7 (C3).

HRMS: *m/z* [M + H]$^+$ calcd for $C_{11}H_{24}NO_2Si$: 230.1571; found: 230.1568.

Previously unknown enamines **1e**,**h**,**r** were prepared by silylation of nitronates **2e**,**h**,**r** with TMSBr, similar to the procedure for **1d**, while enamine **1n** was prepared by silylation of nitronate **2a** with TBSOTf, similar to a known procedure[3] (for details, see Supporting Information).

Optimization of the Reaction Conditions 1a → 3a or 4a

See Supporting Information.

4-(4-Methoxyphenyl)-6,6-dimethyldihydro-2*H*-pyran-3(4*H*)-one *O*-(Trimethylsilyl)oxime (3a)

A 0.5-M soln of enamine **1a** in CH_2Cl_2 (1 mL, 0.5 mmol) was added to a soln of DMAP (6 mg, 0.05 mmol, 0.1 equiv) in CH_2Cl_2 (1 mL). The resulting mixture was stirred for 2 h, then poured into a mixture of Et_2O (30 mL) and $NaHSO_4$ [0.12 g in H_2O (20 mL)]. The organic layer was washed with brine (2 × 30 mL) and concentrated under reduced pressure to give silyl derivative **3a**; yield: 0.15 g (94%); *E*/*Z* = 4.5:1.

E-Isomer

^{1}H NMR: δ = 0.07 (s, 9 H, 7-CH_3), 1.10 (s, 3 H, 13-CH_3), 1.25 (s, 3 H, 14-CH_3), 1.98 (dd, *J* = 14.5, 6.7 Hz, 1 H, H_a5), 2.14 (dd, *J* = 14.5, 7.5 Hz, 1 H, H_b5), 3.80 (s, 3 H, 12-CH_3), 4.25 (d, *J* = 13.7 Hz, 1 H, H_a2), 4.37 (dd, *J* = 7.5, 6.7 Hz, 1 H, H4), 4.46 (d, *J* = 13.7 Hz, 1 H, H_b2), 6.85 (d, *J* = 8.7 Hz, 2 H, H10), 7.09 (d, *J* = 8.7 Hz, 2 H, H9).

^{13}C NMR: δ = –1.0 (C7), 27.5 (C13), 28.5 (C14), 36.5 (C4), 41.4 (C5), 55.2 (C12), 62.3 (C2), 72.5 (C6), 113.8 (C10), 128.2 (C9), 133.3 (C8), 157.9 (C11), 161.3 (C3).

Z-Isomer

^{1}H NMR: δ = 0.08 (s, 9 H, 7-CH_3), 1.26 (s, 3 H, 13-CH_3), 1.36 (s, 3 H, 14-CH_3), 1.86–2.08 (m, 2 H, 5-CH_2), 3.73–3.82 (m, 1 H, H4), 3.81 (s, 3 H, 12-CH_3), 4.46 (d, *J* = 16.9 Hz, 1 H, H_a2), 4.73 (d, *J* = 16.9 Hz, 1 H, H_b2), 6.85 (d, *J* = 8.7 Hz, 2 H, H10), 7.15 (d, *J* = 8.7 Hz, 2 H, H9).

^{13}C NMR: δ = –0.9 (C7), 25.9 (C13), 28.3 (C14), 40.9 (C4), 43.4 (C5), 55.2 (C12), 58.7 (C2), 72.2 (C6), 113.4 (C10), 129.5 (C9), 132.6 (C8), 157.9 (C11), 163.4 (C3).

Oximes 4a–h,l,m; General Procedure (GP-1)

Molecular sieves were dried at ca. 200 °C under reduced pressure (0.7 mbar) for 10 min prior to use. 1 M TBAF in THF (0.1 equiv) (or TBAF·3H_2O) was added to CH_2Cl_2 (1.9–2.2 mL/1 mmol of enamine **1**) under argon atmosphere and stirred with 3 Å MS (1 g/1 mmol of TBAF) for 20 min. This suspension was cooled to –78 °C and a 0.46–0.53 M soln of enamine **1** in CH_2Cl_2 (0.64–1.27 mmol, 1 equiv) was added over 5 min. The resulting mixture was stirred at –78 °C for 1.6 h, then the cooling bath was removed, the mixture was stirred for an additional 1 h, and a mixture of NH_4F (1.5 equiv), AcOH (2 equiv) and MeOH (2 mL/1 mmol of enamine **1**) was added. The resulting mixture was stirred for 1 h, then poured into a mixture of Et_2O (40 mL) and H_2O (30 mL). The aqueous layer was extracted with Et_2O (20 mL). The combined organic layer was washed with brine (2 × 30 mL) and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane–EtOAc, 10:1 to 2:1) to give target oximes **4**.

Oximes 4i–k; General Procedure (GP-2)

Molecular sieves were dried at ca. 200 °C under reduced pressure (0.7 mbar) for 10 min prior to use. 1 M TBAF in THF (0.1 equiv) (or TBAF·3H_2O) was added to CH_2Cl_2 (2 mL/mmol of enamine **1**) under argon atmosphere and stirred with 3 Å MS (1 g/1 mmol of TBAF) for 20 min. This suspension was cooled to –78 °C and a 0.5 M soln of enamine **1** in CH_2Cl_2 (0.8–2.2 mmol, 1 equiv) was added during 5 min. The resulting mixture was stirred at –78 °C for 1 h, then the cooling bath was removed, and the mixture was stirred for an additional 1 h and concentrated. The residue was dissolved in MeOH (4 mL/mmol of enamine **1**) and NH_4F (ca. 10 mg) was added. The resulting mixture was maintained for 1 d, filtered through a short pad of Celite® and the Celite® was washed with EtOAc (ca. 25 mL). The resulting solution was poured into a mixture of Et_2O (40 mL) and H_2O (30 mL). The aqueous layer was extracted with Et_2O (20 mL). The combined organic layer was washed with brine (2 × 30 mL) and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane–EtOAc, 3:1) to give target oximes **4**.

For data for oximes **4b–i**,**k**,**m**, see Supporting Information.

4-(4-Methoxyphenyl)-6,6-dimethyldihydro-2*H*-pyran-3(4*H*)-one Oxime (4a)

From Enamine 1a

Oxime **4a** was obtained as a white solid from enamine **1a** (1 mmol) according to GP-1; yield: 242 mg (97%); *E*/*Z* = 1.5:1.

From Enamine 1n

Molecular sieves were dried at ca. 200 °C under reduced pressure (0.7 mbar) for 10 min prior to use. TBAF·3H_2O (28 mg, 0.09 mmol, 0.3 equiv) was added to CH_2Cl_2 (1.8 mL) under argon atmosphere and stirred with 3 Å MS (90 mg) for 20 min. This suspension was cooled to –78 °C and a 0.33 M soln of enamine **1n** in CH_2Cl_2 (1 mL, 0.3 mmol, 1 equiv) was added during 5 min. The resulting mixture was stirred at –78 °C for 0.5 h, then the cooling bath was removed, the mixture was stirred for an additional 1 h, and a mixture of TFA (103 mg, 67 μL, 0.9 mmol, 3 equiv) and MeOH (1 mL) was added. The resulting mixture was stirred for 1.3 h, then poured into a mixture of Et_2O (40 mL) and H_2O (30 mL). The aqueous layer was extracted with Et_2O (20 mL). The combined organic layer was washed with brine (2 × 30 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane–EtOAc, 5:1 then 3:1) to give oxime **4a** as a white solid; yield: 57 mg (77%); *E*/*Z* = 1:1.5.

Mp 149–155 °C; R_f = 0.62 and 0.53 (hexane–EtOAc, 1:1) (anisaldehyde).

IR: 3244, 2970, 2933, 1614, 1518, 1458, 1369, 1250, 1178, 1033, 944 cm^{-1}.

E-Isomer

^{1}H NMR: δ = 1.08 (s, 3 H, 13-CH_3), 1.25 (s, 3 H, 14-CH_3), 2.00 (dd, *J* = 14.7, 6.6 Hz, 1 H, H_a5), 2.11 (dd, *J* = 14.7, 7.3 Hz, 1 H, H_b5), 3.80 (s, 3 H, 12-CH_3), 4.19 (d, *J* = 13.6 Hz, 1 H, H_a2), 4.34 (dd, *J* = 7.3, 6.6 Hz, 1 H, H4), 4.43 (d, *J* = 13.6 Hz, 1 H, H_b2), 6.87 (d, *J* = 8.4 Hz, 2 H, H10), 7.13 (d, *J* = 8.4 Hz, 2 H, H9), 8.12 (br s, 1 H, H7).

^{13}C NMR (DEPT): δ = 27.4 (C13), 28.5 (C14), 36.0 (C4), 41.4 (C5), 55.3 (C12), 62.1 (C2), 72.7 (C6), 114.1 (C10), 128.0 (C9), 132.9 (C8), 158.5 (C11), 161.0 (C3).

***Z*-Isomer**

^{1}H NMR: δ = 1.30 (s, 3 H, 13-CH_3), 1.36 (s, 3 H, 14-CH_3), 1.89–2.04 (m, 2 H, 5-CH_2), 3.73 (dd, *J* = 12.5, 5.1 Hz, 1 H, H4), 3.79 (s, 3 H, 12-CH_3), 4.41 (d, *J* = 16.9 Hz, 1 H, H_a2), 4.65 (d, *J* = 16.9 Hz, 1 H, H_b2), 6.87 (d, *J* = 8.1 Hz, 2 H, H10), 7.13 (d, *J* = 8.1 Hz, 2 H, H9), 7.91 (br s, 1 H, H7).

^{13}C NMR (DEPT): δ = 25.8 (C13), 28.1 (C14), 40.6 (C4), 42.6 (C5), 55.3 (C12), 58.3 (C2), 72.3 (C6), 114.0 (C10), 129.3 (C9), 131.5 (C8), 158.5 (C11), 161.0 (C3).

Analytically pure sample was obtained after drying over P_2O_5 under reduced pressure at 78 °C in a drying pistol.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found (for *E*/*Z*-mixture): C, 67.23; H, 7.56; N, 5.60.

rel-(4*R*,6*R*)-6-Ethoxy-4-(4-methoxyphenyl)dihydro-2*H*-pyran-3(4*H*)-one Oxime (4j)

Oxime **4j** was obtained as a white solid from enamine **1j** (0.8 mmol) according to GP-2; yield: 161 mg (76%); *Z*/*E* = 1.7:1.

Mp 129–132 °C (MeOH); R_f = 0.55 (hexane–EtOAc, 1:1) (anisaldehyde).

***Z*-Isomer**

^{1}H NMR: δ = 1.27 (t, *J* = 7.0 Hz, 3 H, 14-CH_3), 2.01–2.10 (m, 1 H, H_a5), 2.27–2.36 (m, 1 H, H_b5), 3.55 (dq, *J* = 9.9, 7.0 Hz, 1 H, H_a13), 3.79–3.86 (m, 1 H, H_b13), 3.80 (s, 3 H, 12-CH_3), 3.95 (dd, *J* = 10.5, 5.5 Hz, 1 H, H4), 4.22 (d, *J* = 15.4 Hz, 1 H, H_a2), 4.87 (d, *J* = 15.4 Hz, 1 H, H_b2), 4.97 (br s, 1 H, H6), 6.85 (d, *J* = 8.5 Hz, 2 H, H10), 7.15 (d, *J* = 8.5 Hz, 2 H, H9), 8.30 (br s, 1 H, H7).

^{13}C NMR: δ = 15.1 (C14), 36.7 (C5), 39.3 (C4), 55.2 (C12), 55.7 and 63.2 (C2 and C13), 96.2 (C6), 114.0 (C10), 129.2 (C9), 131.6 (C8), 158.0 (C11), 158.5 (C3).

Characteristic NOE contacts: 13-CH_2–H6, H_a2–H4, H6–5-CH_2, H4–H_a5. Contact 13-CH_2–2-CH_2 was not observed.

***E*-Isomer**

^{1}H NMR: δ = 1.21 (t, *J* = 7.0 Hz, 3 H, 14-CH_3), 2.01–2.10 (m, 1 H, H_a5), 2.27–2.36 (m, 1 H, H_b5), 3.47 (dq, *J* = 9.5, 7.0 Hz, 1 H, H_a13), 3.79–3.86 (m, 1 H, H_b13), 3.80 (s, 3 H, 12-CH_3), 4.22 (d, *J* = 14.0 Hz, 1 H, H_a2), 4.42 (d, *J* = 14.0 Hz, 1 H, H_b2), 4.48 (dd, *J* = 5.5, 3.3 Hz, 1 H, H4), 4.77 (dd, *J* = 7.7, 4.1 Hz, 1 H, H6), 6.87 (d, *J* = 8.8 Hz, 2 H, H10), 7.19 (d, *J* = 8.8 Hz, 2 H, H9), 8.30 (br s, 1 H, H7).

^{13}C NMR: δ = 15.2 (C14), 34.3 (C5), 35.3 (C4), 55.2 (C12), 61.7 and 63.6 (C2 and C13), 97.2 (C6), 114.0 (C10), 128.5 (C9), 131.6 (C8), 157.2 (C3), 158.0 (C11).

Characteristic NOE contacts: 13-CH_2–H6.

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found (for *E*/*Z*-mixture): C, 63.20; H, 7.37; N, 5.09.

5-Phenyldihydrofuran-3(2*H*)-one Oxime (4l)

Oxime **4l** was obtained as a colorless oil, that solidifies upon storage, from enamine **1l** (0.75 mmol) according to GP-1; yield: 111 mg (83%); *E*/*Z* = 5:1.

Mp 106–113 °C; R_f = 0.62 (UV) and 0.48 (UV, anisaldehyde) (hexane–EtOAc, 1:1).

***E*-Isomer**

^{1}H NMR: δ = 2.69 (ddd, *J* = 18.4, 8.8, 1.5 Hz, 1 H, H_a4), 3.26 (dd, *J* = 18.4, 6.6 Hz, 1 H, H_b4), 4.42 (d, *J* = 13.9 Hz, 1 H, H_a2), 4.64 (dd, *J* = 13.9, 1.5 Hz, 1 H, H_b2), 5.10 (dd, *J* = 8.8, 6.6 Hz, 1 H, H5), 7.30–7.41 (m, 5 H, H8, H9 and H10), 8.89 (br s, 1 H, H6).

^{13}C NMR (DEPT): δ = 35.4 (C4), 67.9 (C2), 80.6 (C5), 125.9, 128.1 and 128.6 (C8, C9 and C10), 140.4 (C7), 162.2 (C3).

***Z*-Isomer**

^{1}H NMR: δ = 2.68–2.76 (m, 1 H, H_a4), 3.05 (dd, *J* = 16.1, 5.9 Hz, 1 H, H_b4), 4.55 (dd, *J* = 16.1, 1.5 Hz, 1 H, H_a2), 4.83 (d, *J* = 16.1 Hz, 1 H, H_b2), 5.06–5.11 (m, 1 H, H5), 7.30–7.41 (m, 5 H, H8, H9 and H10), 8.89 (br s, 1 H, H6).

^{13}C NMR (DEPT): δ = 37.7 (C4), 66.6 (C2), 80.4 (C5), 125.9, 128.1 and 128.6 (C8, C9 and C10), 140.0 (C7), 163.4 (C3).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found (for *E*/*Z*-mixture): C, 67.68; H, 6.42; N, 7.82.

4-(4-Methoxyphenyl)-6,6-dimethyldihydro-2*H*-pyran-3(4*H*)-one (9)

Compound **9** was prepared using a modification of a literature procedure[19] used for another compound. To a soln of oxime **4a** (111 mg, 0.45 mmol), NH_4OAc (0.5 g) and AcOH (0.1 mL) in dioxane (1.2 mL) and H_2O (0.1 mL) was added a 10% soln of $TiCl_3$ in 20–30% HCl (1.45 mL, 1.13 mmol, 2.4 equiv) during 4 min. The mixture was stirred for 1 h, diluted with Et_2O (ca. 10 mL), stirred for 2 h, then poured into a mixture of Et_2O (30 mL) and brine (20 mL). The aqueous layer was washed with Et_2O (20 mL). The combined organic layer was washed with sat. aq $NaHCO_3$ soln (20 mL), H_2O (20 mL) and brine (2 × 30 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to give pyranone **9** as a slightly yellow oil; yield: 86 mg (82%).

R_f = 0.30 (hexane–EtOAc, 3:1) (anisaldehyde).

IR: 2972, 2933, 1732, 1613, 1516, 1464, 1369, 1302, 1248, 1180, 1161, 1124, 1093, 1034, 831 cm^{-1}.

^{1}H NMR: δ = 1.37 (s, 3 H, 12-CH_3), 1.48 (s, 3 H, 13-CH_3), 2.14–2.21 (m, 2 H, 5-CH_2), 3.81 (s, 3 H, 11-CH_3), 3.87 (dd, *J* = 11.5, 7.6 Hz, 1 H, H4), 4.09–4.22 (m, 2 H, 2-CH_2), 6.91 (d, *J* = 8.8 Hz, 2 H, H9), 7.07 (d, *J* = 8.8 Hz, 2 H, H8).

^{13}C NMR: δ = 26.6 (C12), 27.3 (C13), 41.7 (C5), 49.3 (C4), 55.2 (C11), 68.5 (C2), 72.9 (C6), 114.1 (C9), 129.5 (C8), 129.9 (C7), 158.8 (C10), 210.5 (C3).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}O_3$: 235.1329; found: 235.1329.

4-(4-Methoxyphenyl)-6,6-dimethyltetrahydro-2*H*-pyran-3-amine (10) and 4-(4-Methoxyphenyl)-6,6-dimethyltetrahydro-2*H*-pyran-3-aminium Chloride (10·HCl)

A 50% slurry of Raney Ni in H_2O (2 mL) was washed with MeOH (4 × 3 mL) prior to use. A soln of oxime **4a** (107 mg, 0.43 mmol) in MeOH (7 mL) was hydrogenated at 20 bar and 70 °C in a steel autoclave for 2 h. The resulting mixture was filtered through Celite® and the Celite® was washed with MeOH (30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc, then $CHCl_3$–MeOH, 20:1) to give amine **10** as a colorless oil; yield: 83 mg (82%); dr = 1:1; R_f = 0.25 ($CHCl_3$–MeOH, 10:1) (ninhydrin).

Amine **10** was dissolved in toluene (1 mL) and 4 M HCl in dioxane (0.1 mL) was added. Slow formation of a white precipitate was observed. The mixture was maintained for 3 h, then concentrated under reduced pressure to give hydrochloride **10**·HCl as a brownish solid; yield: 96 mg (82%, based on initial oxime). Recrystallization (acetone) afforded a white powder; yield: 47 mg (49%, based on amine); *trans*/*cis* = 2.5:1; mp 255–258 °C (dec). Concentration of the mother liquor afforded a brownish oil; yield: 41 mg (43%, based on amine); *trans*/*cis* = 1:2.5.

***trans*-Isomer**

^{1}H NMR (COSY, NOESY, DMSO-d_6): δ = 1.17 (s, 3 H, 13-CH_3), 1.27 (s, 3 H, 14-CH_3), 1.55–1.69 (m, 2 H, 5-CH_2), 3.13–3.28 (m, 2 H, H3 and H4), 3.65–3.73 (m, 1 H, H_a2), 3.73 (s, 3 H, 12-CH_3),

3.89–3.94 (m, 1 H, H_b2), 6.91 (d, J = 8.5 Hz, 2 H, H10), 7.27 (d, J = 8.5 Hz, 2 H, H9), 8.06 (br s, 3 H, H7).

^{1}H NMR (COSY, NOESY, D_2O): δ = 1.23 (s, 3 H, 13-CH_3), 1.31 (s, 3 H, 14-CH_3), 1.77–1.80 (m, 2 H, 5-CH_2), 3.03 (dt, J = 11.7, 8.1 Hz, 1 H, H4), 3.40 (ddd, J = 11.7, 10.3, 5.3 Hz, 1 H, H3), 3.68–3.77 (m, 1 H, $H_{ax}2$), 3.77 (s, 3 H, 12-CH_3), 3.94 (dd, J = 11.7, 5.3 Hz, 1 H, $H_{eq}2$), 6.96 (d, J = 7.9 Hz, 2 H, H10), 7.27 (d, J = 7.9 Hz, 2 H, H9).

Characteristic NOE contacts: H3–5-CH_2, H4–$H_{ax}2$. Contact H3–H4 was not observed.

^{13}C NMR (HSQC, DMSO-d_6): δ = 21.8 (C13), 30.8 (C14), 40.2 (C4), 44.0 (C5), 51.7 (C3), 55.5 (C12), 61.8 (C2), 72.4 (C6), 114.6 (C10), 129.5 (C9), 132.7 (C8), 158.9 (C11).

***cis*-Isomer**

^{1}H NMR (COSY, NOESY, DMSO-d_6): δ = 1.23 (s, 3 H, 13-CH_3), 1.27 (s, 3 H, 14-CH_3), 1.45 (dd, J = 13.9, 2.9 Hz, 1 H, H_a5), 2.27 (t, J = 13.9 Hz, 1 H, H_b5), 3.26–3.40 (m, 2 H, H3 and H4), 3.73 (s, 3 H, 12-CH_3), 3.89 (s, 2 H, 2-CH_2), 6.91 (d, J = 8.8 Hz, 2 H, H10), 7.23 (d, J = 8.8 Hz, 2 H, H9), 7.87 (br s, 3 H, H7).

^{1}H NMR (COSY, NOESY, D_2O): δ = 1.23 (s, 3 H, 13-CH_3), 1.31 (s, 3 H, 14-CH_3), 1.72–1.77 (m, 1 H, H_a5), 2.06 (t, J = 13.9 Hz, 1 H, H_b5), 3.52–3.59 (m, 2 H, H3 and H4), 3.77 (s, 3 H, 12-CH_3), 3.77–3.83 (m, 1 H, H_a2), 4.12 (d, J = 13.2 Hz, 1 H, H_b2), 6.96 (d, J = 7.9 Hz, 2 H, H10), 7.25 (d, J = 7.9 Hz, 2 H, H9).

^{13}C NMR (HSQC, DMSO-d_6): δ = 21.8 (C13), 31.1 (C14), 33.9 (C5), 36.5 (C4), 50.9 (C3), 55.5 (C12), 62.5 (C2), 72.5 (C6), 114.6 (C10), 129.2 (C9), 132.1 (C8), 158.8 (C11).

Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15; Cl, 13.04. Found (for *trans*/*cis*-mixture): C, 61.10; H, 8.14; N, 5.19; Cl, 13.14.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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